

Towards individualized treatment for esophageal cancer

Peter Sylvain Nicolas van Rossum

Towards individualized treatment for esophageal cancer

PhD thesis, Utrecht University, The Netherlands

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For two projects (Chapter 10 and Chapter 13) funding was provided in part by The University of Texas MD Anderson Cancer Center and by the National Cancer Institute Cancer Center Support Grant CA016672.

Publication of this thesis was financially supported by Philips Healthcare, Olympus Nederland B.V., ChipSoft B.V., Nederlandse Vereniging voor Gastroenterologie, and Nederlandse Vereniging voor Endoscopische Chirurgie.

| | |
|------------|-----------------------------|
| Cover | Wim Rebergen |
| Lay-out | Roy Sanders |
| Printed by | Uitgeverij BOXPress, Vianen |
| ISBN | 978-94-6295-464-9 |

Towards individualized treatment for esophageal cancer

Naar een geïndividualiseerde behandeling voor slokdarmkanker
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op vrijdag 9 september 2016 des middags te 4.15 uur

door

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geboren op 20 juli 1989

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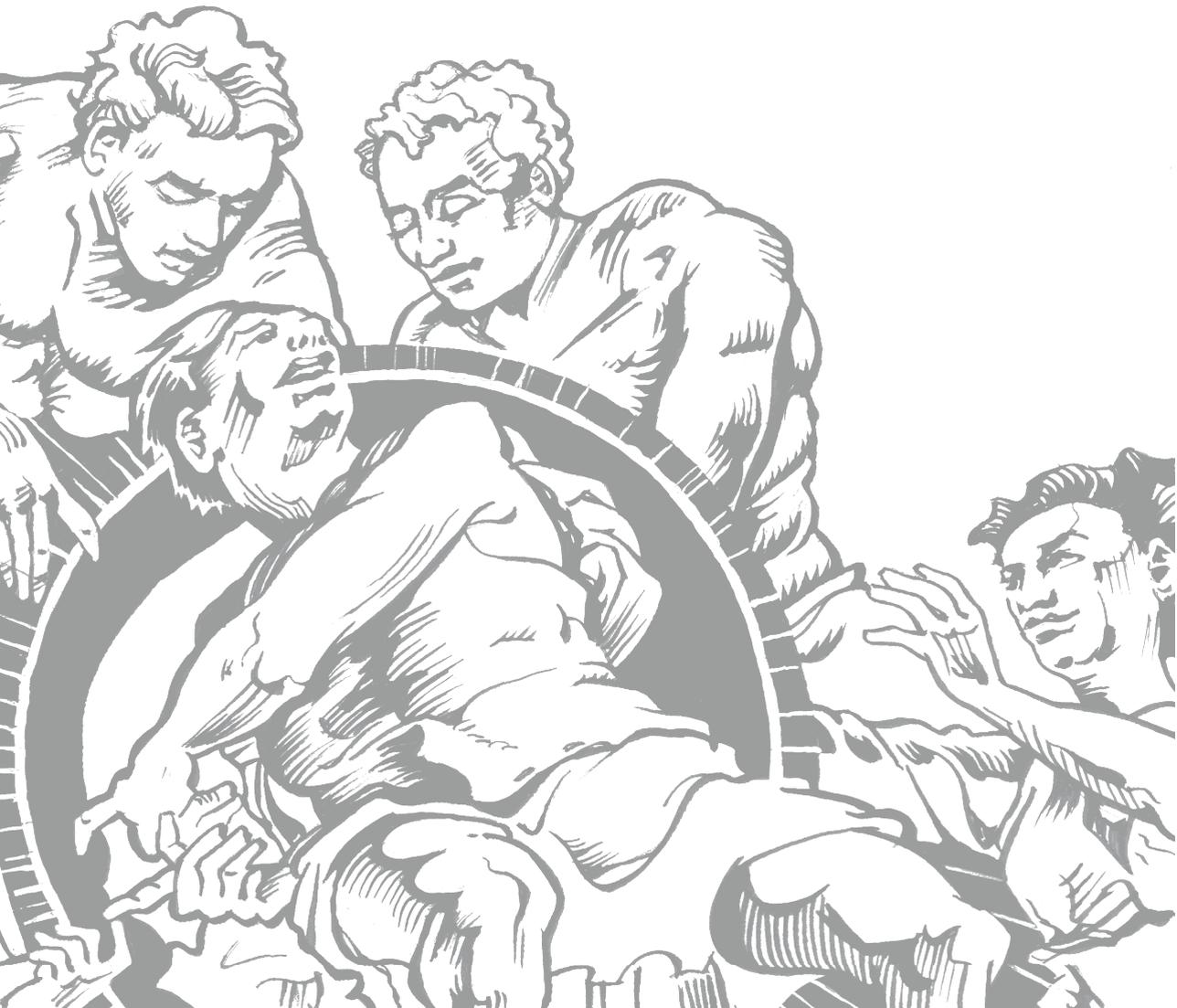
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Chapter 1

General introduction
and thesis outline

ESOPHAGEAL CANCER

Cancer of the esophagus is the eighth most common malignancy and the sixth leading cause of cancer-related mortality worldwide with more than 450,000 new cases and 400,000 deaths every year¹. It remains a devastating disease with an overall survival rate of only 15-25% at 5 years after diagnosis²⁻⁴. The majority of malignant esophageal tumors can be subdivided into two histologic subtypes, which are adenocarcinoma and squamous cell carcinoma. The highest burden of adenocarcinoma is found in Northern and Western Europe, Northern America, and Oceania, whereas squamous cell carcinoma is most common in Asia and Africa⁵.

Esophageal cancer has historically been treated with surgery alone, but the increasing use of multimodality treatment approaches –including different combinations of endoscopic therapies, chemotherapy, radiotherapy, and surgery–took off in the late 1990s and early 2000s. Although the rise of multimodality treatment approaches has resulted in substantial improvement of long-term oncologic outcomes in patients with esophageal cancer, it has come at a price. As more and more patients are treated by means of a multitude of treatment modalities, toxicity and morbidity increase with a detrimental impact on patients' quality of life. In addition, the efficacy of the various treatment modalities largely varies from patient to patient resulting in both over- and under-treatment in current practice. Therefore, it is highly desirable to move from the current broad-brush approaches to more tailor-made strategies for the individual patient with maximization of treatment efficacy and minimization of (unnecessary) toxicity and morbidity. In order to move towards such individualized treatment approaches in esophageal cancer, in this thesis improvements have been sought in the diagnostic work-up, the multimodality treatment strategies, the prediction and assessment of tumor response to chemotherapy and radiotherapy, and the risk prediction, prevention, and management of postoperative complications.

DIAGNOSTIC WORK-UP

Endoscopy with biopsy is used to diagnose esophageal cancer, whereas endoscopic ultrasound (EUS) is frequently employed to determine the local tumor extent (T-stage) and regional lymph node involvement (N-stage)^{6,7}. Integrated ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET)/computed tomography (CT) is also used for determining regional lymph node involvement⁸. However, the most important role of ¹⁸F-FDG PET/CT in esophageal cancer lies in the detection of distant metastases^{9,10}. Although these diagnostic modalities have

established their role in initial staging of esophageal cancer, their usefulness for re-staging after chemo(radio)therapy as well as for the detection of recurrent disease is more questionable and deserves attention in further research.

Magnetic resonance imaging (MRI) is not routinely performed in the clinical work-up for esophageal cancer. However, recent studies suggest that the usefulness of MRI in esophageal cancer may expand as modern MRI with advanced techniques has the potential to complement other imaging modalities¹¹⁻¹³. Although this was suggested in several small descriptive studies, a clear overview of studies performing MRI in esophageal cancer highlighting the current role and future potential of MRI in this setting is lacking.

It is increasingly being recognized that the amount of information currently extracted from the available images in oncology may be substantially enhanced by quantitative imaging analysis¹⁴. The related emerging field of 'radiomics' focuses on these improvements in image analysis, allowing for the acquisition of information on tumor heterogeneity, which is a well-recognized feature of malignancy related to adverse tumor biology, chemoradiation-resistance, and poor prognosis¹⁵. Although several pioneering studies have reported on the use of radiomics in esophageal cancer, an overview outlining the current evidence and future potential is lacking.

MULTIMODALITY TREATMENT STRATEGIES

Best outcomes in esophageal cancer are achieved in patients diagnosed at an early stage in whom endoscopic mucosal or submucosal resection (with or without local ablative techniques) is now increasingly applied, associated with 5-year survival rates of 60-80%^{16,17}. Recently, the prognosis of locally advanced esophageal cancer has been markedly improved by the introduction of multimodality treatment. The 5-year overall survival rate of 23-34% achieved with surgery alone, increased to 36-47% with the addition of neoadjuvant chemoradiotherapy or perioperative chemotherapy¹⁸⁻²⁰. In esophageal squamous cell carcinoma, neoadjuvant chemoradiotherapy is superior to neoadjuvant chemotherapy without radiotherapy²⁰. In esophageal adenocarcinoma, both neoadjuvant chemoradiotherapy and perioperative chemotherapy have convincingly shown superiority over surgery alone, but direct comparisons between these two treatment strategies are limited and highly desired.

The majority of patients diagnosed with esophageal cancer present with unresectable or metastatic disease and even patients with resectable disease have high rates of disease recurrence after treatment with curative intent. An updated

overview on the palliative treatment options in these patients is lacking. Treatment for recurrent disease can be attempted in a fair number of patients and may include chemotherapy, radiotherapy, surgery, or a combination²¹⁻²³. However, there is a need for improved patient selection for the different treatment strategies as not one optimal treatment strategy has been established and patients respond differently to treatment with a wide range in long-term survival²³. As such, seeking factors that affect survival in patients with recurrent disease is of great importance.

TREATMENT RESPONSE ASSESSMENT

In The Netherlands, the current standard of treatment for locally advanced esophageal cancer (including both adenocarcinoma and squamous cell carcinoma) consists of neoadjuvant chemoradiotherapy followed by surgery in accordance with the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS)¹⁸. The degree of pathologic response to neoadjuvant chemoradiotherapy in this setting has appeared as important new determinant of prognosis and key towards more individualized multimodality treatment^{24,25}. Poorly responding patients now suffer from ineffective but toxic treatment and may benefit from intensification, modification or even omission of chemoradiotherapy. On the other hand, in patients with a pathologic complete response a wait-and-see policy including omission of surgery (with accompanying morbidity) and close clinical follow-up after chemoradiotherapy may be preferable. Patients with a good but incomplete response to neoadjuvant chemoradiotherapy (i.e. microscopic residual disease) most likely represent the group that truly benefits from both chemoradiotherapy and surgery. Therefore, seeking powerful tools for predicting response to neoadjuvant treatment for esophageal cancer is an important focus of contemporary research with the ultimate aim to tailor treatment to the individual patient.

Unfortunately, so far no clinical parameters, imaging modality or biomarker has shown the ability to predict pathologic response to neoadjuvant chemoradiotherapy to such reliable extent that they would justify individualized changes in multimodality treatment. A meta-analysis reported that simple metabolic parameters on ¹⁸F-FDG PET before and (during or) after neoadjuvant treatment yields substantial –though insufficient– predictive ability to differentiate poor and good pathologic responders²⁶. There is increasing recognition that radiomics approaches quantifying heterogeneity in tumor ¹⁸F-FDG uptake may provide complementary information that was not looked into in the studies of the meta-analysis^{14,27,28}. Also, some clinical parameters have (limited but non-negligible)

predictive value for treatment response^{29,30}. As such, it is crucial to gain knowledge on the true incremental value of the different described predictors beyond each other using a multivariable approach.

Diffusion-weighted MRI and dynamic contrast-enhanced MRI are functional imaging modalities that recently have demonstrated predictive value for response to chemotherapy and radiotherapy in several malignancies including brain, head-and-neck, breast, prostate, and rectal cancer³¹⁻³⁶. Since more accurate tools for the prediction of pathologic response to chemoradiotherapy in esophageal cancer are highly desired, it would be of great interest to explore the potential value of these two techniques in this setting.

POSTOPERATIVE COMPLICATIONS

Esophagectomy remains the cornerstone of treatment for patients with locally advanced esophageal cancer. Improvements of surgical techniques and perioperative management have led to a steady decrease in postoperative mortality over the past decades³⁷. Nevertheless, anastomotic leakage and pneumonia remain frequently encountered complications after esophagectomy which are associated with increased postoperative morbidity, length of hospital stay, and mortality^{18,38,39}. Identifying risk factors for these complications could aid in early recognition of the complications and in the development of preventative strategies.

Vascular calcification is an important cause of tissue ischemia, and ischemia of the proximal part of the gastric tube is considered a major cause of anastomotic leakage after esophagectomy^{40,41}. As such, it is of interest to explore whether the location and amount of vascular calcification of the arteries supplying the gastric tube is indicative of the risk of postoperative anastomotic leakage. Other potential risk factors for postoperative complications that have not been studied well include intraoperative and postoperative vital parameters and the neoadjuvant radiation dose to the future anastomosis. In multiple experimental and small clinical studies preoperative ischemic conditioning of the stomach emerged as a promising strategy to prevent anastomotic leakage after esophagectomy, but a concise overview assessing its current role and future potential is lacking.

THESIS OUTLINE

The aim of the research presented in this thesis was to evaluate contemporary and new strategies to individualize treatment for patients with esophageal cancer with the ultimate goal to improve the quality of life and prognosis in these patients. To

this regard, the current value and future potential of imaging modalities including CT, ^{18}F -FDG PET, and MRI are explored in part I. Multimodality treatment strategies with curative or palliative intent, for both primary and recurrent disease are evaluated in part II. Part III focuses on the potential ability of endoscopic biopsy, EUS, ^{18}F -FDG PET, diffusion-weighted MRI, and dynamic contrast-enhanced MRI to predict or assess tumor response to neoadjuvant chemoradiotherapy. Part IV includes studies that share the aim of improving perioperative care.

RESEARCH QUESTIONS

The research questions addressed in this thesis can be summarized as follows:

PART I. EXPLORING IMAGING MODALITIES

- Chapter 2** What is the current role and future potential of MRI in the management of esophageal cancer with regard to T-staging, N-staging, tumor delineation for radiotherapy, and treatment response assessment?
- Chapter 3** What are the current and potential future roles of ^{18}F -FDG PET/CT and MRI in the multidisciplinary management of esophageal cancer?
- Chapter 4** What is the available evidence and future potential for the application of radiomics in the management of patients with esophageal cancer?
- Chapter 5** What is the diagnostic performance of ^{18}F -FDG PET and PET/CT for diagnosing recurrent esophageal cancer after initial treatment with curative intent?

PART II. MULTIMODALITY TREATMENT STRATEGIES

- Chapter 6** What are the differences between perioperative chemotherapy and neoadjuvant chemoradiotherapy with regard to toxicity, pathologic outcome, and survival in patients with resectable esophageal cancer?
- Chapter 7** What are the current strategies in palliative care for esophageal cancer?
- Chapter 8** What treatment strategies are applied in patients diagnosed with recurrent disease after esophagectomy and what are prognostic factors affecting survival in these patients?

PART III. TREATMENT RESPONSE PREDICTION

- Chapter 9** How accurate can endoscopic biopsy and EUS after neoadjuvant chemoradiotherapy for esophageal cancer differentiate between residual cancer and pathologic complete response at the primary tumor site and regional lymph nodes?
- Chapter 10** Can subjective and quantitative assessment of baseline and post-chemoradiation ^{18}F -FDG PET improve the accuracy of predicting a pathologic complete response to neoadjuvant chemoradiotherapy in esophageal cancer beyond clinical predictors?
- Chapter 11** Is diffusion-weighted MRI useful to predict pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer?
- Chapter 12** Is dynamic contrast-enhanced MRI useful to predict pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer?
- Chapter 13** What is the value of ^{18}F -FDG PET at baseline and after induction chemotherapy for the early prediction of pathologic response to subsequent preoperative chemoradiotherapy?

PART IV. PERIOPERATIVE CARE

- Chapter 14** Is the amount and location of calcification in the arteries supplying the gastric tube, as determined on routine diagnostic CT, related to the risk of anastomotic leakage after esophagectomy with cervical anastomosis?
- Chapter 15** Is the amount and location of calcification in the arteries supplying the gastric tube, as determined on routine diagnostic CT, related to the risk of anastomotic leakage after esophagectomy with intrathoracic anastomosis?
- Chapter 16** What is the current role and future potential of preoperative ischemic conditioning of the stomach in the prevention of esophagogastric anastomotic leakage after esophagectomy?

- Chapter 17** What is the relationship of intraoperative and postoperative vital parameters with anastomotic leakage and pneumonia after esophagectomy?
- Chapter 18** Is the neoadjuvant radiation dose to the gastric fundus related to the risk of anastomotic leakage after transthoracic esophagectomy for esophageal cancer?
- Chapter 19** What are the management strategies and related outcomes for cervical versus intrathoracic manifestation of cervical anastomotic leakage after transthoracic esophagectomy for cancer?

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359-86
2. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. *Lancet* 2013;381:400-12
3. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003;349:2241-52
4. Omloo JM, Lagarde SM, Hulscher JB, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: Five-year survival of a randomized clinical trial. *Ann Surg* 2007;246:992-1000; discussion 1000-1
5. Arnold M, Soerjomataram I, Ferlay J, et al. Global incidence of oesophageal cancer by histological subtype in 2012. *Gut* 2015;64:381-7
6. Diederich S. Staging of oesophageal cancer. *Cancer Imaging* 2007;7 Spec No A:S63-6
7. Jamil LH, Gill KR, Wallace MB. Staging and restaging of advanced esophageal cancer. *Curr Opin Gastroenterol* 2008;24:530-4
8. van Westreenen HL, Westerterp M, Bossuyt PM, et al. Systematic review of the staging performance of ¹⁸F-fluorodeoxyglucose positron emission tomography in esophageal cancer. *J Clin Oncol* 2004;22:3805-12
9. Rasanen JV, Sihvo EI, Knuuti MJ, et al. Prospective analysis of accuracy of positron emission tomography, computed tomography, and endoscopic ultrasonography in staging of adenocarcinoma of the esophagus and the esophagogastric junction. *Ann Surg Oncol* 2003;10:954-60
10. Munden RF, Macapinlac HA, Erasmus JJ. Esophageal cancer: The role of integrated CT-PET in initial staging and response assessment after preoperative therapy. *J Thorac Imaging* 2006;21:137-45
11. Riddell AM, Hillier J, Brown G, et al. Potential of surface-coil MRI for staging of esophageal cancer. *Am J Roentgenol* 2006;187:1280-7
12. Riddell AM, Allum WH, Thompson JN, et al. The appearances of oesophageal carcinoma demonstrated on high-resolution, T2-weighted MRI, with histopathological correlation. *Eur Radiol* 2007;17:391-9
13. Riddell AM, Davies DC, Allum WH, et al. High-resolution MRI in evaluation of the surgical anatomy of the esophagus and posterior mediastinum. *Am J Roentgenol* 2007;188:W37-43
14. Lambin P, Rios-Velazquez E, Leijenaar R, et al. Radiomics: Extracting more information from medical images using advanced feature analysis. *Eur J Cancer* 2012;48:441-6
15. Ganeshan B, Skogen K, Pressney I, et al. Tumour heterogeneity in oesophageal cancer assessed by CT texture analysis: Preliminary evidence of an association with tumour metabolism, stage, and survival. *Clin Radiol* 2012;67:157-64
16. Rice TW, Rusch VW, Ishwaran H, et al. Cancer of the esophagus and esophagogastric junction: Data-driven staging for the seventh edition of the american joint committee on Cancer/International union against cancer cancer staging manuals. *Cancer* 2010;116:3763-73

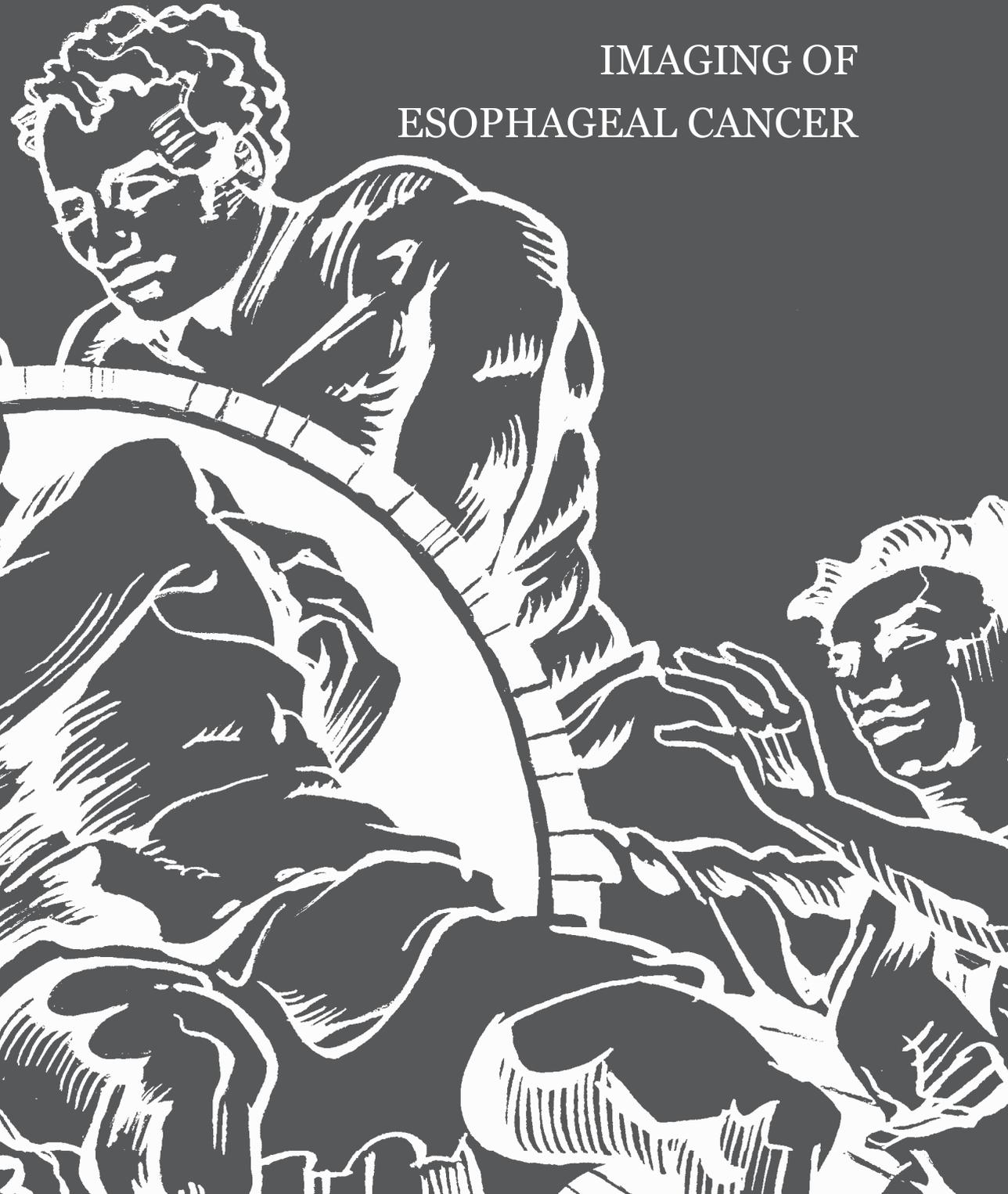
17. Bhatt A, Abe S, Kumaravel A, et al. Indications and techniques for endoscopic submucosal dissection. *Am J Gastroenterol* 2015;110:784-91
18. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
19. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20
20. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: An updated meta-analysis. *Lancet Oncol* 2011;12:681-92
21. Blom RL, Lagarde SM, van Oudenaarde K, et al. Survival after recurrent esophageal carcinoma has not improved over the past 18 years. *Ann Surg Oncol* 2013;20:2693-8
22. Hiyoshi Y, Morita M, Kawano H, et al. Clinical significance of surgical resection for the recurrence of esophageal cancer after radical esophagectomy. *Ann Surg Oncol* 2015;22:240-6
23. Su XD, Zhang DK, Zhang X, et al. Prognostic factors in patients with recurrence after complete resection of esophageal squamous cell carcinoma. *J Thorac Dis* 2014;6:949-57
24. Chiriac LR, Swisher SG, Ajani JA, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. *Cancer* 2005;103:1347-55
25. Holscher AH, Bollsweiler E, Bogoevski D, et al. Prognostic impact of neoadjuvant chemoradiation in cT3 esophageal cancer - A propensity score matched analysis. *Eur J Cancer* 2014;50:2950-7
26. Kwee RM. Prediction of tumor response to neoadjuvant therapy in patients with esophageal cancer with use of ¹⁸F FDG PET: A systematic review. *Radiology* 2010;254:707-17
27. Elliott JA, O'Farrell NJ, King S, et al. Value of CT-PET after neoadjuvant chemoradiation in the prediction of histological tumour regression, nodal status and survival in oesophageal adenocarcinoma. *Br J Surg* 2014;101:1702-11
28. Cheedella NK, Suzuki A, Xiao L, et al. Association between clinical complete response and pathological complete response after preoperative chemoradiation in patients with gastroesophageal cancer: Analysis in a large cohort. *Ann Oncol* 2013;24:1262-6
29. Ajani JA, Correa AM, Hofstetter WL, et al. Clinical parameters model for predicting pathologic complete response following preoperative chemoradiation in patients with esophageal cancer. *Ann Oncol* 2012;23:2638-42
30. Toxopeus EL, Nieboer D, Shapiro J, et al. Nomogram for predicting pathologically complete response after neoadjuvant chemoradiotherapy for oesophageal cancer. *Radiother Oncol* 2015;115:392-8
31. Vandecaveye V, Dirix P, De Keyser F, et al. Diffusion-weighted magnetic resonance imaging early after chemoradiotherapy to monitor treatment response in head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2012;82:1098-1107
32. Mardor Y, Pfeffer R, Spiegelmann R, et al. Early detection of response to radiation therapy in patients with brain malignancies using conventional and high b-value diffusion-weighted magnetic resonance imaging. *J Clin Oncol* 2003;21:1094-1100

33. Decker G, Murtz P, Gieseke J, et al. Intensity-modulated radiotherapy of the prostate: Dynamic ADC monitoring by DWI at 3.0 T. *Radiother Oncol* 2014;113:115-20
34. Cho N, Im SA, Park IA, et al. Breast cancer: Early prediction of response to neo-adjuvant chemotherapy using parametric response maps for MR imaging. *Radiology* 2014;272:385-96
35. Chawla S, Kim S, Dougherty L, et al. Pre-treatment diffusion-weighted and dynamic contrast-enhanced MRI for prediction of local treatment response in squamous cell carcinomas of the head and neck. *Am J Roentgenol* 2013;200:35-43
36. Intven M, Monninkhof EM, Reerink O, et al. Combined T2w volumetry, DW-MRI and DCE-MRI for response assessment after neo-adjuvant chemoradiation in locally advanced rectal cancer. *Acta Oncol* 2015;54:1729-36
37. Lerut T, Coosemans W, Decker G, et al. Anastomotic complications after esophagectomy. *Dig Surg* 2002;19:92-8
38. Kassis ES, Kosinski AS, Ross P, et al. Predictors of anastomotic leak after esophagectomy: An analysis of the society of thoracic surgeons general thoracic database. *Ann Thorac Surg* 2013;96:1919-26
39. Avendano CE, Flume PA, Silvestri GA, et al. Pulmonary complications after esophagectomy. *Ann Thorac Surg* 2002;73:922-6
40. Urschel JD. Esophagogastrostomy anastomotic leaks complicating esophagectomy: A review. *Am J Surg* 1995;169:634-40
41. Ndoye JM, Dia A, Ndiaye A, et al. Arteriography of three models of gastric oesophagoplasty: The whole stomach, a wide gastric tube and a narrow gastric tube. *Surg Radiol Anat* 2006;28:429-37



PART I

IMAGING OF ESOPHAGEAL CANCER





Chapter 2

Imaging strategies
in the management
of esophageal cancer:
what's the role of MRI?

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ABSTRACT

OBJECTIVES

To outline the current role and future potential of magnetic resonance imaging (MRI) in the management of esophageal cancer regarding T-staging, N-staging, tumor delineation for radiotherapy (RT) and treatment response assessment.

METHODS

PubMed, Embase and the Cochrane library were searched identifying all articles related to the use of MRI in esophageal cancer. Data regarding the value of MRI in the areas of interest were extracted in order to calculate sensitivity, specificity, predictive values, and accuracy for group-related outcome measures.

RESULTS

Although historically poor, recent improvements in MRI protocols and techniques have resulted in better imaging quality and the valuable addition of functional information. In recent studies, similar or even better results have been reached using optimized MRI compared with other imaging strategies for T- and N-staging. No studies clearly report on the role of MRI in esophageal tumor delineation and real-time guidance for RT so far. Recent pilot studies showed that functional MRI might be capable of predicting pathologic response to treatment and patient prognosis.

CONCLUSIONS

In the near future MRI has the potential to bring improvement in staging, tumor delineation and real-time guidance for RT and assessment of treatment response, thereby complementing the limitations of currently used imaging strategies.

INTRODUCTION

Esophageal cancer is the eighth most common malignancy in the world and the incidence is rapidly increasing^{1,2}. It is associated with an overall 5-year survival rate of 5–20%^{3,4}. Due to the late onset of symptoms most patients with esophageal cancer present in an advanced stage with a poor prognosis⁵. Surgical resection remains the only curative treatment with a 5-year survival rate of 34–36% for resectable esophageal cancer treated with surgery alone⁶. Preoperative chemoradiotherapy (CRT) has recently become the standard of care improving the median overall survival among all patients with potentially curable esophageal cancer (49.4 versus 24.0 months)². This implemented standard is further supported by earlier meta-analyses showing a 7–13% survival benefit for preoperative CRT^{7,8}.

Current diagnostic work-up in the Netherlands consists of endoscopic biopsy with histopathologic evaluation to diagnose esophageal cancer, combined with endoscopic ultrasound (EUS)^{9–12}. Computed tomography (CT) plays a role in defining tumor and lymph node status¹³. Endobronchial ultrasound (EBUS) may be of additional value when tracheobronchial invasion is suspected¹⁴. CT and ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET), or even combined ¹⁸F-FDG PET/CT, play an important role in detecting distant metastases^{15–19}.

These imaging techniques all have their limitations in three important areas. Firstly, suboptimal imaging quality often leads to incorrect assessment of local tumor extent (T-stage) and regional lymph node involvement (N-stage). A second challenge in esophageal cancer imaging is to precisely define tumor margins for radiotherapy (RT). Thirdly, accurate methods of assessing the evaluation of response to neo-adjuvant therapy or definitive CRT are lacking. The mentioned shortcomings can lead to inappropriate treatment in the individual patient and improvement of imaging of esophageal cancer should therefore be a comprehensive aim for research.

Magnetic resonance imaging (MRI) is a minimally invasive imaging technique that provides excellent soft-tissue contrast (**Figure 1**). Thus far, the role of MRI in esophageal cancer staging has been limited as there are several technical challenges²⁰. Initial results were disappointing and inferior accuracies were found using MRI compared with CT in determining tumor stage and resectability^{21,22}. Along with technical improvements of conventional MRI, new functional MRI features have been discovered and fundamental research in esophageal cancer initiated^{23–28}. The usefulness of MRI in esophageal cancer may expand, as these improvements allow for new interesting opportunities in tumor delineation for RT and treatment response assessment.

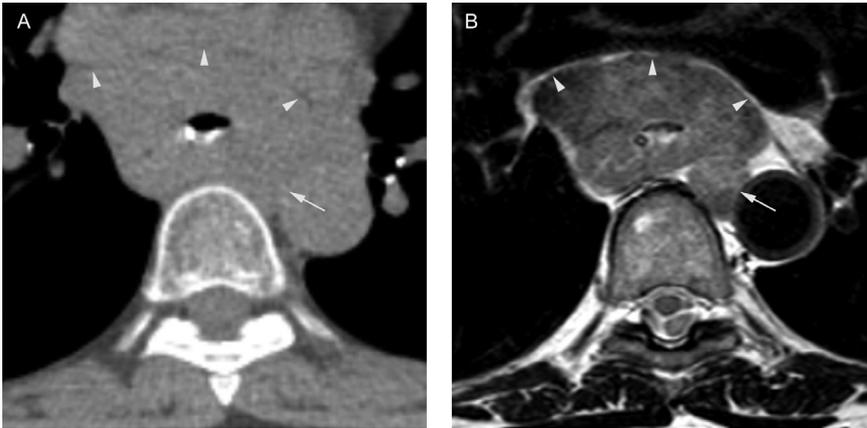


Figure 1 **A)** Standard axial non-contrast-enhanced CT image for radiotherapy purposes in a patient with a cT3N3M1 esophageal squamous cell carcinoma. Direct tumor contact with the aorta (*arrow*) and/or pericardium (*arrowheads*) may be suspected based on this image. **B)** An axial T2W 1.5-T MR image clearly reveals an enlarged peritumoral lymph node with suspected metastasis (*arrow*) adjacent to the aorta, rather than the primary tumor itself. Also, the delineation of the tumor at the pericardial site seems more clearly depicted (*arrowheads*).

In this review, we aim to outline the value of different imaging techniques in esophageal cancer for TN-staging, tumor delineation for RT, and treatment response assessment, with an emphasis on the current role and future potential of MRI.

MATERIALS AND METHODS

A PubMed, Embase and Cochrane literature search was performed identifying all articles related to the use of MRI in patients with esophageal cancer. Search terms that were used to identify such articles were combinations of ‘esophagus’, ‘cancer’, ‘magnetic resonance imaging’ and synonyms. Abstracts obtained from these searches were evaluated. All articles containing information on the results of MRI in esophageal cancer in the English, German or Dutch literature before January 2012, regardless of study design, intervention, reference standard, follow-up or outcome measure, were included and reviewed. The references of articles and reviews found in the literature search were also examined to find additional articles. Eligible articles were then clustered into four groups concerning T-staging, N-staging, tumor delineation for RT, or treatment response assessment. The authors noted that there were few articles in the ‘tumor delineation for RT’ and ‘treatment response assessment’ groups (0 and 4, respectively) and therefore recorded the key findings of all the eligible studies to process in this review textually.

Only the 'T-staging' and 'N-staging' groups of articles were suitable for direct comparison. From these studies the necessary data were retrieved in order to reconstruct diagnostic 2-by-2 contingency tables, and sensitivity, specificity, predictive values and accuracy were calculated along with 95% confidence intervals. Other extracted characteristics were publication year, sample size, age of patients, proportion of men, tumor histology, and both the MRI technique used and the reference standard.

RESULTS

T-STAGING

Importance

Accurate tumor staging is of great importance for determining prognosis and therapy in the individual patient and is aimed at determining resectability based on precise assessment of tumor infiltration depth and invasion into surrounding structures²². The TNM staging system for esophageal cancer provided by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is generally used (Table 1)^{29,30}. Besides its role in prognostication³¹, TNM staging is also important for treatment decision-making. Accurate differentiation between early stages (T1a/T1b/T2) is particularly important for determining the possibility of endomucosal resection (EMR) as curative treatment for T1a tumors. Also, the differentiation between T1 and T2 status is important in deciding whether to treat a patient neo-adjuvantly before surgery in T2 or higher tumors³². The T4a or T4b tumors show invasion into resectable or unresectable adjacent structures respectively, implying that differentiation between these stages is particularly crucial for the decision whether to perform surgery or not.

Table 1 TNM staging for esophageal cancer

| Type | Description |
|------|---|
| Tis | High-grade dysplasia |
| T1a | Tumor invades lamina propria or muscularis mucosae |
| T1b | Tumor invades submucosa |
| T2 | Tumor invades muscularis propria |
| T3 | Tumor invades adventitia |
| T4a | Resectable tumor invading pleura, pericardium, diaphragm or adjacent peritoneum |
| T4b | Unresectable tumor invading other adjacent structures, such as aorta, trachea, vertebral body |
| N0 | No regional lymph node metastases |
| N1 | 1–2 regional lymph node metastases |
| N2 | 3–6 regional lymph node metastases |
| N3 | ≥7 regional lymph node metastases |
| M0 | No distant metastases |
| M1 | Distant metastases |

Current imaging

Endoscopic ultrasound (EUS) is the current technique of choice for primary tumor staging³³. A recent meta-analysis including 49 studies on the diagnostic performance of EUS for T-staging of esophageal cancer found pooled sensitivities for diagnosing distinct T-stages of 82–92%, with EUS performing better with advanced (T4) than with early (T1) disease³⁴. Another study reported a median accuracy for T-staging of 83% in 43 studies, with results ranging from 53% to 94%³⁵. EUS is an invasive technique and there is a known failure rate of 14–25% because of stenotic tumors that prevent the passage of the endoscope^{36,37}. Also, the diagnostic performance of EUS is highly dependent on the experience of the endoscopist³⁸.

Endoscopic ultrasound is superior to CT in the evaluation of T-stage^{37,39}. Unlike EUS, CT is incapable of distinguishing the layers of the esophageal wall in order to determine the tumor infiltration depth (e.g. T1a vs. T1b disease)³³. However, CT is fairly reliable in determining resectability by excluding T4b tumors, which is suggested by the preservation of fat planes between the esophagus and surrounding structures^{33,40,41}. Interestingly, in a recent study no difference was found in preoperative sensitivity for predicting surgical resectability of CT, compared with CT *plus* EUS (88% versus 87%), suggesting EUS to be of limited added value for excluding T4b disease⁴². However, suspected aortic invasion is difficult to prove with reported sensitivity, specificity and accuracy figures for CT of 6%, 85%, and 58%, respectively⁴³. Therefore, this determination is often made intraoperatively.

Tumor spread into the central airways is suggested by flattening or indentation of the wall of the trachea or left main stem bronchus by an adjacent esophageal mass. The overall reported sensitivity of CT for tracheobronchial invasion ranges from 31% to 100%, specificity from 68% to 98%, and accuracy from 74% to 97%^{22,33}. One study found accuracy rates for tracheobronchial invasion of 85% with EUS, 91% with EBUS, and 78% with conventional bronchoscopy¹⁴. With the invasiveness of EBUS and the relatively high burden for the patient taken into account, EBUS might be useful after EUS and CT in selected patients with suspected airway invasion^{44–46}. After EUS, conventional bronchoscopy was shown to have no additional value for this purpose⁴⁷. In most cases ¹⁸F-FDG PET plays no role in assessing local tumor status owing to limited spatial resolution compared with EUS, CT and MRI.

MRI

In the available literature there are only a few studies describing the diagnostic performance of conventional MRI in determining tumor stage (**Table 2**)^{5,21,22,43,48}.

Tumor detection rates using T1-weighted (T1W) sagittal images of a 1.5-T MRI system were disappointing for earlier tumor stages (T1-2)⁴⁹. However, along with technical improvements, a more recent study performing 1.5-T MRI examinations with faster sequences and cardiac/respiratory gating using both T2W and diffusion-weighted images reported that T1 tumors were detected in 33% of cases, T2 in 58%, T3 in 96% and T4 in 100%²⁵.

The reported accuracy for correctly assessing T-stage with conventional T1W plus T2W 1.5-T MRI was found to be 60%⁵. Poor results were obtained in this study with MRI differentiating between $<T3$ and $\geq T3$ tumors, with a sensitivity and specificity of 40% and 63%, respectively⁵. Similar to CT, 1.5-T MRI with cardiac triggering is more capable of differentiating between $\leq T4a$ and $T4b$ tumors, with a sensitivity, specificity and accuracy of 86–100%, 67–84% and 75–87%, respectively^{22,48}. Tracheobronchial or aortic invasion was correctly diagnosed with conventional MRI in 67–100% of patients^{21,22,43,48}. Contrary to these earlier studies a more recent study using high-resolution T2W 1.5-T MRI with cardiac triggering achieved superior results regarding T-staging⁵⁰. This study group was able to correctly assess T-stage in 28/37 patients (81%), using histopathology as reference standard, with understaging in 6/37 (16%) and overstaging in 1/37 (3%). Overall, the diagnostic value of MRI for T-staging in patients with esophageal cancer seems to have improved over the years, although the number of available studies was insufficient to draw any firm conclusions.

N-STAGING

Importance

Histopathologic evidence of lymph node metastases is the single most important prognostic factor in resectable esophageal cancer⁵¹. Accurate preoperative assessment of the extent of lymph node metastases is crucial for both surgical and radiotherapeutic treatment planning and prediction of prognosis. A node-negative status is assigned to patients without nodal involvement, with an associated overall 5-year survival rate after surgical resection of 70–92%, compared with 18–47% for patients with lymph node metastasis (N1–3)^{51–53}.

Current imaging

Regional lymph node involvement is currently evaluated using EUS, CT and/or ¹⁸F-FDG PET¹¹. An advantage of EUS is that in the same session material for cytologic differentiation can be obtained via fine needle aspiration (FNA). Several studies showed better results of EUS-FNA compared with EUS alone for

Table 2 Overview of clinical studies on the diagnostic performance of MRI for T-staging in patients with

| Ref. | Author | Year | n | Age (y), mean [range] | Male, n (%) | SCC, n (%) | MRI technique used | Reference standard |
|----------------------------------|-----------|------|----|-----------------------------|----------------|---------------|--------------------------------|-----------------------|
| Differentiating T-stages | | | | | | | | |
| [21] | Quint | 1985 | 13 | NA | NA | 4 (31) | Conventional (0.35 T) | Histology |
| [5] | Wu | 2003 | 86 | 62 [39-73] | 56 (65) | 8 (94) | Conventional (1.5 T) | Histology |
| [50] | Riddell | 2007 | 37 | 62 [45-78] | 29 (88) | 0 (0) | High-resolution T2W (1.5 T) | Histology |
| Determining resectability | | | | | | | | |
| [48] | Petrillo | 1990 | 32 | 61 [42-74] | 29 (91) | 32 (100) | Conventional (0.5/1.5 T) | Histology |
| [22] | Takashima | 1991 | 33 | 64 [43-77] | NA | 30 (91) | Conventional (1.5 T) | Histology |
| Tracheobronchial invasion | | | | | | | | |
| [21] | Quint | 1985 | 13 | NA | NA | 4 (31) | Conventional (0.35 T) | Histology |
| [43] | Lehr | 1988 | 60 | NA | NA | 30 (50) | Conventional (0.5 T) | Surgery |
| [48] | Petrillo | 1990 | 32 | 61 [42-74] | 29 (91) | 32 (100) | Conventional (0.5/1.5 T) | Surgery |
| [22] | Takashima | 1991 | 33 | 64 [43-77] | NA | 30 (91) | Conventional (1.5 T) | Surgery |
| Aortic invasion | | | | | | | | |
| [21] | Quint | 1985 | 13 | NA | NA | 4 (31) | Conventional (0.35 T) | Histology |
| [43] | Lehr | 1988 | 60 | NA | NA | 30 (50) | Conventional (0.5 T) | Surgery |
| [48] | Petrillo | 1990 | 32 | 61 [42-74] | 29 (91) | 32 (100) | Conventional (0.5/1.5 T) | Surgery |
| [22] | Takashima | 1991 | 33 | 64 [43-77] | NA | 30 (91) | Conventional (1.5 T) | Surgery |

^a: sensitivity defined as the ability to correctly stage T1/T2 and not overstage tumors as T3/T4, and conversely definition indicated. [‡]: triangular fat space between esophagus–aorta–spine. NA: not applicable. NPV: negative

esophageal cancer

| Definition of endpoint | Over-staging, % | Under-staging, % | Accuracy, % (95% CI) | PPV, % (95% CI) | NPV, % (95% CI) | Sensitivity, % (95% CI) | Specificity, % (95% CI) |
|--|-----------------|------------------|----------------------|------------------------|-------------------------|-------------------------|-------------------------|
| Correct prediction of T-stage | 13 | 63 | 25 (NA) | NA | NA | NA | NA |
| Correct prediction of T-stage | 13 | 27 | 60 (NA) | 12 (2-24) ^a | 89 (84-97) ^a | 40 (7-82) ^a | 63 (58-68) ^a |
| Correct prediction of T-stage | 3 | 16 | 81 (NA) | NA | NA | NA | NA |
| T≤3N0 versus T≥4 or N>0 | 19 | 6 | 75 (55-85) | 67 (49-76) | 86 (63-97) | 86 (63-97) | 67 (49-76) |
| T≤3 versus T≥4 | 13 | 0 | 87 (70-87) | 60 (34-60) | 100 (88-100) | 100 (57-100) | 84 (74-84) |
| Extension into airway lumen | 0 | 0 | 100 (NA) | NA | 100 (NA) | NA | 100 (NA) |
| Opinion radiologist ^b | 11 | 17 | 71 (62-83) | 46 (20-72) | 79 (72-86) | 36 (15-57) | 85 (77-92) |
| Absence of fat plane + compression trachea | 13 | 0 | 87 (71-87) | 64 (39-64) | 100 (87-100) | 100 (62-100) | 84 (73-84) |
| Extension into airway lumen | 0 | 0 | 100 (88-100) | 100 (37-100) | 100 (93-100) | 100 (37-100) | 100 (93-100) |
| Contact >90 ⁰ of aortic circumference | 25 | 0 | 75 (NA) | 0 (NA) | 100 (NA) | NA | 75 (NA) |
| Opinion radiologist ^b | 29 | 4 | 67 (58-73) | 20 (8-28) | 94 (87-99) | 67 (25-94) | 67 (62-71) |
| Contact >90 ⁰ of aortic circumference | 3 | 6 | 91 (81-97) | 67 (13-98) | 93 (88-96) | 50 (10-74) | 97 (91-100) |
| Obliteration triangular fat space ^c | 14 | 0 | 87 (74-87) | 43 (14-43) | 100 (92-100) | 100 (33-100) | 86 (79-86) |

specificity defined as the ability to correctly stage T3/T4 and not understage tumors as T1/T2⁵. ^b: no further predictive value. PPV: positive predictive value. SCC: squamous cell carcinoma. T: Tesla. T2W: T2-weighted.

determining N-stage^{54,55}. The most common sites of nodal involvement within the mediastinum and around the coeliac axis are often easily reached by EUS(-FNA). As for T-staging however, the value of EUS for N-staging is limited when tumors are non-traversable by the scope.

A pooled sensitivity of 80% and specificity of 70% for N-staging were reported in a recent meta-analysis including both EUS and EUS-FNA studies⁵⁶. Both understaging (3%) and overstaging (25%) of lymph node involvement was reported⁵⁷. A study that compared EUS (without FNA) with ¹⁸F-FDG PET and CT, found that the accuracy of EUS was not significantly higher than ¹⁸F-FDG PET or CT (75% vs. 66% and 63%, respectively, $P>0.05$)¹⁵. Similar results were found in a third study where the accuracy of EUS in diagnosing lymph node metastases was 65% and only 44% for small-sized lymph node metastases (<1 cm)⁵⁸.

Likewise, the limited value of CT in determining lymph node status is indicated by a meta-analysis reporting a sensitivity of 50% (95% CI: 41–60%) and specificity of 83% (95% CI: 77–89%)⁵⁶. Regarding ¹⁸F-FDG PET in the assessment of regional lymph node metastases, a meta-analysis revealed a poor pooled sensitivity of 51% (95% CI: 34–69%) and specificity of 84% (95% CI: 76–91%)⁵⁹.

MRI

So far, research into the diagnostic value of MRI focuses more on lymph node staging than on tumor staging, in part because of the current inadequacy regarding N-staging performance of the established techniques. An overview of the current literature with the MRI techniques used and reported or calculated predictive values, sensitivity, specificity and accuracy with 95% confidence intervals is presented in **Table 3**^{5,21,22,25,48,50,60-62}.

Early studies, using conventional MRI of 0.35–1.5 T without fast sequences, report on sensitivities, specificities and accuracies of 25–58%, 67–88% and 56–72%, respectively^{21,22,48}. More recent studies support these findings using similar conventional MRI techniques, by revealing comparable sensitivities, specificities and accuracies of 38–62%, 68–85% and 64–77%, respectively^{5,61}. The latter study also reports superior results using superparamagnetic iron-oxide-enhanced (SPIO) 1.5-T MRI, with a sensitivity, specificity and accuracy of 100%, 95% and 96%, respectively⁶¹. However, it must be noted that these values were based on differentiating positive from negative lymph-node groups instead of differentiating node-positive (N1) from node-negative (N0) patients.

Compared with earlier reports, one study reached higher sensitivity, specificity and accuracy of 70%, 93% and 89%, respectively, by expanding the traditional definition of positive lymph nodes on MRI, from nodes with a short-axis diameter of '>10 mm', to '>5 mm' instead⁶⁰. A recent study showed that diffusion-weighted whole-body imaging with background body signal suppression (DWIBS) combined with fast short tau inversion recovery (STIR) fat suppression did not result in major diagnostic improvements for N-staging (sensitivity, specificity and accuracy of 75, 62 and 68%, respectively)²⁵. The most recent study that was found to be eligible after inclusion used ECG-triggered 1.5-T MRI with turbo spin-echo (TSE) and STIR fat suppression, and reached a sensitivity, specificity and accuracy of 81%, 98% and 95%, respectively⁶². In general, the diagnostic values of MRI for N-staging in patients with esophageal cancer showed an improvement over the years. Unfortunately, owing to the heterogeneity of the MRI techniques used in the different studies, proper pooling of results or performing a statistical meta-analysis was impossible.

TUMOR DELINEATION IN RADIOTHERAPY PLANNING

Importance

RT is an important component in the multimodality treatment for esophageal cancer⁶³. For radiation oncology purposes, accurate tumor delineation is crucial to ensure adequate target coverage and simultaneously limit the dose to surrounding critical organs including lungs and heart⁶⁴.

Current imaging

In RT practice, tumor delineation is based on available CT images and clinical information obtained by endoscopy. In a recent study, assessment of esophageal tumor length using CT was found not to reflect histopathologic tumor extent⁶⁵. Once the tumor was delineated, a longitudinal margin of 30 mm was applied proximally and distally to the gross tumor volume to include possible microscopic disease in the radiation field⁶⁶. The requisite margin of 30 mm combined with inaccurate tumor delineation by CT owing to inferior soft-tissue contrast and tumor motion ultimately limits the possible amount of RT dose and thereby leads to suboptimal cure rates⁶⁷. EUS has been suggested to accurately assess the longitudinal extent of an esophageal tumor, and may be useful for selection of nodal regions to include in the radiation field⁶⁷. However, EUS results are difficult to translate into the RT planning process⁶⁸. A few studies report on methods of incorporating EUS information into the CT planning process by using anatomical landmarks such as the tracheal bifurcation or aortic arch⁶⁸⁻⁷⁰.

Table 3 Overview of clinical studies on the diagnostic performance of MRI for N-staging in patients with esophageal cancer

| Ref. | Author | Year | n | Age (y), mean [range] | Male, n (%) | SCC, n (%) | MRI technique used | Reference standard |
|------|-----------|------|----|--------------------------|----------------|---------------|---|------------------------|
| [21] | Quint | 1985 | 13 | NA | NA | 4 (31) | Conventional (0.35 T) | Histology |
| [48] | Petrillo | 1990 | 32 | 61 [42-74] | 29 (91) | 32 (100) | Conventional (0.5/1.5 T) | Histology |
| [22] | Takashima | 1991 | 33 | 64 [43-77] | NA | 30 (91) | Conventional (1.5 T) | Histology |
| [60] | Mizowaki | 1996 | 58 | 64 [43-84] | 48 (83) | 56 (97) | Conventional (1.5 T) | Histology |
| [5] | Wu | 2003 | 86 | 62 [39-73] | 56 (65) | 81 (94) | Conventional (1.5 T) | Histology |
| [61] | Nishimura | 2006 | 16 | 66 [37-76] | 13 (81) | 16 (100) | Conventional (1.5 T) 1.5 T SPIO-enhanced | Histology Histology |
| [50] | Riddell | 2007 | 37 | 62 [45-78] | 29 (88) | 0 (0) | High-resolution T2W (1.5 T) | Histology |
| [25] | Sakurada | 2009 | 24 | 65 [41-82] | 20 (83) | 23 (96) | 1.5 T DWIBS +STIR | Histology |
| [62] | Alper | 2011 | 35 | 57 [16-80] | 19 (54) | 29 (83) | 1.5 T +STIR TSE | Histology |

^a: definition of lymph node considered metastatic. ^b: lymph-node-group based instead of patient-group based considered metastatic. Ø: diameter of lymph node considered metastatic. DWIBS: diffusion-weighted imaging PPV: positive predictive value. SI: signal intensity. SPIO: superparamagnetic iron-oxide. STIR: short tau inversion

| Definition LNN+ | Accuracy, % (95% CI) | PPV, % (95% CI) | NPV, % (95% CI) | Sensitivity, % (95% CI) | Specificity, % (95% CI) |
|------------------------|-------------------------|--------------------|--------------------|----------------------------|----------------------------|
| Ø>10mm | 56 (21-77) | 75 (36-99) | 40 (9-59) | 50 (24-66) | 67 (15-98) |
| Ø>10mm | 72 (62-85) | 40 (8-81) | 78 (72-85) | 25 (5-51) | 88 (81-96) |
| Ø>10mm | 68 (48-78) | 85 (61-97) | 56 (38-65) | 58 (41-75) | 83 (57-97) |
| Ø> 5mm | 89 (79-96) | 69 (40-89) | 94 (88-98) | 70 (40-89) | 93 (88-98) |
| Ø>10mm | 89 (80-93) | 82 (40-99) | 90 (85-92) | 52 (24-60) | 98 (92-100) |
| Ø>10mm | 64 (48-78) | 73 (56-87) | 57 (40-70) | 62 (47-73) | 68 (49-84) |
| Ø>10mm ^b | 77 (71-83) | 36 (20-53) | 86 (82-90) | 38 (21-56) | 85 (82-89) |
| SPIO ^b | 96 (91-96) | 83 (71-83) | 100 (97-100) | 100 (86-100) | 95 (92-96) |
| Ø> 2mm ^c | 73 (53-87) | 75 (59-87) | 69 (44-87) | 79 (62-91) | 64 (41-81) |
| Ø> 5mm | 68 (45-84) | 64 (43-79) | 73 (46-91) | 75 (51-92) | 62 (39-77) |
| Ø> 5mm ^b | 86 (83-90) | 42 (27-58) | 92 (90-94) | 39 (25-54) | 93 (91-95) |
| High SI ^{b,d} | 95 (90-97) | 93 (79-99) | 95 (92-97) | 81 (69-86) | 98 (95-100) |

values. ^c: studied lymph nodes in peri-esophageal tissues only. ^d: focal or overall high signal intensity was with body signal suppression. SCC: squamous cell carcinoma. NA: not applicable. NPV: negative predictive value. recovery. T: Tesla. TSE: turbo spin echo.

Reviews on the additional value of ^{18}F -FDG PET for tumor delineation and radiotherapy planning in esophageal cancer patients do not support implementing ^{18}F -FDG PET in clinical practice for this purpose, as the literature is very limited and no studies demonstrate the use of ^{18}F -FDG PET in terms of improved locoregional control or survival^{71,72}. Ideally, a more precise definition of target volumes with optimised imaging techniques might enable tailored dose escalation, thereby reducing toxicity and improving local control and patient prognosis.

MRI

For accurate tumor delineation and radiotherapy planning, MRI has already been shown to be useful in malignancies of the head and neck, prostate and cervix⁷³⁻⁷⁶. MRI may also be useful for esophageal tumor delineation and radiation treatment planning (**Figure 2**). However, so far no studies have been published reporting the value of MRI for this purpose. First, future studies should investigate possible target definition improvement by MRI for esophageal cancer. Thereafter, clinical tailored dose escalation studies should point out its value for improving local control and patient outcome in both neo-adjuvant and definitive treatment settings.

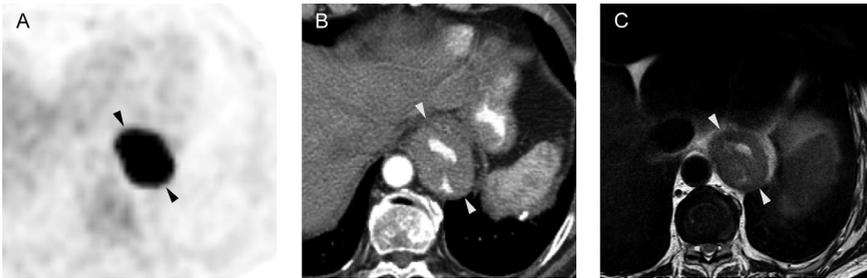


Figure 2 A direct comparison of (A) ^{18}F -FDG PET, (B) CT and (C) MR images in one patient with a cT3N1M0 distal esophageal tumor (*arrowheads*). By providing excellent soft-tissue contrast MRI potentially allows for more precise tumor delineation and radiotherapy planning.

MRI-GUIDED RADIOTHERAPY

In conformal RT techniques, such as three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT), the radiation dose is distributed highly conformal to the delineated target volume to obtain adequate coverage of the target and to avoid surrounding healthy tissues⁷⁷. Therefore, accurate target delineation and patient positioning are crucial. Currently, daily

image-guided setup techniques, such as those using three-dimensional mega- or kilo-voltage imaging, portal imaging, and ultrasound imaging are recommended to reduce patient setup errors⁷⁸. However, geometric misses occur during IMRT treatment because of tight margins, inaccurate patient positioning and target motion⁷⁹. Such dose deviations could compromise clinical outcomes in terms of decreased tumor control and increased normal organ toxicity⁷⁸.

Recently, investigators succeeded in integrating an MRI system with a radiotherapy accelerator, allowing for simultaneous irradiation and MR imaging^{80,81}. Real-time MRI guidance could provide superior position verification and irradiation of prompt precision⁷⁹. The proof of this concept for esophageal cancer enables clinical studies in patients and may imply significant changes in patient management and prognosis.

TREATMENT RESPONSE ASSESSMENT AND RESTAGING

Importance

The purpose of preoperative CRT is to improve local control and ultimately to prolong patient survival. Several meta-analyses indicate significantly improved overall survival^{7,8,82,83}, although future high-quality trials are necessary for a better understanding of the role of neo-adjuvant treatment for resectable esophageal cancer⁸⁴. Complete histopathologic response is observed in 28–34% of patients treated with preoperative CRT, with an additional group of 30% showing partial histopathologic response^{85,86}. Non-responders most probably do not benefit from preoperative CRT but are exposed to its toxicity, with a negative impact on quality of life^{2,87}. Also, continued but ineffective preoperative CRT will inevitably delay surgical therapy and therefore may affect long-term outcome negatively. Accurate identification of non-responders early *during* CRT would allow individualised decision making in the continuation or discontinuation of CRT. Accurate restaging *after* completion of CRT may prove to be of clinical value for individual prognostication. Moreover, following studies in rectal carcinoma, some experts even speculate that if precise restaging after completion of CRT is possible, surgery may initially be withheld from complete responders in the near future ('wait-and-see' approach)⁸⁸. Furthermore, initially irresectable tumors may prove to be downstaged to resectable tumors.

Current imaging

Currently, both EUS and ¹⁸F-FDG PET are used for assessment of response to neo-adjuvant therapy in esophageal cancer patients, showing similar moderately poor overall accuracies in systematic reviews^{89,90}. EUS appears to be of limited value

owing to the difficulty in differentiating residual carcinoma from inflammation and fibrosis⁹¹. This limitation is supported by the finding in a systematic review that EUS after CRT had poor accuracy for restaging, ranging from 27 to 82%⁸⁹. A large recent study evaluating serial ¹⁸F-FDG PET imaging before and 2 weeks after the start of neo-adjuvant CRT reported that 25% of patients identified by ¹⁸F-FDG PET as non-responders were actually histopathologic responders and 50% of histopathologic non-responders were erroneously identified as responders by ¹⁸F-FDG PET⁸⁵. Non-specific glucose uptake by inflamed tissue caused by CRT, together with low or no FDG uptake in a subgroup of tumors, limits the value of ¹⁸F-FDG PET in treatment response monitoring⁹². CT is also found to be of limited value for the determination of treatment response after CRT^{89,93}.

MRI

After a thorough literature search we conclude that so far no studies have reported on the value of anatomical MRI in the assessment of CRT response in esophageal cancer. In view of the aforementioned improvements in the imaging quality of MRI however, in future studies MRI may prove to become beneficial for early neo-adjuvant CRT response assessment or restaging after completion of CRT. In particular, functional MRI techniques, such as diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE-)MRI may provide interesting information regarding tumor regression in response to CRT in esophageal cancer, as described in a few pilot studies^{23,24,26,27}.

A recent study found that apparent diffusion coefficient (ADC) values, as determined with DWI, corresponded to clinical findings such as tumor diameter, serum tumor marker levels and clinical T- and N-stages²⁶. In another study, the same authors reported that high ADC values were associated with better response to CRT and higher survival rates, which could imply a future role for functional MRI in the prediction of CRT response and patient selection²⁷. Promisingly, pilot studies using DWI in rectal cancer have reached sensitivities and specificities of up to 100% for the prediction of pathologic complete response early during neo-adjuvant CRT⁹⁴. In DCE-MRI, altered vascularity and/or vascular permeability of malignancies are detected by measurement of subsequent changes in signal intensity during contrast agent passage⁹⁵. Preliminary experience with DCE-MRI in esophageal cancer showed that this technique could indicate differences in microcirculation between esophageal squamous cell carcinoma and esophageal adenocarcinoma²⁴. Furthermore, small studies in both histopathologic types found a decrease in contrast agent exchange across the vascular wall after chemoradiotherapy^{23,24}. Future studies on the role of both DWI and DCE-MRI should clarify the potential clinical implications of these findings.

DISCUSSION

The imaging strategies currently used in the management of esophageal cancer all have their specific limitations concerning the important areas of TN staging, tumor delineation for RT and treatment response assessment. MRI is a minimally invasive imaging technique that provides excellent soft-tissue contrast and therefore has the potential to complement these limitations. However, the role of MRI in esophageal cancer has been limited as there are several technical challenges²⁰.

Rather poor results in early studies on MR imaging of esophageal cancer were due to long imaging times causing a severe reduction in imaging quality because of motion artefacts³. The increasing field strength (from a previous standard of 0.5 T to the present standards of 1.5 and 3 T, with experimental systems of 7 T) and the development of faster sequences and cardiac and respiratory gating yielded better imaging quality over time (**Figure 3**)⁹⁶. Furthermore, contrast between tissues was improved by the introduction of fat signal suppression and contrast enhancement of the lumen with gadolinium-based agents⁹⁷. Along with technical improvements of conventional MRI, new functional MRI features, e.g. diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE-)MRI, have been discovered and fundamental research in esophageal cancer is being performed^{23,24,28,98}.

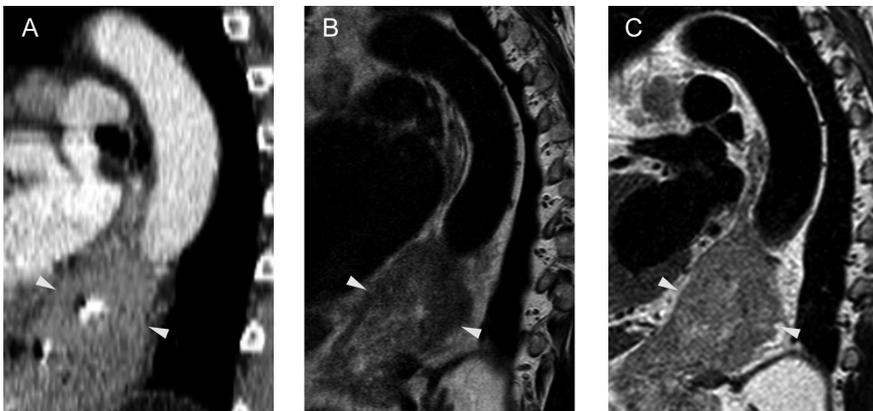


Figure 3 An example of improving MRI for esophageal cancer with cardiac triggering and breathhold in a patient with a cT3N3M1 (hepatogeneously metastasised) distal esophageal squamous cell carcinoma (*arrowheads*). **A**) Standard sagittal planning CT image, acquired for radiotherapy purposes. **B**) Normal sagittal T1W 1.5-T MR image of the chest without motion gating. **C**) Similar sagittal T1W 1.5-T MR image in the same patient after applying cardiac triggering and breathhold.

Recent studies were able to reach high accuracies (81%) with high-resolution MRI for T-staging, drawing near the range of the reported pooled accuracy for standard EUS in a systematic review (81–92%)^{34,50}. Furthermore, MRI has been shown to be of similar value in the assessment of resectability compared with CT^{22,48}. For this cause EUS was shown to be of limited additional value⁴². Future research should carefully determine the additional values of the different imaging techniques.

A systematic literature search revealed sensitivities, specificities and accuracies of conventional MRI for N-staging of 25–62%, 67–88% and 56–77%, respectively^{5,22,33,48,60,61}. Based on these studies, we conclude that MRI in its conventional form is of moderately poor diagnostic value for lymph node staging in patients with esophageal cancer. EUS+FNA was shown to be of superior value in large meta-analyses (pooled sensitivity 80%, specificity 70%)⁵⁶ and should therefore remain the technique of first choice. With newer techniques, higher imaging quality resulted in better diagnostic performance with reported accuracies of up to 95–96% for both fast sequences (STIR-TSE) with SPIO contrast agent^{61,62}. We believe that in the near future optimised MRI could bring additional improvement in determining the lymph node status.

A few potential limitations regarding the T- and N-staging studies must be noted. As neo-adjuvant strategies are known to downstage esophageal tumors in a significant number of patients, the accuracy of pre- and/or post-treatment imaging compared with histopathology should be interpreted with caution. Several studies lack to mention the application of neo-adjuvant treatment and/or the exact timing of the imaging examinations, hereby compromising the possibilities for proper comparison. With the growing importance of neo-adjuvant strategies the aim of reliably improving T- and N-assessment is more and more shifting towards means to assess the treatment response. Another potential limitation of T-staging studies is the impossibility of histopathologic confirmation of T4b disease, biasing towards early disease in the selection of patients. Regarding N-staging, it must be noted that no devoted attempt has been made in the studies to exactly match the nodes identified by imaging and those assessed by histopathology. A suspicious node on imaging may well be negative at histopathology, but as an undetected node at another location might prove positive, the N-stage can be predicted correctly for the wrong reasons. However, the mentioned shortcomings apply equally well to CT-, EUS-, ¹⁸F-FDG PET- and MRI-studies.

There is a growing interest in the areas of optimising tumor delineation for RT to ensure sparing of the organs at risk. In malignancies of the head and neck, prostate and cervix great progress has already been made in improving organ-sparing using MRI⁷³⁻⁷⁶. Improved visualisation of the esophagus using MRI may also become useful for improved tumor delineation and RT planning. Treatment response assessment is another area of growing interest and studies have already been performed to assess the value of MRI for this purpose in breast, rectal and head and neck cancer⁹⁹⁻¹⁰¹. However, so far no studies have been published on the value of MRI for either tumor delineation or treatment response assessment in esophageal cancer.

Although MRI plays a limited role in the current work-up for patients with esophageal cancer, its quality is improving over time. In recent studies, similar or even better results have been reached using optimised MRI compared with EUS and CT for T- and N-staging. The role of MRI in tumor delineation and real-time guidance for radiation therapy and assessment of neo-adjuvant treatment response and restaging remains largely unidentified. We believe that in the near future MRI has the potential to bring improvement in determining local tumor extent and lymph node status, as well as for these other functions. Furthermore, prediction of responders to neo-adjuvant treatment and accurate response evaluation could improve the effect and applicability of current non-surgical therapies. Future studies on the value of MRI in these challenging areas should bring more clarity.

REFERENCES

1. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003;349:2241-52
2. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
3. Kumbasar B. Carcinoma of esophagus: Radiologic diagnosis and staging. *Eur J Radiol* 2002;42:170-80
4. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;62:10-29
5. Wu LF, Wang BZ, Feng JL, et al. Preoperative TN staging of esophageal cancer: Comparison of miniprobe ultrasonography, spiral CT and MRI. *World J Gastroenterol* 2003;9:219-24
6. Omloo JM, Lagarde SM, Hulscher JB, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: Five-year survival of a randomized clinical trial. *Ann Surg* 2007;246:992-1000; discussion 1000-1
7. Gebski V, Burmeister B, Smithers BM, et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: A meta-analysis. *Lancet Oncol* 2007;8:226-34
8. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: An updated meta-analysis. *Lancet Oncol* 2011;12:681-92
9. Association of Comprehensive Cancer Centers. Oesophageal carcinoma. Comprehensive Cancer Center, The Netherlands, 2010. Available via <http://www.oncoline.nl/oesofaguscarcinoom>; accessed on 26 March 2012
10. Koch J, Halvorsen RA. Staging of esophageal cancer: Computed tomography, magnetic resonance imaging, and endoscopic ultrasound. *Semin Roentgenol* 1994;29:364-72
11. Diederich S. Staging of oesophageal cancer. *Cancer Imaging* 2007;7 Spec No A:S63-6
12. Jamil LH, Gill KR, Wallace MB. Staging and restaging of advanced esophageal cancer. *Curr Opin Gastroenterol* 2008;24:530-34
13. Kim TJ, Kim HY, Lee KW, et al. Multimodality assessment of esophageal cancer: Preoperative staging and monitoring of response to therapy. *Radiographics* 2009;29:403-21
14. Nishimura Y, Osugi H, Inoue K, et al. Bronchoscopic ultrasonography in the diagnosis of tracheobronchial invasion of esophageal cancer. *J Ultrasound Med* 2002;21:49-58
15. Rasanen JV, Sihvo EI, Knuuti MJ, et al. Prospective analysis of accuracy of positron emission tomography, computed tomography, and endoscopic ultrasonography in staging of adenocarcinoma of the esophagus and the esophagogastric junction. *Ann Surg Oncol* 2003;10:954-60
16. Smyth EC, Shah MA. Role of (F) 2-fluoro-2-deoxyglucose positron emission tomography in upper gastrointestinal malignancies. *World J Gastroenterol* 2011;17:5059-74
17. Pfau PR, Perlman SB, Stanko P, et al. The role and clinical value of EUS in a multimodality esophageal carcinoma staging program with CT and positron emission tomography. *Gastrointest Endosc* 2007;65:377-84
18. Munden RF, Macapinlac HA, Erasmus JJ. Esophageal cancer: The role of integrated CT-PET in initial staging and response assessment after preoperative therapy. *J Thorac Imaging* 2006;21:137-45

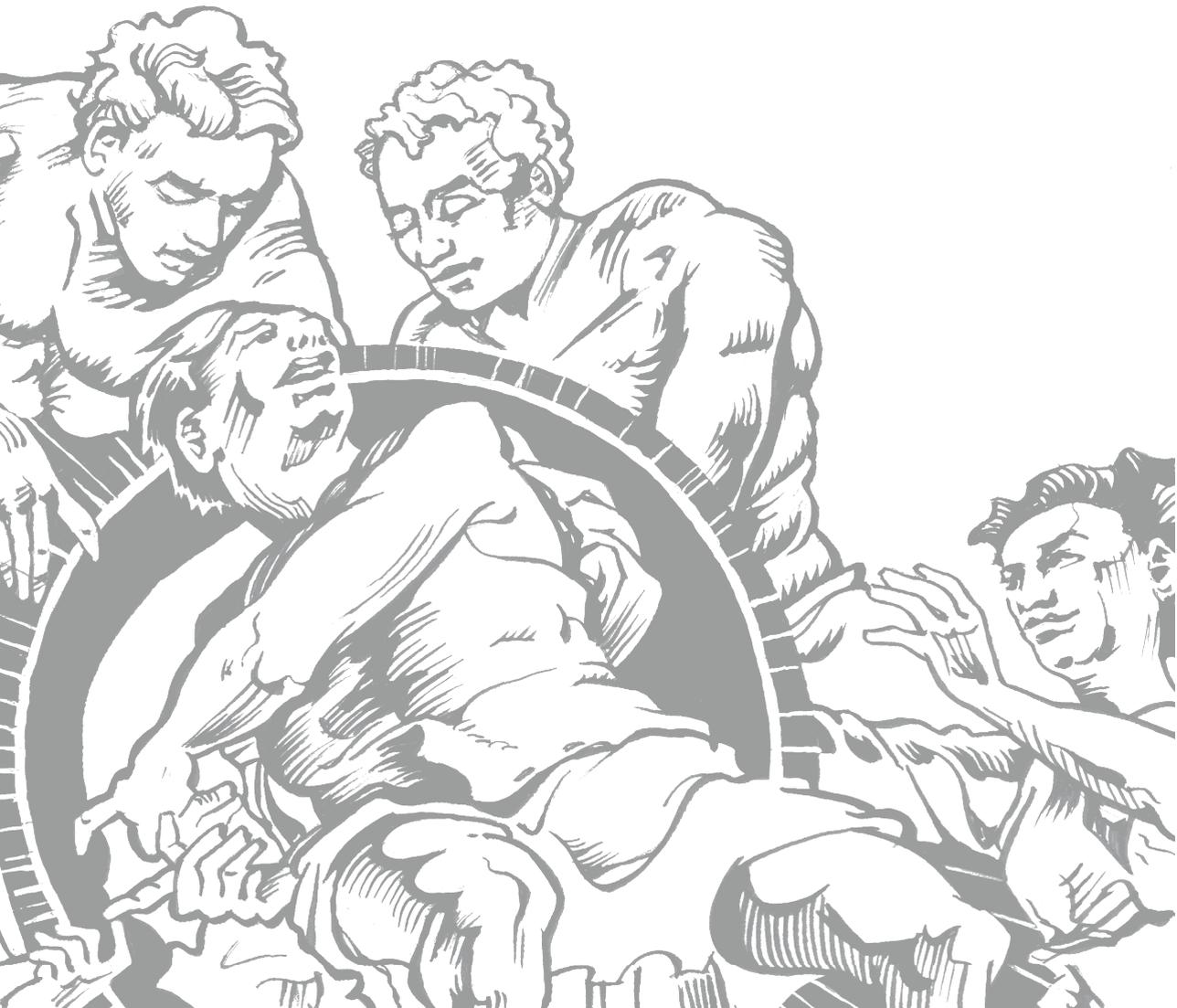
19. Bruzzi JF, Truong MT, Macapinlac H, et al. Integrated CT-PET imaging of esophageal cancer: Unexpected and unusual distribution of distant organ metastases. *Curr Probl Diagn Radiol* 2007;36:21-9
20. Giovagnoni A, Valeri G, Ferrara C. MRI of esophageal cancer. *Abdom Imaging* 2002;27:361-6
21. Quint LE, Glazer GM, Orringer MB. Esophageal imaging by MR and CT: Study of normal anatomy and neoplasms. *Radiology* 1985;156:727-31
22. Takashima S, Takeuchi N, Shiozaki H, et al. Carcinoma of the esophagus: CT vs MR imaging in determining resectability. *Am J Roentgenol* 1991;156:297-302
23. Chang EY, Li X, Jerosch-Herold M, et al. The evaluation of esophageal adenocarcinoma using dynamic contrast-enhanced magnetic resonance imaging. *J Gastrointest Surg* 2008;12:166-75
24. Oberholzer K, Pohlmann A, Schreiber W, et al. Assessment of tumor microcirculation with dynamic contrast-enhanced MRI in patients with esophageal cancer: Initial experience. *J Magn Reson Imaging* 2008;27:1296-1301
25. Sakurada A, Takahara T, Kwee TC, et al. Diagnostic performance of diffusion-weighted magnetic resonance imaging in esophageal cancer. *Eur Radiol* 2009;19:1461-9
26. Aoyagi T, Shuto K, Okazumi S, et al. Evaluation of the clinical staging of esophageal cancer by using diffusion-weighted imaging. *Exp Ther Med* 2010;1:847-51
27. Aoyagi T, Shuto K, Okazumi S, et al. Apparent diffusion coefficient values measured by diffusion-weighted imaging predict chemoradiotherapeutic effect for advanced esophageal cancer. *Dig Surg* 2011;28:252-7
28. Yamada I, Izumi Y, Kawano T, et al. Esophageal carcinoma: Evaluation with high-resolution three-dimensional constructive interference in steady state MR imaging in vitro. *J Magn Reson Imaging* 2006;24:1326-32
29. Rice TW, Rusch VW, Ishwaran H, et al. Cancer of the esophagus and esophagogastric junction: Data-driven staging for the seventh edition of the american joint committee on Cancer/International union against cancer cancer staging manuals. *Cancer* 2010;116:3763-73
30. Edge S, Byrd D, Compton C. AJCC cancer staging manual. 7th edition, 2010. New York, NY: Springer:103-15
31. Talsma K, van Hagen P, Grotenhuis BA, et al. Comparison of the 6th and 7th editions of the UICC-AJCC TNM classification for esophageal cancer. *Ann Surg Oncol* 2012;19:2142-8
32. Ajani JA, Barthel JS, Bentrem DJ, et al. Esophageal and esophagogastric junction cancers. *J Natl Compr Canc Netw* 2011;9:830-87
33. Quint LE, Bogot NR. Staging esophageal cancer. *Cancer Imaging* 2008;8 Spec No A:S33-42
34. Puli SR, Reddy JB, Bechtold ML, et al. Staging accuracy of esophageal cancer by endoscopic ultrasound: A meta-analysis and systematic review. *World J Gastroenterol* 2008;14:1479-90
35. van Vliet EP, Eijkemans MJ, Kuipers EJ, et al. Publication bias does not play a role in the reporting of the results of endoscopic ultrasound staging of upper gastrointestinal cancers. *Endoscopy* 2007;39:325-32

36. Preston SR, Clark GW, Martin IG, et al. Effect of endoscopic ultrasonography on the management of 100 consecutive patients with oesophageal and junctional carcinoma. *Br J Surg* 2003;90:1220-4
37. Wakelin SJ, Deans C, Crofts TJ, et al. A comparison of computerised tomography, laparoscopic ultrasound and endoscopic ultrasound in the preoperative staging of oesophago-gastric carcinoma. *Eur J Radiol* 2002;41:161-7
38. van Vliet EP, Eijkemans MJ, Poley JW, et al. Staging of esophageal carcinoma in a low-volume EUS center compared with reported results from high-volume centers. *Gastrointest Endosc* 2006;63:938-47
39. Kelly S, Harris KM, Berry E, et al. A systematic review of the staging performance of endoscopic ultrasound in gastro-oesophageal carcinoma. *Gut* 2001;49:534-9
40. Rice TW. Clinical staging of esophageal carcinoma. CT, EUS, and PET. *Chest Surg Clin N Am* 2000;10:471-85
41. Wayman J, Chakraverty S, Griffin SM, et al. Evaluation of local invasion by oesophageal carcinoma: a prospective study of prone computed tomography scanning. *Postgrad Med J* 2001;77:181-4
42. van Zoonen M, van Oijen MG, van Leeuwen MS, et al. Low impact of staging EUS for determining surgical resectability in esophageal cancer. *Surg Endosc* 2012;26:2828-34
43. Lehr L, Rupp N, Siewert JR. Assessment of resectability of esophageal cancer by computed tomography and magnetic resonance imaging. *Surgery* 1988;103:344-50
44. Osugi H, Nishimura Y, Takemura M, et al. Bronchoscopic ultrasonography for staging supracarinal esophageal squamous cell carcinoma: Impact on outcome. *World J Surg* 2003;27:590-4
45. Wakamatsu T, Tsushima K, Yasuo M, et al. Usefulness of preoperative endobronchial ultrasound for airway invasion around the trachea: Esophageal cancer and thyroid cancer. *Respiration* 2006;73:651-7
46. Garrido T, Maluf-Filho F, Sallum RA, et al. Endobronchial ultrasound application for diagnosis of tracheobronchial tree invasion by esophageal cancer. *Clinics (Sao Paulo)* 2009;64:499-504
47. Omloo JM, van Heijl M, Bergman JJ, et al. Value of bronchoscopy after EUS in the preoperative assessment of patients with esophageal cancer at or above the carina. *J Gastrointest Surg* 2008;12:1874-9
48. Petrillo R, Balzarini L, Bidoli P, et al. Esophageal squamous cell carcinoma: MRI evaluation of mediastinum. *Gastrointest Radiol* 1990;15:275-8
49. Nakashima A, Nakashima K, Seto H, et al. Thoracic esophageal carcinoma: Evaluation in the sagittal section with magnetic resonance imaging. *Abdom Imaging* 1997;22:20-3
50. Riddell AM, Allum WH, Thompson JN, et al. The appearances of oesophageal carcinoma demonstrated on high-resolution, T2-weighted MRI, with histopathological correlation. *Eur Radiol* 2007;17:391-9
51. Kayani B, Zacharakis E, Ahmed K, et al. Lymph node metastases and prognosis in oesophageal carcinoma: a systematic review. *Eur J Surg Oncol* 2011;37:747-53
52. Waterman TA, Hagen JA, Peters JH, et al. The prognostic importance of immunohistochemically detected node metastases in resected esophageal adenocarcinoma. *Ann Thorac Surg* 2004;78:1161-9
53. Lerut TE, de Leyn P, Coosemans W, et al. Advanced esophageal carcinoma. *World J Surg* 1994;18:379-87

54. Eloubeidi MA, Wallace MB, Reed CE, et al. The utility of EUS and EUS-guided fine needle aspiration in detecting celiac lymph node metastasis in patients with esophageal cancer: A single-center experience. *Gastrointest Endosc* 2001;54:714-9
55. Vazquez-Sequeiros E, Norton ID, Clain JE, et al. Impact of EUS-guided fine-needle aspiration on lymph node staging in patients with esophageal carcinoma. *Gastrointest Endosc* 2001;53:751-7
56. van Vliet EP, Heijnenbroek-Kal MH, Hunink MG, et al. Staging investigations for oesophageal cancer: A meta-analysis. *Br J Cancer* 2008;98:547-57
57. Salminen JT, Farkkila MA, Ramo OJ, et al. Endoscopic ultrasonography in the preoperative staging of adenocarcinoma of the distal oesophagus and oesophagogastric junction. *Scand J Gastroenterol* 1999;34:1178-82
58. Luketich JD, Schauer P, Landreneau R, et al. Minimally invasive surgical staging is superior to endoscopic ultrasound in detecting lymph node metastases in esophageal cancer. *J Thorac Cardiovasc Surg* 1997;114:817-21; discussion 821-3
59. van Westreenen HL, Westerterp M, Bossuyt PM, et al. Systematic review of the staging performance of ¹⁸F-fluorodeoxyglucose positron emission tomography in esophageal cancer. *J Clin Oncol* 2004;22:3805-12
60. Mizowaki T, Nishimura Y, Shimada Y, et al. Optimal size criteria of malignant lymph nodes in the treatment planning of radiotherapy for esophageal cancer: Evaluation by computed tomography and magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* 1996;36:1091-8
61. Nishimura H, Tanigawa N, Hiramatsu M, et al. Preoperative esophageal cancer staging: Magnetic resonance imaging of lymph node with ferumoxtran-10, an ultrasmall superparamagnetic iron oxide. *J Am Coll Surg* 2006;202:604-11
62. Alper F, Turkyilmaz A, Kurtcan S, et al. Effectiveness of the STIR turbo spin-echo sequence MR imaging in evaluation of lymphadenopathy in esophageal cancer. *Eur J Radiol* 2011;80:625-8
63. Berger B, Belka C. Evidence-based radiation oncology: Oesophagus. *Radiother Oncol* 2009;92:276-90
64. Njeh CF. Tumor delineation: The weakest link in the search for accuracy in radiotherapy. *J Med Phys* 2008;33:136-40
65. Sillah K, Williams LR, Laasch HU, et al. Computed tomography overestimation of esophageal tumor length: Implications for radiotherapy planning. *World J Gastrointest Oncol* 2010;2:197-204
66. Gao XS, Qiao X, Wu F, et al. Pathological analysis of clinical target volume margin for radiotherapy in patients with esophageal and gastroesophageal junction carcinoma. *Int J Radiat Oncol Biol Phys* 2007;67:389-96
67. Whitfield GA, Jackson A, Moore C, et al. Radical chemoradiotherapy for adenocarcinoma of the distal oesophagus and oesophagogastric junction: What planning margins should we use? *Br J Radiol* 2008;81:921-34
68. Konski A, Doss M, Milestone B, et al. The integration of 18-fluoro-deoxy-glucose positron emission tomography and endoscopic ultrasound in the treatment-planning process for esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 2005;61:1123-8
69. Thomas E, Crellin A, Harris K, et al. The role of endoscopic ultrasound (EUS) in planning radiotherapy target volumes for oesophageal cancer. *Radiother Oncol* 2004;73:149-51

70. Button MR, Morgan CA, Croydon ES, et al. Study to determine adequate margins in radiotherapy planning for esophageal carcinoma by detailing patterns of recurrence after definitive chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 2009;73:818-23
71. Lambrecht M, Haustermans K. Clinical evidence on PET-CT for radiation therapy planning in gastro-intestinal tumors. *Radiation Oncol* 2010;96:339-46
72. Muijs CT, Beukema JC, Pruim J, et al. A systematic review on the role of FDG-PET/CT in tumour delineation and radiotherapy planning in patients with esophageal cancer. *Radiation Oncol* 2010;97:165-71
73. Rasch C, Steenbakkers R, van Herk M. Target definition in prostate, head, and neck. *Semin Radiat Oncol* 2005;15:136-45
74. Hunter KU, Eisbruch A. Advances in imaging: Target delineation. *Cancer J* 2011;17:151-4
75. Groenendaal G, Borren A, Moman MR, et al. Pathologic validation of a model based on diffusion-weighted imaging and dynamic contrast-enhanced magnetic resonance imaging for tumor delineation in the prostate peripheral zone. *Int J Radiat Oncol Biol Phys* 2012;82:e537-44
76. Wang B, Kwon A, Zhu Y, et al. Image-guided intracavitary high-dose-rate brachytherapy for cervix cancer: A single institutional experience with three-dimensional CT-based planning. *Brachytherapy* 2009;8:240-7
77. Hawkins MA, Bedford JL, Warrington AP, et al. Volumetric modulated arc therapy planning for distal oesophageal malignancies. *Br J Radiol* 2012;85:44-52
78. Han C, Schiffner DC, Schultheiss TE, et al. Residual setup errors and dose variations with less-than-daily image guided patient setup in external beam radiotherapy for esophageal cancer. *Radiation Oncol* 2012;102:309-14
79. Kerkhof EM, Raaymakers BW, van der Heide UA, et al. Online MRI guidance for healthy tissue sparing in patients with cervical cancer: An IMRT planning study. *Radiation Oncol* 2008;88:241-9
80. Lagendijk JJ, Raaymakers BW, Raaijmakers AJ, et al. MRI/linac integration. *Radiation Oncol* 2008;86:25-9
81. Raaymakers BW, Lagendijk JJ, Overweg J, et al. Integrating a 1.5 T MRI scanner with a 6 MV accelerator: Proof of concept. *Phys Med Biol* 2009;54:N229-37
82. Boonstra JJ, Kok TC, Wijnhoven BP, et al. Chemotherapy followed by surgery versus surgery alone in patients with resectable oesophageal squamous cell carcinoma: Long-term results of a randomized controlled trial. *BMC Cancer* 2011;11:181
83. Jin HL, Zhu H, Ling TS, et al. Neoadjuvant chemoradiotherapy for resectable esophageal carcinoma: A meta-analysis. *World J Gastroenterol* 2009;15:5983-91
84. Wijnhoven BP, van Lanschot JJ, Tilanus HW, et al. Neoadjuvant chemoradiotherapy for esophageal cancer: A review of meta-analyses. *World J Surg* 2009;33:2606-14
85. van Heijl M, Omloo JM, van Berge Henegouwen MI, et al. Fluorodeoxyglucose positron emission tomography for evaluating early response during neoadjuvant chemoradiotherapy in patients with potentially curable esophageal cancer. *Ann Surg* 2011;253:56-63
86. Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol* 2001;19:305-13

87. Blazeby JM, Sanford E, Falk SJ, et al. Health-related quality of life during neoadjuvant treatment and surgery for localized esophageal carcinoma. *Cancer* 2005;103:1791-9
88. Habr-Gama A, Perez RO, Sao Juliao GP, et al. Nonoperative approaches to rectal cancer: A critical evaluation. *Semin Radiat Oncol* 2011;21:234-9
89. Westerterp M, van Westreenen HL, Reitsma JB, et al. Esophageal cancer: CT, endoscopic US, and FDG PET for assessment of response to neoadjuvant therapy--systematic review. *Radiology* 2005;236:841-51
90. Ngamruengphong S, Sharma VK, Nguyen B, et al. Assessment of response to neoadjuvant therapy in esophageal cancer: An updated systematic review of diagnostic accuracy of endoscopic ultrasonography and fluorodeoxyglucose positron emission tomography. *Dis Esophagus* 2010;23:216-31
91. Zuccaro G, Rice TW, Goldblum J, et al. Endoscopic ultrasound cannot determine suitability for esophagectomy after aggressive chemoradiotherapy for esophageal cancer. *Am J Gastroenterol* 1999;94:906-12
92. Flamen P, van Cutsem E, Lerut A, et al. Positron emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. *Ann Oncol* 2002;13:361-8
93. van Heijl M, Phoa SS, van Berge Henegouwen ML, et al. Accuracy and reproducibility of 3D-CT measurements for early response assessment of chemoradiotherapy in patients with oesophageal cancer. *Eur J Surg Oncol* 2011;37:1064-71
94. Lambrecht M, Vandecaveye V, De Keyzer F, et al. Value of diffusion-weighted magnetic resonance imaging for prediction and early assessment of response to neoadjuvant radiochemotherapy in rectal cancer: Preliminary results. *Int J Radiat Oncol Biol Phys* 2012;82:863-70
95. Verstraete KL, van der Woude HJ, Hogenboom PC, et al. Dynamic contrast-enhanced MR imaging of musculoskeletal tumors: Basic principles and clinical applications. *J Magn Reson Imaging* 1996;6:311-21
96. Ferraris R, Del Piano A, Galli JJ. Role of magnetic resonance imaging in the staging of gastrointestinal neoplasms. *Semin Surg Oncol* 2001;20:122-9
97. Pavone P, Cardone GP, Di Girolamo M, et al. Magnetic resonance imaging of the esophagus with lumen opacification using a specific contrast agent. *Radiol Med* 1992;84:756-60
98. Shuto K, Saito H, Ohira G, et al. Diffusion-weighted MR imaging for postoperative nodal recurrence of esophageal squamous cell cancer in comparison with FDG-PET. *Gan To Kagaku Ryoho* 2009;36:2468-70
99. Tateishi U, Miyake M, Nagaoka T, et al. Neoadjuvant chemotherapy in breast cancer: Prediction of pathologic response with PET/CT and dynamic contrast-enhanced MR imaging--prospective assessment. *Radiology* 2012;263:53-63
100. Cho YB, Chun HK, Kim MJ, et al. Accuracy of MRI and ¹⁸F-FDG PET/CT for restaging after preoperative concurrent chemoradiotherapy for rectal cancer. *World J Surg* 2009;33:2688-94
101. Kikuchi M, Shinohara S, Nakamoto Y, et al. Sequential FDG-PET/CT after neoadjuvant chemotherapy is a predictor of histopathologic response in patients with head and neck squamous cell carcinoma. *Mol Imaging Biol* 2011;13:368-77



Chapter 3

Imaging of esophageal cancer with ^{18}F -FDG PET/CT and MRI

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Clinical Radiology 2015;70:81-95

ABSTRACT

Integrated ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET)/computed tomography (CT) and magnetic resonance imaging (MRI) with functional features of diffusion-weighted imaging (DWI) are advancing imaging technologies that have current and future potential to overcome important limitations of conventional staging methods in the management of patients with esophageal cancer. ^{18}F -FDG PET/CT has emerged as an important part of the standard work-up of patients with esophageal cancer. Besides its important ability to detect unsuspected metastatic disease, ^{18}F -FDG PET/CT may be useful in the assessment of treatment response, radiation treatment planning, and detection of recurrent disease. In addition, high-resolution T2-weighted MRI and DWI have potential complementary roles. Recent improvements in MRI protocols and techniques have resulted in better imaging quality with the potential to bring improvement in staging, radiation treatment planning, and the assessment of treatment response. Optimal use and understanding of ^{18}F -FDG PET/CT and MRI in esophageal cancer will contribute to the impact of these advancing technologies in tailoring treatment to the individual patient and achieving best possible outcomes. In this article, we graphically outline the current and potential future roles of ^{18}F -FDG PET/CT and MRI in the multidisciplinary management of esophageal cancer.

INTRODUCTION

Over the past decade integrated positron emission tomography – computed tomography (PET/CT) with ^{18}F -fluorodeoxyglucose (^{18}F -FDG) has emerged as an important and recommended part of routine staging of patients with esophageal cancer in (inter)national guidelines^{1,2}. ^{18}F -FDG PET/CT imaging - followed by endoscopic ultrasonography (EUS) - has been proposed as the most cost-effective strategy for initial staging of patients with esophageal cancer, mainly due to its ability to detect unsuspected metastatic disease³⁻⁵. In addition, with increasing availability and body of evidence, the role of ^{18}F -FDG PET/CT may further expand to include assessment of treatment response, radiation treatment planning, and detection of recurrent disease⁶.

Besides ^{18}F -FDG PET/CT, another recently advancing imaging modality is high-resolution T2-weighted magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI), which might have complementary roles in staging, treatment response assessment and radiation planning. A good understanding of ^{18}F -FDG PET/CT and MRI results - along with their advantages and limitations in esophageal cancer - is important for proper interpretation of images and will contribute to the impact of these advancing technologies in tailoring treatment to the individual patient and achieving best possible outcomes. Therefore, the aim of this review is to graphically outline the current and potential future roles of ^{18}F -FDG PET/CT and MRI in the management of esophageal cancer.

^{18}F -FDG PET/CT

^{18}F -FDG PET/CT provides additional information when compared to ^{18}F -FDG PET or CT alone in different types of malignancies including esophageal cancer⁷. Studies in esophageal cancer have shown that the overall accuracy for initial staging improved from 83-86% for standalone ^{18}F -FDG PET to 90-92% for integrated ^{18}F -FDG PET/CT^{8,9}.

IMAGING TECHNIQUE

^{18}F -FDG PET/CT scanning is performed on an integrated hybrid system combining PET capabilities with multi-detector CT components in two sequential gantries. Since no patient repositioning is required between the two acquisitions, an accurate co-registration of ^{18}F -FDG PET and CT datasets can be performed. Although no general consensus on all scanning variables exists, the currently applied protocols share some common features.

Patient preparation includes fasting for at least 6 hours before the ^{18}F -FDG PET/CT examination, with a preferred serum glucose level of less than 10 mmol/L, and emptying of the bladder just before examination. Sixty to ninety minutes after administration of ^{18}F -FDG, PET images are acquired in a two- or three-dimensional mode. Administered activity and time per bed-position are interrelated and may be highly variable. Reconstruction of ^{18}F -FDG PET images is performed by using standard iterative reconstruction algorithms that incorporate ordered-subset expectation maximization¹⁰. Attenuation data from the CT part of the examination is used to perform attenuation correction of the ^{18}F -FDG PET images.

The CT examination comprises a multi-detector CT scan with a tube potential of 120-140 kV and an effective tube current of 40-120 mA. CT images are usually reconstructed with slice thicknesses of 3-5 mm. Administration of oral and intravenous contrast agents improves the ability to identify the anatomical location and boundaries of lesions detected on the ^{18}F -FDG PET images. In addition to qualitative assessment, the ^{18}F -FDG uptake within specific lesions can be analyzed quantitatively by measuring the standardized uptake value (SUV), often expressed as its maximum (SUV_{max}), which is derived from the activity within the region of interest (Bq/g) multiplied by grams of body weight, divided by the total injected dose of ^{18}F -FDG (Bq).

MRI

MRI of the esophagus is often considered technically challenging. Reasons for the difficult depiction of the esophagus include organ motion due to respiratory and cardiac action, and considerable blood flow in the aorta and pulmonary vessels, which leads to motion and flow artifacts. Additionally, the central location of the mediastinum in the body is associated with a reduced receiver coil sensitivity, resulting in a degraded signal-to-noise ratio (SNR). Over the past decade, several technical innovations became available to reduce the mentioned image artifacts. For instance, effects of respiratory motion can be reduced by automatic gated imaging using navigators, and the availability of multi-channel receiver coils resulted in improved SNR in the thorax. These improvements enable proper visualization of the esophagus using MRI. SNR may further be increased by scanning at a higher magnetic field strength (i.e. 3-Tesla instead of 1.5-Tesla). However, a disadvantage of scanning at higher field strength is the larger effect of magnetic susceptibility variations on the geometrical fidelity of MR images. As large susceptibility variations are present in the thorax and mediastinum due to the numerous air-tissue transitions, MRI scanning of the esophagus at higher field strengths may be less optimal despite the higher SNR.

IMAGING TECHNIQUE

In previous ex-vivo and in-vivo studies the optimal type of anatomical contrast (i.e. T1- or T2-weighted scans), along with the most suitable combination of repetition times (TR) and echo times (TE) was determined for visualization of the esophagus and surrounding structures¹¹⁻¹⁴. High-resolution T2-weighted scans, rather than T1-weighted scans, enable clear depiction of the different layers of the esophageal wall (**Figure 1a**). Optimized in-vivo high-resolution T2-weighted MRI in addition provides excellent contrast between the esophagus and its surrounding structures, with esophageal wall thickening at the level of a tumor (**Figure 1b, c**).

Further optimization of high-resolution T2-weighted MRI includes automatic respiratory motion compensation. In our institution, a navigator that monitors the position of the diaphragm using a fast 1D-MRI acquisition is applied to trigger scanning exclusively during the end-exhale position of the diaphragm, as the end-exhale position was found to reflect the most stable position of esophageal tumors during the respiratory cycle¹⁵.

A functional MRI technique that clearly depicts esophageal tumors is diffusion-weighted imaging (DWI). With DWI, variations in the diffusion of water molecules (i.e. random mobility) among tissues are visualized (**Figure 1d**). To achieve image contrast, the MRI signal is labeled for diffusion using spatially varying magnetic fields (diffusion gradients)¹⁶. This results in a lower signal in mobile water molecules compared to immobile water molecules. If DW images with two or more diffusion-weighting strengths (expressed in s/mm²) are scanned, it is possible to calculate the apparent diffusion coefficient (ADC), a quantitative measure for diffusion. Low ADC values represent restricted diffusion of water molecules in a region of interest as a result of high cell density and intact cell membranes (e.g. spinal cord, spleen, malignant tissue), whereas high ADC values represent less restricted diffusion of water molecules in tissues with low cell density or defective cell membranes (e.g. healthy gastro-intestinal organs or malignant tissues that responded well to treatment)^{16,17}.

In our experience, an anticipated MRI scan protocol that is potentially useful for future clinical practice in esophageal cancer consists of both T2-weighted and DWI sequences. Depending on the clinical purpose of the MR examination, in our opinion the field-of-view should at least include the cranio-caudal extent of the posterior mediastinum and upper abdomen to be able to visualize the primary tumor along with potentially involved lymph nodes. Scanning in the transverse plane seems appropriate for the assessment of tumor depth and ingrowth into adjacent structures, whereas sagittal and coronal scans may be useful in the determination of the cranio-caudal tumor extent.

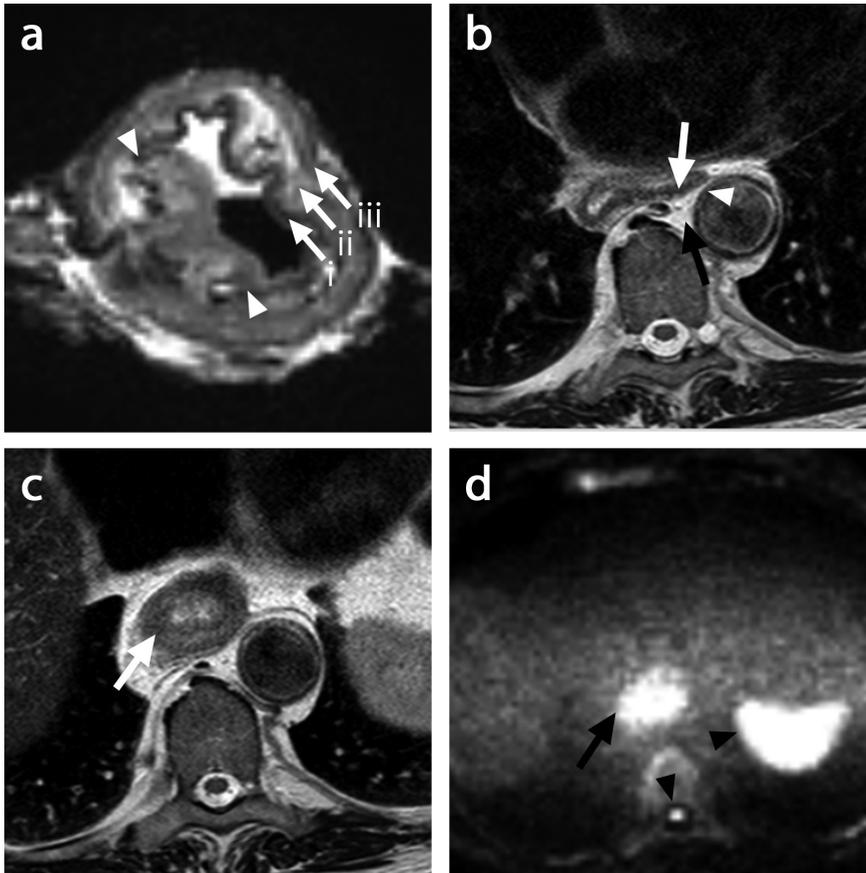


Figure 1 (a) Transverse ex-vivo T2-weighted MRI of an esophageal resection specimen demonstrating the potential of T2-weighted scanning for accurate visualization of the esophageal wall. The mucosal layer has a low signal intensity (i), whereas the surrounding submucosa provides a higher signal intensity (ii). Finally, the muscularis propria presents a lower signal intensity (iii). The low intensity band of the mucosa is partly failing on the left side of the image, indicating the location of the esophageal tumor (arrowheads). (b) In-vivo high-resolution T2-weighted MRI provides excellent contrast between the esophagus (white arrow), its surrounding mediastinal fat (black arrow), and the aortic wall (arrowhead). (c) In the presence of tumor, esophageal wall thickening is observed (arrow). Also, slightly higher signal intensities are observed at the location of the tumor (c), compared to healthy esophageal tissue (b). (d) Corresponding transverse DW image ($b=800 \text{ s/mm}^2$) clearly depicts the tumor by its restricted diffusivity (arrow). Also, the spinal cord and spleen are visible due to physiologic diffusion restriction of these structures (arrowheads).

ESOPHAGEAL CANCER STAGING

Esophageal cancer is the eighth most common cancer worldwide and the incidence is rapidly increasing^{18,19}. The disease is highly lethal due to the late onset of symptoms, with poor overall 5-year survival rates ranging from 15% to 25%²⁰. Curative treatment of esophageal cancer combines neoadjuvant chemoradiotherapy (CRT) with surgery, and palliative treatment options include chemotherapy and local therapies, such as radiotherapy and endoscopic stenting²⁰⁻²³. Optimal use and understanding of staging techniques is essential to predict prognosis and tailor treatment to individuals in order to achieve the best possible outcomes.

Staging includes upper-gastrointestinal endoscopy with biopsy to confirm the diagnosis, EUS to acquire additional information on local tumor invasion and loco-regional lymph node status, and ¹⁸F-FDG PET/CT to assess loco-regional spread and distant metastases²⁴. Although MRI plays no role in current routine staging guidelines, it has the potential to serve as an alternative or complementary non-invasive form of staging in the near future^{14,25}.

PRIMARY TUMOR

¹⁸F-FDG PET/CT

Visible ¹⁸F-FDG avidity of tumors relies on sufficient tumor volume and a metabolic activity to exceed a certain detection threshold (currently approximately 5 mm)^{26,27}. In a recent meta-analysis a pooled primary esophageal tumor detection rate with ¹⁸F-FDG PET/CT of 92.7% was reported²⁸. The limited spatial resolution of ¹⁸F-FDG PET particularly limits visualization of early-stage carcinomas with small volumes (i.e. Tis, T1 and T2)^{5,29}.

On the other hand, false-positive results may result from benign lesions such as leiomyoma or secondary inflammation caused by chemotherapy, radiation treatment, candida infection, gastro-esophageal reflux disease, esophageal spasm, Barrett's esophagus, or bacterial infection with peptic strictures³⁰⁻³⁵. However, non-malignant ¹⁸F-FDG PET hypermetabolism is often linear in shape involving a long cranio-caudal segment with relatively low intensity and can therefore often be easily distinguished from more focal and intense malignant lesions^{29,36}.

Another consequence of the poor spatial resolution of PET and the poor contrast resolution of CT, is the limited role of these techniques in evaluating the depth of invasion (e.g. T-stage) of esophageal cancers³⁷. EUS is the preferred method for primary tumor staging, as supported by a meta-analysis that found pooled

sensitivities for diagnosing distinct T-stages of 81-92%³⁸. One direct comparative study reported that T-staging was performed correctly by CT and ¹⁸F-FDG PET in only 42% of patients with esophageal cancer, compared to 71% with EUS³⁹. However, the CT component of ¹⁸F-FDG PET/CT is valuable for excluding irresectable T4b disease by demonstrating preservation of fat planes between the esophagus and surrounding structures^{40,41}.

MRI

In early MRI studies, primary tumor detection rates were disappointing for early-stage esophageal cancers (i.e. T1 and T2)⁴². A more recent study performed high-resolution T2-weighted MRI with faster sequences and cardiorespiratory motion gating in combination with DWI, and reported detection rates of 33% for T1, 58% for T2, 96% for T3, and 100% for T4 carcinomas⁴³.

Using conventional T1- and T2-weighted MRI, T-stage was correctly assessed in 60% of patients only⁴⁴. However, high-resolution T2-weighted MRI has been shown to enable detailed imaging of the anatomic layers of the esophageal wall and surrounding peri-esophageal tissues¹¹⁻¹⁴. An accuracy of 81% was reported for T-staging in a recent study using this technique, with understaging in 16% and overstaging in 3% of cases¹⁴. As such, high-resolution T2-weighted MRI has the potential to serve as an alternative or complementary non-invasive form of local staging in esophageal cancer.

In early studies, 1.5-Tesla MRI with cardiac triggering has shown to be of similar value compared with CT for the assessment of surgical resectability (i.e. distinguishing \leq T4a from T4b tumors) with an accuracy of 75-87%^{45,46}. So far, no studies have reported on the value of modern high-resolution T2-weighted MRI (standalone or fused with DWI) in the preoperative assessment of tumor invasion into adjacent non-resectable structures (**Figure 2**). Modern high-resolution T2-weighted MRI with faster sequences and motion gating might prove to be of superior value in future studies.

LYMPH NODES

¹⁸F-FDG PET/CT

¹⁸F-FDG PET/CT has a limited value in the assessment of loco-regional lymph node involvement in esophageal cancer^{40,47-49}. A meta-analysis reported a pooled sensitivity and specificity with ¹⁸F-FDG PET of 51% and 84%, respectively⁴⁸. ¹⁸F-FDG uptake of the primary tumor may obscure uptake in peri-tumoral lymph

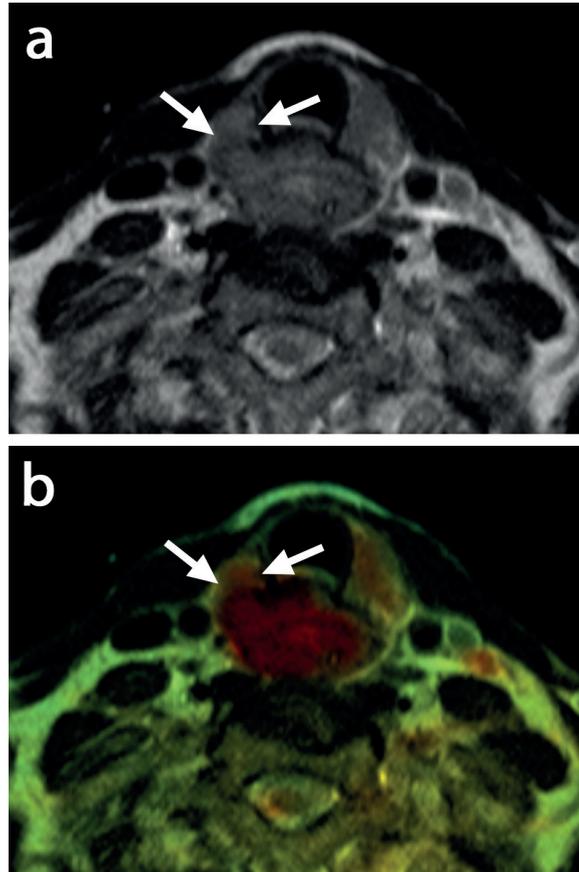


Figure 2 A 59 year-old man diagnosed with a proximal stenotic esophageal squamous cell carcinoma. (a) Transverse high-resolution T2-weighted MRI at the level of the neck demonstrated invasion of the esophageal tumor into the right thyroid gland (*arrows*). (b) The corresponding fusion T2-weighted/DW image showed diffusion restriction within the tumor (*color*) including the suspected site of thyroïdal ingrowth (*arrows*). External ultrasonography of the neck confirmed the clinical T4b disease.

nodes due to the limited spatial resolution of ^{18}F -FDG PET^{40,50}. In addition, lymph nodes with microscopic involvement may lack both sufficient ^{18}F -FDG uptake and sufficient abnormal growth for detection with ^{18}F -FDG PET/CT⁴⁷. Furthermore, false-positive findings can result from inflammatory processes in lymph nodes⁴⁸. ^{18}F -FDG PET/CT therefore seems rather an adjunct than an alternative to conventional CT and EUS for the assessment of lymph nodes (**Figure 3a, b**).

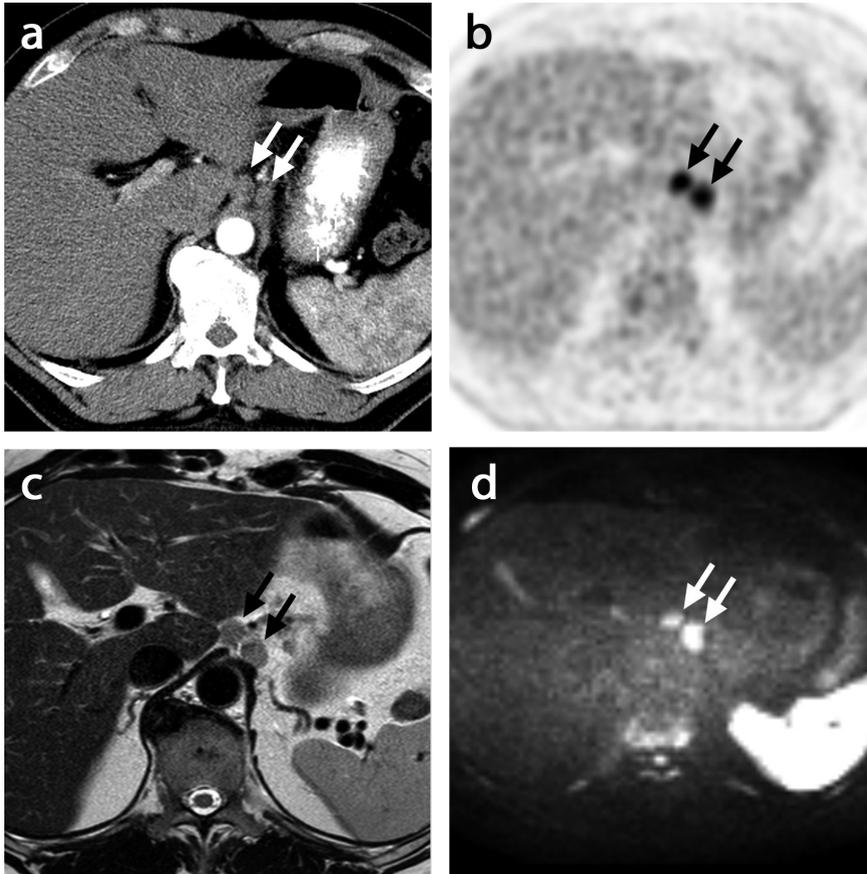


Figure 3 A 56 year-old man was diagnosed with a biopsy-proven cT2N1M0 adenocarcinoma of the distal third of the esophagus. (a) Diagnostic CT revealed two suspected lymph nodes in the lesser omentum with maximum diameters of 16mm and 14mm respectively (*arrows*), and (b) a transverse ^{18}F -FDG PET image confirmed pathologic ^{18}F -FDG uptake of the two nodes. (c) High-resolution T2-weighted MRI was similarly capable of identifying the two enlarged lymph nodes (*arrows*), and both these nodes in (d) clearly showed restricted diffusivity on the corresponding DW image ($b=800 \text{ s/mm}^2$). After neoadjuvant chemoradiotherapy followed by esophagectomy, histopathology confirmed two lymph nodes in the lesser omentum with residual disease.

MRI

A recent systematic review demonstrated a moderately poor diagnostic value of conventional MRI for lymph node staging in esophageal cancer, with a sensitivity and specificity of 25-62% and 67-88%, respectively (**Figure 3c, d**)²⁵. However, high-resolution MRI may prove more valuable in the near future as a recent study with

modern motion gating techniques and fast fat-suppressive sequences achieved a sensitivity and specificity of 81% and 98%⁵¹. Because current evidence is sparse and significant heterogeneity of reported methodology and outcomes among different studies exists, it is difficult to extract specific nodal features that may help identify malignant nodes on MRI. In most studies using conventional MRI, size criteria have been used to identify malignant lymph nodes (i.e. short-axis diameter of >5 mm or >10 mm)²⁵. Rather than using dimensional criteria, a focal or overall high signal intensity of lymph nodes on high-resolution T2-weighted MRI was considered metastatic in one study⁵¹.

Unfortunately, application of whole-body DWI with background body signal suppression (DWIBS) did not result in major diagnostic improvements for lymph node staging in one study⁴³. Lymph nodes with a higher signal intensity (i.e. showing more diffusion restriction) than the spinal cord on DWIBS were considered metastatic in this study. To the best of our knowledge, no studies have reported on the value of quantitative assessment of DW images of lymph nodes by means of ADC measurements so far.

DISTANT METASTASES

¹⁸F-FDG PET/CT

Many studies have demonstrated that the most important incremental value of ¹⁸F-FDG PET/CT in the management of esophageal cancer lies in its complementary ability to detect unexpected distant metastases in 5-28% of patients at initial presentation^{5,8,48,49,52-58}. In this respect, ¹⁸F-FDG PET provides additional diagnostic information over CT, leading to significant management changes in 14-40% of patients^{35,59-63}. Metastatic spread from esophageal cancer can occur in unusual and unexpected locations and whole-body ¹⁸F-FDG PET/CT allows for detection of those metastases that are not covered with conventional strategies, that are radiologically occult or that are difficult to diagnose prospectively^{64,65}. By detecting unexpected distant metastases preoperatively, ¹⁸F-FDG PET/CT decreases the number of inappropriate attempts of surgical exploration and should therefore be performed as a routine part of initial staging (**Figures 4 and 5**)^{3,57,66,67}.

Several studies have also reported usefulness of ¹⁸F-FDG PET/CT for detection of new interval metastases after neoadjuvant therapy, which occur in 8-17% of patients⁶⁸⁻⁷⁰. Some authors therefore advocate a restaging ¹⁸F-FDG PET/CT as part of the standard work-up of surgical candidates.

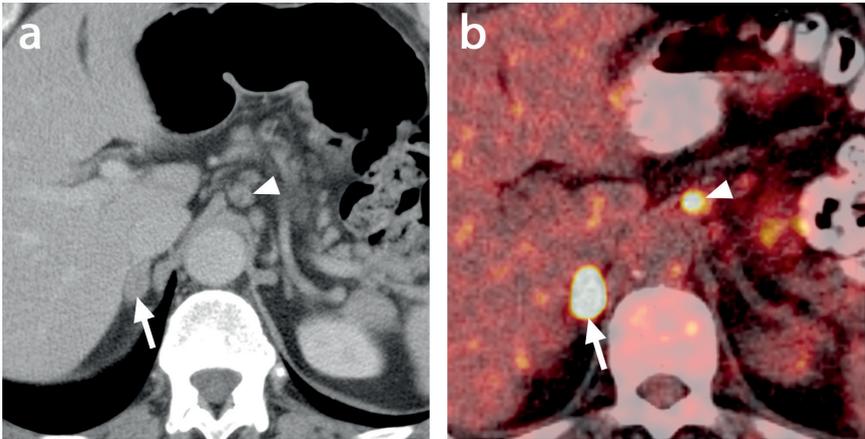


Figure 4 A 72 year-old man was referred to our institution with a biopsy-proven cT3N1M0 adenocarcinoma of the gastro-esophageal junction. In addition to prior endoscopy, EUS, and diagnostic CT (a) at the referring center, we performed a staging ^{18}F -FDG PET/CT (b) that revealed an oval-shaped focus of increased ^{18}F -FDG uptake in the right adrenal gland (arrow). CT-guided biopsy of the lesion demonstrated a metastatic poorly differentiated adenocarcinoma matching the known primary esophageal tumor. In retrospect, with advancing knowledge from the ^{18}F -FDG PET/CT examination the lesion in the adrenal gland may already have been detected on the diagnostic CT from the referring center. Although this patient was referred for treatment with curative intent, the proven M1 disease precluded surgical resection and ^{18}F -FDG PET/CT changed the treatment plan to palliative chemotherapy. *Note* - In addition, an enlarged lymph node just above the celiac trunk was detected on CT (a; arrowhead) and showed intense ^{18}F -FDG uptake on ^{18}F -FDG PET/CT (b; arrowhead). In the most recent (seventh) edition of the TNM-classification, however, celiac node involvement is no longer considered distant metastatic (M1) disease and is no contra-indication for treatment with curative intent.

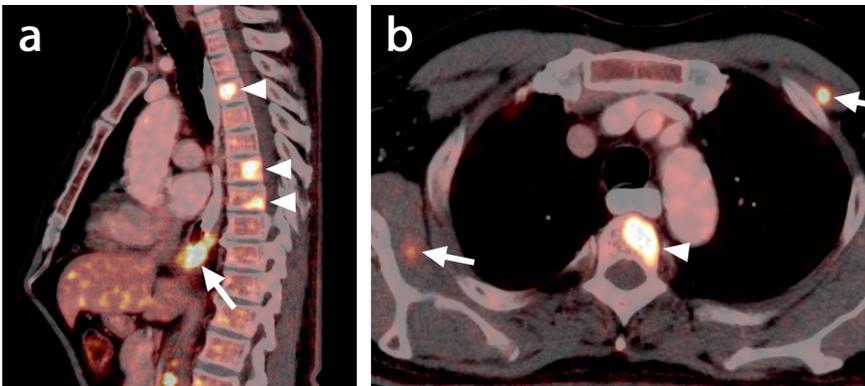


Figure 5 A 66 year-old man presented with a cT3N2Mx adenocarcinoma of the gastro-esophageal junction. (a) ^{18}F -FDG PET/CT demonstrated the ^{18}F -FDG-avid junction tumor (arrow) along with previously unexpected distant metastatic spread to the spine (arrowheads). (b) In addition to the unexpected osseous metastases (middle arrowhead) two locations suspected of skeletal muscle metastases were identified by ^{18}F -FDG PET/CT (lateral arrowheads; right subscapular muscle and left pectoral muscle, respectively). After histologic confirmation of the (osseous) metastases palliative chemotherapy was initiated.

Additionally, synchronous primary malignancies may be revealed by ^{18}F -FDG PET/CT in 1.5-8% of patients with esophageal cancer at initial staging^{62,71-74}. Approximately 75% of these synchronous tumors were not detected by routine imaging in a large retrospective study⁷¹. The most common synchronously involved sites included the colon and rectum (55%), followed by lung, kidney, thyroid, and head and neck.

MRI

To date no studies have been published on the value of MRI in detecting distant metastases from esophageal cancer. Although specific MRI protocols may provide valuable information on distant spread to specific organs such as the liver in some cases, MRI is unlikely to be of additional value in the assessment of the whole body.

TREATMENT RESPONSE ASSESSMENT

^{18}F -FDG PET/CT

Over the past two decades contradictory results have been published on the usefulness of ^{18}F -FDG PET and PET/CT for the assessment of response to neoadjuvant chemo(radio)therapy or definitive CRT⁷⁵⁻⁸². CRT-induced esophagitis or ulceration of the esophagus can cause increased ^{18}F -FDG accumulation and persistently raised SUVs, which leads to false-positive results on ^{18}F -FDG PET/CT and precludes accurate detection of residual cancer⁸³⁻⁸⁵.

Esophagitis generally manifests after the first two weeks of treatment and evaluation of treatment response within the first two weeks has therefore been suggested to be the least prone to false-positive findings^{77,80,86,87}. In addition, accurate prediction of early response during treatment may allow for early modifications of the treatment protocol in non-responders that suffer from ineffective toxic CRT and unnecessarily delayed surgery⁸⁸. Indeed, a meta-analysis showed that a 50% reduction in SUV_{max} or SUV_{mean} between pre-treatment ^{18}F -FDG PET and a ^{18}F -FDG PET performed within the first two weeks of neoadjuvant CRT was the optimal condition for response prediction in esophageal cancer⁸⁹. However, this meta-analysis and another recent meta-analysis on the value of ^{18}F -FDG PET(/CT) for response evaluation found pooled sensitivities and specificities of 67% to 70% only, and recommended that ^{18}F -FDG PET(/CT) should not yet be used in routine clinical practice to guide neoadjuvant therapy decisions^{89,90}.

Although a clinical complete response based on ^{18}F -FDG PET/CT may well reflect a true pathologic complete response (**Figure 6a-c**), it is important to note that this finding should be interpreted with caution when considering omission of surgical resection. A subsequent loco-regional recurrence rate as high as 42% has been reported in ^{18}F -FDG PET-based clinical complete responders that did not undergo esophagectomy⁹¹. In the largest series published to date ($n=284$), the specificity of combined ^{18}F -FDG PET- and endoscopic biopsy-based clinical complete response for true pathologic complete response was very low (30%)²¹. Therefore, until more accurate tools for response evaluation have been developed, surgery-eligible esophageal cancer patients should be encouraged to undergo esophagectomy following CRT despite achieving a clinical complete response based on ^{18}F -FDG PET/CT and endoscopic biopsies^{21,82,92}.

MRI

DWI may provide complementary information regarding tumor regression in response to CRT (**Figures 6d-f and 7**), besides measurements of dimensional changes in tumor diameter or volume on anatomical MRI. Encouraging pilot studies using DWI in rectal cancer have reported sensitivities and specificities of up to 100% for the prediction of pathologic complete response early during neoadjuvant CRT⁹³.

Initial experience with DWI in esophageal cancer has been published in the last few years and more pilot studies are currently ongoing⁹⁴⁻⁹⁷. The difference between pre-treatment and post-treatment median ADC values (or ΔADC) was inversely correlated with the histopathologic tumor regression grade and may therefore be helpful to discriminate responders from non-responders⁹⁶. In another study in 27 patients with clinical T4 esophageal carcinomas undergoing definitive CRT, the difference between pre-treatment ADC and ADC early during treatment had a predictive value of 100% for responders (suboptimally defined by RECIST criteria⁹⁸ using CT and esophagography)⁹⁷.

However, before clinical consequences may be justified, further studies are required to optimize MRI scan protocols, timing of scans, and confirm the preliminary clinical evidence in larger populations. In a recently embarked study at our institution we aim to determine the complementary value of DWI in addition to ^{18}F -FDG PET/CT for response evaluation by performing both optimized MRI and ^{18}F -FDG PET/CT before, during and after neoadjuvant CRT for esophageal cancer⁹⁹. In future efforts additional attention should be paid to the assessment of metastatic lymph nodes, because a complete local tumor response may be accompanied by residual malignancy in the loco-regional lymph nodes in approximately 10% of local pathologic complete responders (e.g. ypT0N1)¹⁰⁰.

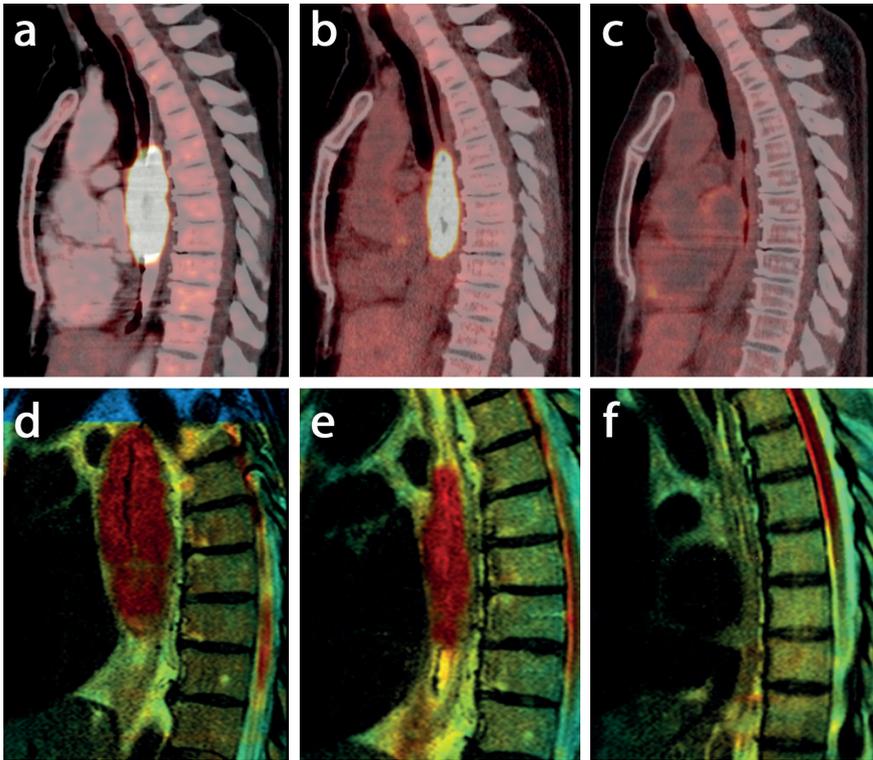


Figure 6 A 53 year-old woman diagnosed with a biopsy-proven cT4aN2M0 squamous cell carcinoma of the mid-esophagus. EUS showed ingrowth of the tumor into the adjacent right pleura and suspected lymph nodes in the mediastinum and at the level of the coeliac trunk (confirmed by ^{18}F -FDG-avidity on ^{18}F -FDG PET/CT) and aortopulmonary window (non- ^{18}F -FDG-avid). ^{18}F -FDG PET/CT and MRI scans were performed before (a,d), during (b,e), and after (c,f) neoadjuvant chemoradiotherapy to assess response to treatment. (a) Sagittal fusion ^{18}F -FDG PET/CT image before start of neoadjuvant chemoradiotherapy shows a mid-esophageal ^{18}F -FDG-avid tumor with a length of 9.2 cm, which in (b) showed some tumor shrinkage to 8.4 cm on a corresponding ^{18}F -FDG PET/CT image obtained after the first 10 days of neoadjuvant treatment, and in (c) a complete metabolic regression in both primary tumor and previously suspected lymph nodes (*not shown*) at 55 days after completion of chemoradiotherapy. (d) Corresponding pre-treatment fusion T2-weighted/DW sagittal image ($b=800$ s/mm 2) shows the tumor with homogeneous restricted diffusivity and a length of 9.3 cm, with an early response in (e) after 10 days of chemoradiotherapy (length 7.8 cm) and a complete regression with normalized diffusivity in (f) at 55 days post-chemoradiotherapy, similar to ^{18}F -FDG PET/CT. Histology after subsequent surgical resection confirmed a ypT0N0 pathologic complete response (Mandard 1).

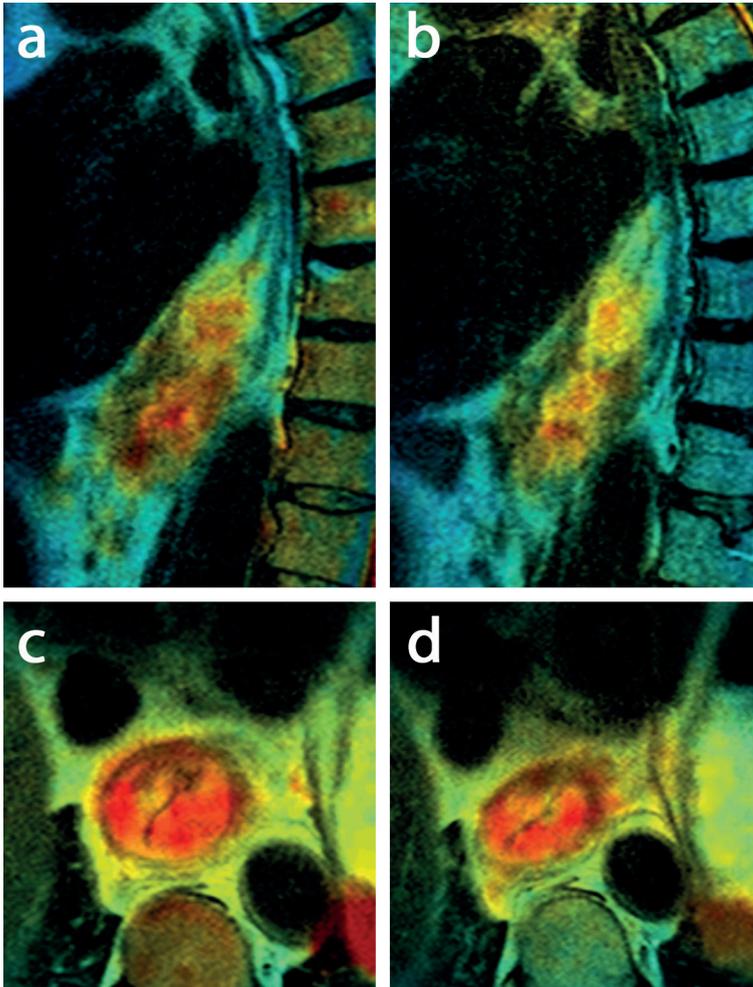


Figure 7 A 65 year-old man with a biopsy-proven cT3N3M0 adenocarcinoma of the distal third of the esophagus was treated with neoadjuvant chemoradiotherapy followed by transthoracic esophagectomy and underwent three consecutive MRI scans. (**a,c**) Sagittal and transverse pre-treatment fusion T2-weighted/DW images ($b=800 \text{ s/mm}^2$) clearly depicted the esophageal tumor which showed heterogeneous diffusion restriction. (**b,d**) MR images acquired 4 weeks after completion of neoadjuvant treatment demonstrated minimal reduction in tumor volume and diffusion restriction. Histologic examination of the subsequently resected specimen confirmed minor tumor regression (Mandard 4) with an estimated viable tumor cells percentage of 70%.

RADIATION TREATMENT PLANNING

¹⁸F-FDG PET/CT

In order to maximize the chances of acquiring loco-regional tumor control by means of radiation therapy, accurate delineation of tumor volume is crucial to optimize the dose to the target and simultaneously minimize the volume of irradiated surrounding tissues¹⁰¹. CT images (together with available information from EUS) are most commonly used for this purpose in esophageal cancer, but unfortunately CT is not able to precisely demonstrate the proximal and distal margins of esophageal tumors in many cases. Indeed, in a recent study the assumed esophageal tumor length based on CT was found not to reflect histopathologic tumor extent¹⁰². In contrast, ¹⁸F-FDG PET/CT enables delineation of the biologically active tumor volume, and its depiction of esophageal tumors has been shown to correlate well with histopathologic extent¹⁰³. ¹⁸F-FDG PET/CT therefore has great potential to provide valuable information for radiation treatment planning^{18,104}.

The use of ¹⁸F-FDG PET/CT for tumor delineation results in both decreases and increases of the target volume when compared to CT and EUS in 10-63% of patients (**Figure 8a-c**)¹⁰⁵⁻¹⁰⁸. These changes may ultimately allow for improvement in coverage of the true malignant volume and for relevant additional sparing of normal surrounding tissues. However, there are no studies demonstrating the impact of such modifications by ¹⁸F-FDG PET/CT in terms of improved loco-regional control or survival. One study reported that the addition of ¹⁸F-FDG PET to CT-based planning decreased both inter- and intra-observer variability¹⁰⁹, but this finding could not be confirmed in another study¹¹⁰. Therefore, standard implementation of ¹⁸F-FDG PET/CT into the tumor delineation process for radiation treatment planning remains subject of debate and requires further clinical validation¹⁰⁸.

MRI

The usefulness of MRI in the radiation treatment planning process has already been established for malignancies of the head and neck, prostate, rectum and cervix¹¹¹⁻¹¹⁴. Although current available evidence on MRI for radiation treatment planning in esophageal cancer is scarce, recent technical improvements of both anatomical and functional MRI may allow for further target definition improvement using MRI (**Figure 8d-f**)²⁵.

DWI scans can be fused with T2-weighted MRI or CT images in radiation treatment planning systems to delineate the target volume. Promisingly, in a recent study with 42 esophageal squamous cell carcinoma patients the cranio-caudal tumor length was most precisely delineated according to DWI (followed by T2-weighted

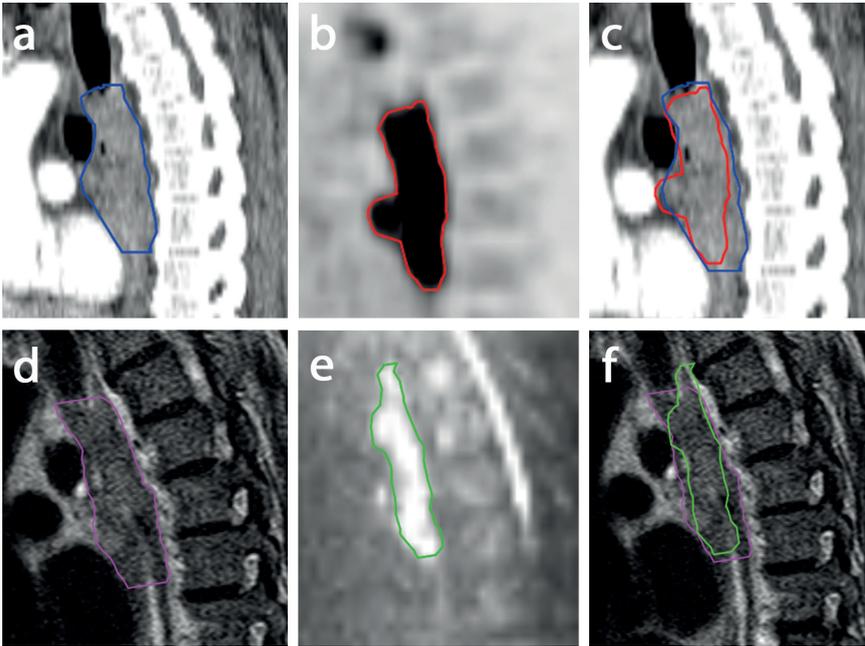


Figure 8 (a) Delineation of the gross tumor volume (GTV) for radiation treatment planning in esophageal cancer is generally performed on a low-dose contrast-enhanced CT (*blue contour*). (b,c) Corresponding ^{18}F -FDG PET may aid to determine the biologically active volume and subsequently alter the shape and volume of the GTV (*red contour*). (d) T2-weighted MRI provides higher soft-tissue contrast resolution compared to CT and may allow for further target definition improvement (*pink contour*). (e,f) Similar to ^{18}F -FDG PET, DWI ($b=800 \text{ s/mm}^2$) may provide a better reflection of the true (functional) malignant volume and cranio-caudal length (*green contour*).

MRI and conventional CT) when compared to the postoperative pathologic lesion length¹¹⁵. However, more studies are required to clarify the potential role of high-resolution MRI including DWI for this purpose before any firm recommendations can be made. In addition, future clinical studies in esophageal cancer should aim to determine the potential value of the recently developed MR-linac system that integrates an MRI system with a radiotherapy accelerator, allowing for simultaneous irradiation and real-time MR imaging^{15,116,117}.

RECURRENT DISEASE

^{18}F -FDG PET/CT

^{18}F -FDG PET/CT allows for accurate detection of recurrent disease after initial treatment with curative intent. Sensitivities of 93-100%, specificities of 67-88% and

accuracies of 84-92% have been reported for the detection of recurrent esophageal cancer^{59,118-122}. ^{18}F -FDG PET after surgical resection was of additional value to conventional surveillance methods in 27% of patients in one study⁵⁹. In this way, ^{18}F -FDG PET/CT may change clinical decision-making in palliative management and ultimately improve patient survival^{123,124}.

In particular, the sensitivity for the detection of loco-regional recurrence is higher with ^{18}F -FDG PET than with CT, because postoperative changes and scarring on CT is often difficult to differentiate from recurrent disease (**Figure 9**)¹¹⁹.

However, the specificity of CT was found to be higher than that of ^{18}F -FDG PET as false-positive ^{18}F -FDG accumulation in the gastric tube and thoracic lymph nodes may also occur¹¹⁹. In other studies, integrated ^{18}F -FDG PET/CT was more accurate than CT alone for detection of nodal recurrence and distant metastases^{120,125}.

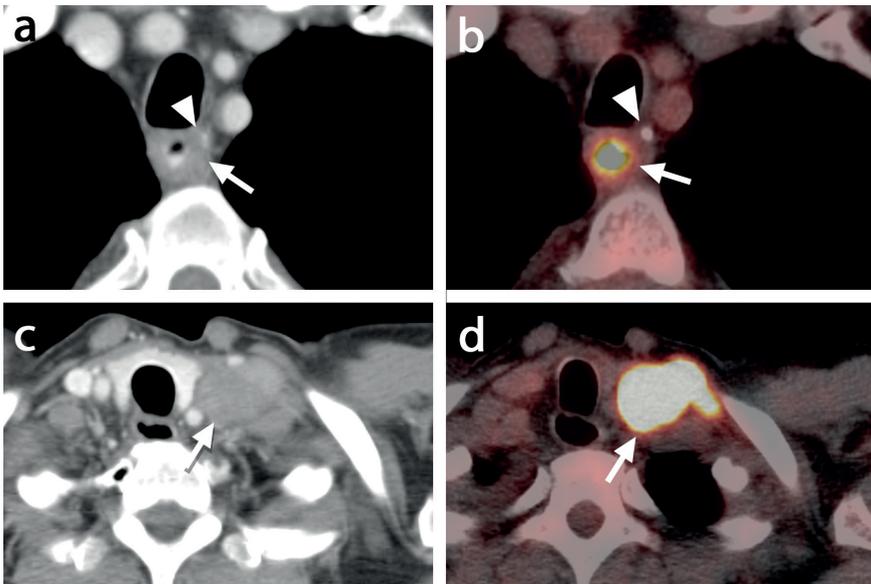


Figure 9 A 60 year-old man with a history of neoadjuvant chemoradiotherapy followed by transthoracic esophagectomy for a ypT2N1M0 adenocarcinoma of the distal third of the esophagus presented 6 months after surgery with dysphagia and a noted swelling in the cervical region. (a) Conventional CT was not able to clearly distinguish between normal postoperative changes or local recurrent disease at the cranial part of the gastric tube (*arrow*), but ^{18}F -FDG PET/CT showed intense ^{18}F -FDG uptake at the local site, highly suspected of local recurrence (*arrow*). Arrowheads in (a) and (b) indicate a surgical staple along the gastric tube. (c) CT revealed a large lymphadenopathy (*arrow*) in the left lower cervical region (level V), which in (d) showed high ^{18}F -FDG uptake on ^{18}F -FDG PET images. Cytologic examination of a fine needle aspiration of this node revealed recurrent metastatic adenocarcinoma.

Therefore, integrated ^{18}F -FDG PET/CT appears to be the most accurate modality for the detection of recurrent esophageal cancer (Figures 9 and 10).

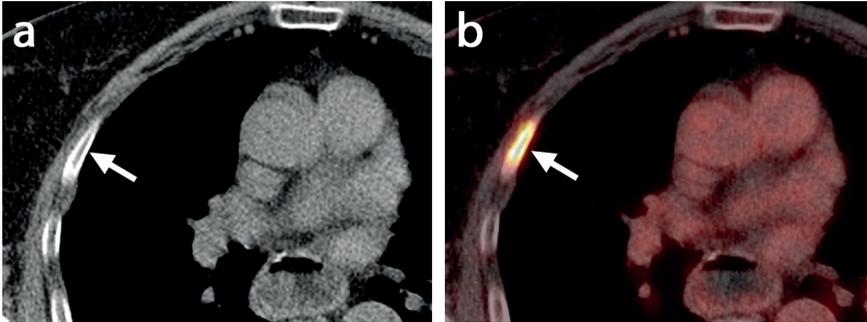


Figure 10 An example of a case demonstrating the incremental value of integrated ^{18}F -FDG PET/CT over standalone CT for the detection of distant recurrent disease after initial treatment with curative intent for esophageal cancer. A 71 year-old woman with a history of a ypT3N2 microscopically irradiated (R1) adenocarcinoma of the gastro-esophageal junction and a pathologic non-response to preoperative chemotherapy (Mandard 5) presented 18 months after surgery with painful complaints of the right anterior chest wall. (a) Initially a conventional CT was performed that could not provide any detection of recurrent disease or another explanation for the symptoms. (b) Subsequently, a ^{18}F -FDG PET/CT was performed revealing a pathologically increased ^{18}F -FDG uptake of the 4th right rib, fitting metastatic disease that could explain patient's complaints. *Note* - The stretched appearance of the costal ^{18}F -FDG uptake typically represents malignant disease rather than healing of a (recent or old) fracture.

MRI

The current available literature on the value of MRI for the detection of recurrent esophageal cancer is limited. One study comparing CT with conventional T2-weighted MRI concluded that MRI has a higher diagnostic accuracy than CT in differentiating local recurrence from fibrosis and detecting osseous metastases¹²⁶. A more recent study implemented DWI in the MRI protocol and found that recurrent lymph nodes show evident diffusion restriction with an accuracy of 81%¹²⁷. However, due to the lack of evidence and the introduction of integrated ^{18}F -FDG PET/CT with its excellent diagnostic accuracy for the detection of both loco-regional and distant recurrent disease, MRI seems to play no important role for this purpose in current or future practice.

CONCLUSION

¹⁸F-FDG PET/CT has emerged as a useful adjunct to conventional staging modalities in esophageal cancer and is of particular importance for the detection of unexpected distant metastases and recurrent disease. Current evidence for MRI is limited, but a future complementary role is expected in staging and radiation treatment planning based on first trials. The clinical role of ¹⁸F-FDG PET/CT and MRI in assessing response to treatment remains uncertain and will continue to evolve with ongoing research and more widespread application of these techniques.

REFERENCES

1. Wong R, Walker-Dilks C, Raifu A. Evidence-based guideline recommendations on the use of positron emission tomography imaging in oesophageal cancer. *Clin Oncol (R Coll Radiol)* 2012;24:86-104
2. Allum WH, Blazeby JM, Griffin SM, et al. Guidelines for the management of oesophageal and gastric cancer. *Gut* 2011;60:1449-72
3. van Westreenen HL, Heeren PA, van Dullemen HM, et al. Positron emission tomography with F-18-fluorodeoxyglucose in a combined staging strategy of esophageal cancer prevents unnecessary surgical explorations. *J Gastrointest Surg* 2005;9:54-61
4. Wallace MB, Nietert PJ, Earle C, et al. An analysis of multiple staging management strategies for carcinoma of the esophagus: computed tomography, endoscopic ultrasound, positron emission tomography, and thoracoscopy/laparoscopy. *Ann Thorac Surg* 2002;74:1026-32
5. Kato H, Miyazaki T, Nakajima M, et al. The incremental effect of positron emission tomography on diagnostic accuracy in the initial staging of esophageal carcinoma. *Cancer* 2005;103:148-56
6. Chowdhury FU, Bradley KM, Gleeson FV. The role of ¹⁸F-FDG PET/CT in the evaluation of oesophageal carcinoma. *Clin Radiol* 2008;63:1297-1309
7. Antoch G, Freudenberg LS, Beyer T, et al. To enhance or not to enhance? ¹⁸F-FDG and CT contrast agents in dual-modality ¹⁸F-FDG PET/CT. *J Nucl Med* 2004;45 Suppl 1:56S-65S
8. Bar-Shalom R, Guralnik L, Tsalic M, et al. The additional value of PET/CT over PET in FDG imaging of oesophageal cancer. *Eur J Nucl Med Mol Imaging* 2005;32:918-24
9. Yuan S, Yu Y, Chao KS, et al. Additional value of PET/CT over PET in assessment of locoregional lymph nodes in thoracic esophageal squamous cell cancer. *J Nucl Med* 2006;47:1255-9
10. Mesina CT, Boellaard R, van den Heuvel OA, et al. Effects of attenuation correction and reconstruction method on PET activation studies. *Neuroimage* 2003;20:898-908
11. Yamada I, Izumi Y, Kawano T, et al. Superficial esophageal carcinoma: an in vitro study of high-resolution MR imaging at 1.5T. *J Magn Reson Imaging* 2001;13:225-31
12. Yamada I, Izumi Y, Kawano T, et al. Esophageal carcinoma: evaluation with high-resolution three-dimensional constructive interference in steady state MR imaging in vitro. *J Magn Reson Imaging* 2006;24:1326-32
13. Riddell AM, Hillier J, Brown G, et al. Potential of surface-coil MRI for staging of esophageal cancer. *Am J Roentgenol* 2006;187:1280-7
14. Riddell AM, Allum WH, Thompson JN, et al. The appearances of oesophageal carcinoma demonstrated on high-resolution, T2-weighted MRI, with histopathological correlation. *Eur Radiol* 2007;17:391-9
15. Lever FM, Lips IM, Crijns SP, et al. Quantification of esophageal tumor motion on cine-magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* 2014;88:419-24

16. Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. *Am J Roentgenol* 2007;188:1622-35
17. Thoeny HC, Ross BD. Predicting and monitoring cancer treatment response with diffusion-weighted MRI. *J Magn Reson Imaging* 2010;32:2-16
18. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003;349:2241-52
19. Crane LM, Schaapveld M, Visser O, et al. Oesophageal cancer in The Netherlands: increasing incidence and mortality but improving survival. *Eur J Cancer* 2007;43:1445-51
20. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. *Lancet* 2013;381:400-12
21. Cheedella NK, Suzuki A, Xiao L, et al. Association between clinical complete response and pathological complete response after preoperative chemoradiation in patients with gastroesophageal cancer: analysis in a large cohort. *Ann Oncol* 2013;24:1262-6
22. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
23. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011;12:681-92
24. Rice TW, Blackstone EH. Esophageal cancer staging: past, present, and future. *Thorac Surg Clin* 2013;23:461-9
25. van Rossum PS, van Hillegersberg R, Lever FM, et al. Imaging strategies in the management of oesophageal cancer: what's the role of MRI? *Eur Radiol* 2013;23:1753-65
26. Flamen P. Positron emission tomography in gastric and esophageal cancer. *Curr Opin Oncol* 2004;16:359-63
27. Little SG, Rice TW, Bybel B, et al. Is FDG-PET indicated for superficial esophageal cancer? *Eur J Cardiothorac Surg* 2007;31:791-6
28. Cheung GS. Contribution of PET-CT in radiotherapy planning of oesophageal carcinoma: A review. *Radiography* 2013;19:259-69
29. Dehdashti F, Siegel BA. Neoplasms of the esophagus and stomach. *Semin Nucl Med* 2004;34:198-208
30. Bural GG, Kumar R, Mavi A, et al. Reflux esophagitis secondary to chemotherapy detected by serial FDG-PET. *Clin Nucl Med* 2005;30:182-3
31. Bhargava P, Reich P, Alavi A, et al. Radiation-induced esophagitis on FDG PET imaging. *Clin Nucl Med* 2003;28:849-50
32. Shrikanthan S, Aydin A, Dhurairaj T, et al. Intense esophageal FDG activity caused by Candida infection obscured the concurrent primary esophageal cancer on PET imaging. *Clin Nucl Med* 2005;30:695-7
33. Kamel EM, Thumshirn M, Truninger K, et al. Significance of incidental ¹⁸F-FDG accumulations in the gastrointestinal tract in PET/CT: correlation with endoscopic and histopathologic results. *J Nucl Med* 2004;45:1804-10
34. Bakheet SM, Amin T, Alia AG, et al. F-18 FDG uptake in benign esophageal disease. *Clin Nucl Med* 1999;24:995-7

- 3
35. Fukunaga T, Okazumi S, Koide Y, et al. Evaluation of esophageal cancers using fluorine-18-fluorodeoxyglucose PET. *J Nucl Med* 1998;39:1002-7
 36. Salavati A, Basu S, Heidari P, et al. Impact of fluorodeoxyglucose PET on the management of esophageal cancer. *Nucl Med Commun* 2009;30:95-116
 37. Munden RF, Macapinlac HA, Erasmus JJ. Esophageal cancer: the role of integrated CT-PET in initial staging and response assessment after preoperative therapy. *J Thorac Imaging* 2006;21:137-45
 38. Puli SR, Reddy JB, Bechtold ML, et al. Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. *World J Gastroenterol* 2008;14:1479-90
 39. Lowe VJ, Booya F, Fletcher JG, et al. Comparison of positron emission tomography, computed tomography, and endoscopic ultrasound in the initial staging of patients with esophageal cancer. *Mol Imaging Biol* 2005;7:422-30
 40. Rice TW. Clinical staging of esophageal carcinoma. CT, EUS, and PET. *Chest Surg Clin N Am* 2000;10:471-85
 41. van Zoonen M, van Oijen MG, van Leeuwen MS, et al. Low impact of staging EUS for determining surgical resectability in esophageal cancer. *Surg Endosc* 2012;26:2828-34
 42. Nakashima A, Nakashima K, Seto H, et al. Thoracic esophageal carcinoma: evaluation in the sagittal section with magnetic resonance imaging. *Abdom Imaging* 1997;22:20-3
 43. Sakurada A, Takahara T, Kwee TC, et al. Diagnostic performance of diffusion-weighted magnetic resonance imaging in esophageal cancer. *Eur Radiol* 2009;19:1461-9
 44. Wu LF, Wang BZ, Feng JL, et al. Preoperative TN staging of esophageal cancer: comparison of miniprobe ultrasonography, spiral CT and MRI. *World J Gastroenterol* 2003;9:219-24
 45. Takashima S, Takeuchi N, Shiozaki H, et al. Carcinoma of the esophagus: CT vs MR imaging in determining resectability. *Am J Roentgenol* 1991;156:297-302
 46. Petrillo R, Balzarini L, Bidoli P, et al. Esophageal squamous cell carcinoma: MRI evaluation of mediastinum. *Gastrointest Radiol* 1990;15:275-8
 47. Lerut T, Flamen P, Ectors N, et al. Histopathologic validation of lymph node staging with FDG-PET scan in cancer of the esophagus and gastroesophageal junction: A prospective study based on primary surgery with extensive lymphadenectomy. *Ann Surg* 2000;232:743-52
 48. van Westreenen HL, Westerterp M, Bossuyt PM, et al. Systematic review of the staging performance of ¹⁸F-fluorodeoxyglucose positron emission tomography in esophageal cancer. *J Clin Oncol* 2004;22:3805-12
 49. Heeren PA, Jager PL, Bongaerts F, van Dullemen H, Sluiter W, Plukker JT. Detection of distant metastases in esophageal cancer with ¹⁸F-FDG PET. *J Nucl Med* 2004;45:980-7
 50. Bruzzi JF, Munden RF, Truong MT, et al. PET/CT of esophageal cancer: its role in clinical management. *Radiographics* 2007;27:1635-52

51. Alper F, Turkyilmaz A, Kurtcan S, et al. Effectiveness of the STIR turbo spin-echo sequence MR imaging in evaluation of lymphadenopathy in esophageal cancer. *Eur J Radiol* 2011;80:625-8
52. Rankin SC, Taylor H, Cook GJ, et al. Computed tomography and positron emission tomography in the pre-operative staging of oesophageal carcinoma. *Clin Radiol* 1998;53:659-65
53. Choi JY, Lee KH, Shim YM, et al. Improved detection of individual nodal involvement in squamous cell carcinoma of the esophagus by FDG PET. *J Nucl Med* 2000;41:808-15
54. Yoon YC, Lee KS, Shim YM, et al. Metastasis to regional lymph nodes in patients with esophageal squamous cell carcinoma: CT versus FDG PET for presurgical detection prospective study. *Radiology* 2003;227:764-70
55. Kole AC, Plukker JT, Nieweg OE, et al. Positron emission tomography for staging of oesophageal and gastroesophageal malignancy. *Br J Cancer* 1998;78:521-7
56. Luketich JD, Friedman DM, Weigel TL, et al. Evaluation of distant metastases in esophageal cancer: 100 consecutive positron emission tomography scans. *Ann Thorac Surg* 1999;68:1133-6; discussion 1136-7
57. Meyers BF, Downey RJ, Decker PA, et al. The utility of positron emission tomography in staging of potentially operable carcinoma of the thoracic esophagus: results of the American College of Surgeons Oncology Group Z0060 trial. *J Thorac Cardiovasc Surg* 2007;133:738-45
58. Flamen P, Lerut A, Van Cutsem E, et al. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. *J Clin Oncol* 2000;18:3202-10
59. Flamen P, Lerut A, Van Cutsem E, et al. The utility of positron emission tomography for the diagnosis and staging of recurrent esophageal cancer. *J Thorac Cardiovasc Surg* 2000;120:1085-92
60. Yeung HW, Macapinlac HA, Mazumdar M, et al. FDG-PET in esophageal cancer. Incremental value over computed tomography. *Clin Positron Imaging* 1999;2:255-60
61. Imdahl A, Hentschel M, Kleimaier M, et al. Impact of FDG-PET for staging of esophageal cancer. *Langenbecks Arch Surg* 2004;389:283-8
62. Salahudeen HM, Balan A, Naik K, et al. Impact of the introduction of integrated PET-CT into the preoperative staging pathway of patients with potentially operable oesophageal carcinoma. *Clin Radiol* 2008;63:765-73
63. Duong CP, Hicks RJ, Weih L, et al. FDG-PET status following chemoradiotherapy provides high management impact and powerful prognostic stratification in esophageal cancer. *Eur J Nucl Med Mol Imaging* 2006;33:770-8
64. Bruzzi JE, Swisher SG, Truong MT, et al. Detection of interval distant metastases: clinical utility of integrated CT-PET imaging in patients with esophageal carcinoma after neoadjuvant therapy. *Cancer* 2007;109:125-34
65. Erasmus JJ, Munden RF. The role of integrated computed tomography positron-emission tomography in esophageal cancer: staging and assessment of therapeutic response. *Semin Radiat Oncol* 2007;17:29-37
66. Liberale G, Van Laethem JL, Gay F, et al. The role of PET scan in the preoperative management of esophageal cancer. *Eur J Surg Oncol* 2004;30:942-7

67. Weber WA, Ott K. Imaging of esophageal and gastric cancer. *Semin Oncol* 2004;31:530-41
68. Blom RL, Schreurs WM, Belgers HJ, et al. The value of post-neoadjuvant therapy PET-CT in the detection of interval metastases in esophageal carcinoma. *Eur J Surg Oncol* 2011;37:774-8
69. Cerfolio RJ, Bryant AS, Ohja B, et al. The accuracy of endoscopic ultrasonography with fine-needle aspiration, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy. *J Thorac Cardiovasc Surg* 2005;129:1232-41
70. Flamen P, Van Cutsem E, Lerut A, et al. Positron emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. *Ann Oncol* 2002;13:361-8
71. van Westreenen HL, Westerterp M, Jager PL, et al. Synchronous primary neoplasms detected on ¹⁸F-FDG PET in staging of patients with esophageal cancer. *J Nucl Med* 2005;46:1321-5
72. Kumagai Y, Kawano T, Nakajima Y, et al. Multiple primary cancers associated with esophageal carcinoma. *Surg Today* 2001;31:872-6
73. Agress H, Cooper BZ. Detection of clinically unexpected malignant and premalignant tumors with whole-body FDG PET: histopathologic comparison. *Radiology* 2004;230:417-22
74. Ishimori T, Patel PV, Wahl RL. Detection of unexpected additional primary malignancies with PET/CT. *J Nucl Med* 2005;46:752-7
75. Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet Oncol* 2007;8:797-805
76. Westerterp M, van Westreenen HL, Reitsma JB, et al. Esophageal cancer: CT, endoscopic US, and FDG PET for assessment of response to neoadjuvant therapy--systematic review. *Radiology* 2005;236:841-51
77. Westerterp M, Omloo JM, Sloof GW, et al. Monitoring of response to pre-operative chemoradiation in combination with hyperthermia in oesophageal cancer by FDG-PET. *Int J Hyperthermia* 2006;22:149-60
78. Weber WA, Ott K, Becker K, et al. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. *J Clin Oncol* 2001;19:3058-65
79. Wieder HA, Ott K, Lordick F, et al. Prediction of tumor response by FDG-PET: comparison of the accuracy of single and sequential studies in patients with adenocarcinomas of the esophagogastric junction. *Eur J Nucl Med Mol Imaging* 2007;34:1925-32
80. Wieder HA, Brucher BL, Zimmermann F, et al. Time course of tumor metabolic activity during chemoradiotherapy of esophageal squamous cell carcinoma and response to treatment. *J Clin Oncol* 2004;22:900-8
81. Ajani JA, Correa AM, Hofstetter WL, et al. Clinical parameters model for predicting pathologic complete response following preoperative chemoradiation in patients with esophageal cancer. *Ann Oncol* 2012;23:2638-42

82. Piessen G, Petyt G, Duhamel A, et al. Ineffectiveness of ¹⁸F-fluorodeoxyglucose positron emission tomography in the evaluation of tumor response after completion of neoadjuvant chemoradiation in esophageal cancer. *Ann Surg* 2013;258:66-76
83. Erasmus JJ, Munden RF, Truong MT, et al. Preoperative chemo-radiation-induced ulceration in patients with esophageal cancer: a confounding factor in tumor response assessment in integrated computed tomographic-positron emission tomographic imaging. *J Thorac Oncol* 2006;1:478-86
84. van Heijl M, Omluo JM, van Berge Henegouwen MI, et al. Fluorodeoxyglucose positron emission tomography for evaluating early response during neoadjuvant chemoradiotherapy in patients with potentially curable esophageal cancer. *Ann Surg* 2011;253:56-63
85. Yuan ST, Brown RK, Zhao L, et al. Timing and intensity of changes in FDG uptake with symptomatic esophagitis during radiotherapy or chemo-radiotherapy. *Radiat Oncol* 2014;9:37
86. Hautzel H, Muller-Gartner HW. Early changes in fluorine-18-FDG uptake during radiotherapy. *J Nucl Med* 1997;38:1384-6
87. Ott K, Weber WA, Lordick F, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. *J Clin Oncol* 2006;24:4692-8
88. Hsu PK, Chien LI, Huang CS, et al. Comparison of survival among neoadjuvant chemoradiation responders, non-responders and patients receiving primary resection for locally advanced oesophageal squamous cell carcinoma: does neoadjuvant chemoradiation benefit all? *Interact Cardiovasc Thorac Surg* 2013;17:460-6
89. Chen YM, Pan XF, Tong LJ, et al. Can ¹⁸F-fluorodeoxyglucose positron emission tomography predict responses to neoadjuvant therapy in oesophageal cancer patients? A meta-analysis. *Nucl Med Commun* 2011;32:1005-10
90. Kwee RM. Prediction of tumor response to neoadjuvant therapy in patients with esophageal cancer with use of ¹⁸F FDG PET: a systematic review. *Radiology* 2010;254:707-17
91. Nakamura R, Obara T, Katsuragawa S, et al. Failure in presumption of residual disease by quantification of FDG uptake in esophageal squamous cell carcinoma immediately after radiotherapy. *Radiat Med* 2002;20:181-6
92. Piessen G, Messenger M, Mirabel X, et al. Is there a role for surgery for patients with a complete clinical response after chemoradiation for esophageal cancer? An intention-to-treat case-control study. *Ann Surg* 2013;258:793-9; discussion 799-800
93. Lambrecht M, Vandecaveye V, De Keyzer F, et al. Value of diffusion-weighted magnetic resonance imaging for prediction and early assessment of response to neoadjuvant radiochemotherapy in rectal cancer: preliminary results. *Int J Radiat Oncol Biol Phys* 2012;82:863-70
94. Aoyagi T, Shuto K, Okazumi S, et al. Apparent diffusion coefficient values measured by diffusion-weighted imaging predict chemoradiotherapeutic effect for advanced esophageal cancer. *Dig Surg* 2011;28:252-7
95. Aoyagi T, Shuto K, Okazumi S, et al. Evaluation of the clinical staging of esophageal cancer by using diffusion-weighted imaging. *Exp Ther Med* 2010;1:847-51

96. De Cobelli F, Giganti F, Orsenigo E, et al. Apparent diffusion coefficient modifications in assessing gastro-oesophageal cancer response to neoadjuvant treatment: comparison with tumour regression grade at histology. *Eur Radiol* 2013;23:2165-74
97. Imanishi S, Shuto K, Aoyagi T, et al. Diffusion-weighted magnetic resonance imaging for predicting and detecting the early response to chemoradiotherapy of advanced esophageal squamous cell carcinoma. *Dig Surg* 2013;30:240-8
98. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-47
99. University Medical Center Utrecht. Preoperative identification of response to neoadjuvant chemoradiotherapy for esophageal cancer (PRIOR). Available from: <http://clinicaltrials.gov/show/NCT02125448>, NLM Identifier: NCT02125448
100. Blom RL, Steenbakkers IR, Lammering G, et al. PET/CT-based metabolic tumour volume for response prediction of neoadjuvant chemoradiotherapy in oesophageal carcinoma. *Eur J Nucl Med Mol Imaging* 2013;40:1500-6
101. Njeh CF. Tumor delineation: The weakest link in the search for accuracy in radiotherapy. *J Med Phys* 2008;33:136-40
102. Sillah K, Williams LR, Laasch HU, et al. Computed tomography overestimation of esophageal tumor length: Implications for radiotherapy planning. *World J Gastrointest Oncol* 2010;2:197-204
103. Mamede M, El Fakhri G, Abreu-e-Lima P, et al. Pre-operative estimation of esophageal tumor metabolic length in FDG-PET images with surgical pathology confirmation. *Ann Nucl Med* 2007;21:553-62
104. Vinjamuri S, Ray S. Added value of PET and PET-CT in oesophageal cancer: a review of current practice. *Nucl Med Commun* 2008;29:4-10
105. Vrieze O, Haustermans K, De Wever W, et al. Is there a role for FGD-PET in radiotherapy planning in esophageal carcinoma? *Radiother Oncol* 2004;73:269-75
106. Moureau-Zabotto L, Touboul E, Lerouge D, et al. Impact of CT and ¹⁸F-deoxyglucose positron emission tomography image fusion for conformal radiotherapy in esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 2005;63:340-5
107. Muijs CT, Schreurs LM, Busz DM, et al. Consequences of additional use of PET information for target volume delineation and radiotherapy dose distribution for esophageal cancer. *Radiother Oncol* 2009;93:447-53
108. Muijs CT, Beukema JC, Pruijm J, et al. A systematic review on the role of FDG-PET/CT in tumour delineation and radiotherapy planning in patients with esophageal cancer. *Radiother Oncol* 2010;97:165-71
109. Vesprini D, Ung Y, Dinniwell R, et al. Improving observer variability in target delineation for gastro-oesophageal cancer--the role of (18F)fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography. *Clin Oncol (R Coll Radiol)* 2008;20:631-8
110. Schreurs LM, Busz DM, Paardekooper GM, et al. Impact of 18-fluorodeoxyglucose positron emission tomography on computed tomography defined target volumes in radiation treatment planning of esophageal cancer: reduction in geographic misses with equal inter-observer variability: PET/CT improves esophageal target definition. *Dis Esophagus* 2010;23:493-501

111. Lambrecht M, Dirix P, Vandecaveye V, et al. Role and value of diffusion-weighted MRI in the radiotherapeutic management of head and neck cancer. *Expert Rev Anticancer Ther* 2010;10:1451-9
112. Sander L, Langkilde NC, Holmberg M, et al. MRI target delineation may reduce long-term toxicity after prostate radiotherapy. *Acta Oncol* 2014;53:809-14
113. Wang YY, Zhe H. Clinical application of multimodality imaging in radiotherapy treatment planning for rectal cancer. *Cancer Imaging* 2013;13:495-501
114. Dimopoulos JC, Petrow P, Tanderup K, et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): Basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy. *Radiother Oncol* 2012;103:113-22
115. Hou DL, Shi GF, Gao XS, et al. Improved longitudinal length accuracy of gross tumor volume delineation with diffusion weighted magnetic resonance imaging for esophageal squamous cell carcinoma. *Radiat Oncol* 2013;8:169.
116. Lagendijk JJ, Raaymakers BW, Raaijmakers AJ, et al. MRI/linac integration. *Radiother Oncol* 2008;86:25-9
117. Raaymakers BW, Lagendijk JJ, Overweg J, et al. Integrating a 1.5 T MRI scanner with a 6 MV accelerator: proof of concept. *Phys Med Biol* 2009;54:N229-37
118. Guo H, Zhu H, Xi Y, et al. Diagnostic and prognostic value of ¹⁸F-FDG PET/CT for patients with suspected recurrence from squamous cell carcinoma of the esophagus. *J Nucl Med* 2007;48:1251-8
119. Kato H, Miyazaki T, Nakajima M, et al. Value of positron emission tomography in the diagnosis of recurrent oesophageal carcinoma. *Br J Surg* 2004;91:1004-9
120. Sharma P, Jain S, Karunanithi S, et al. Diagnostic accuracy of ¹⁸F-FDG PET/CT for detection of suspected recurrence in patients with oesophageal carcinoma. *Eur J Nucl Med Mol Imaging* 2014;41:1084-92
121. Sun L, Su XH, Guan YS, et al. Clinical usefulness of ¹⁸F-FDG PET/CT in the restaging of esophageal cancer after surgical resection and radiotherapy. *World J Gastroenterol* 2009;15:1836-42
122. Jain S, Sharma P, Jain T, et al. ¹⁸F-FDG PET-CT for detection of suspected recurrence in patients with esophageal carcinoma: Single institutional experience. *Eur J Nucl Med Mol Imaging* 2012;39:S573
123. You JJ, Inculet RI, Sukhbinder KD, et al. Positron emission tomography/computed tomography (PET/CT) for the diagnosis of recurrent cancer (PETREC): A multicenter, prospective cohort study. *J Clin Oncol* 2012;30.
124. Shirakawa Y, Tanabe S, Fujiwara Y, et al. The transition of therapy for recurrent esophageal cancer by PET-CT. *Jpn J Cancer Chemother* 2009;36:2465-7
125. Teyton P, Metges JP, Atmani A, et al. Use of positron emission tomography in surgery follow-up of esophageal cancer. *J Gastrointest Surg* 2009;13:451-8
126. Kantarci M, Polat P, Alper F, et al. Comparison of CT and MRI for the diagnosis recurrent esophageal carcinoma after operation. *Dis Esophagus* 2004;17:32-7
127. Shuto K, Saito H, Ohira G, et al. Diffusion-weighted MR imaging for postoperative nodal recurrence of esophageal squamous cell cancer in comparison with FDG-PET. *Gan To Kagaku Ryoho* 2009;36:2468-70



Chapter 4

The emerging field of radiomics in esophageal cancer: current evidence and future potential

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Translational Cancer Research 2016 [In press]

ABSTRACT

‘Radiomics’ is the name given to the emerging field of extracting additional information from standard medical images using advanced feature analysis. This innovative form of quantitative image analysis appears to have future potential for clinical practice in patients with esophageal cancer by providing an additional layer of information to the standard imaging assessment. There is a growing body of evidence suggesting that radiomics may provide incremental value for staging, predicting treatment response, and predicting survival in esophageal cancer, for which the current work-up has substantial limitations. This review outlines the available evidence and future potential for the application of radiomics in the management of patients with esophageal cancer. In addition, an overview of the current evidence on the importance of reproducibility of image features and the substantial influence of varying smoothing scales, quantization levels, and segmentation methods is provided.

INTRODUCTION

Esophageal cancer continues to affect more than 450,000 people worldwide, making it the eighth most common malignancy and the sixth leading cause of cancer-related mortality¹. Despite recent improvements in staging, multimodality treatment, and perioperative care, it remains a devastating disease with a 5-year overall survival rate of 15-25%¹⁻³. Best outcomes are achieved in patients with early carcinoma of the esophagus for which endoscopic mucosal (or submucosal) resection with or without local ablative techniques is now more extensively employed, associated with 5-year survival rates of 60-80%^{4,5}. Recently, prognosis of locally advanced esophageal cancer has been markedly improved from a 5-year overall survival rate of 23-34% with surgery alone, to 36-47% with the addition of neoadjuvant chemoradiotherapy (nCRT) or perioperative chemotherapy⁶⁻⁸. Due to the late onset of symptoms, the majority of patients present at an advanced stage with unresectable or metastatic disease, for which concurrent chemoradiotherapy (CRT) and combination chemotherapy are considered the best palliative options, respectively⁹⁻¹¹.

Current diagnostic work-up consists of endoscopy with biopsy for histopathologic confirmation of the diagnosis and endoscopic ultrasound (EUS) for determination of the local tumor extent (T-stage) and regional lymph node involvement (N-stage)^{12,13}. Integrated ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET)/computed tomography (CT) is also used for N-staging, and particularly important for the detection of distant metastasis (M-stage)¹⁴⁻¹⁶. In addition, ¹⁸F-FDG PET/CT is increasingly applied for the detection of interval metastasis after (neoadjuvant) treatment as well as for follow-up after treatment with curative intent¹⁷⁻²⁰. Unfortunately, these modalities all have their limitations regarding three clinically relevant areas that are in need of improvement, including staging, prediction of response to treatment, and prediction of survival.

It is increasingly recognized that the amount of information currently extracted from available images may be substantially enhanced by quantitative imaging analysis²¹. The emerging field of 'radiomics' focuses on these improvements of image analysis by extracting large amounts of quantitative image features from volumes of interest on medical images²¹. Radiomics approaches can extract more information from medical images by post-processing techniques including quantification of the heterogeneity within a tumor, which is a well-recognized feature of malignancy associated with adverse tumor biology²². Substantial spatial heterogeneity in metabolism, vasculature, oxygenation, and gene expression is often

4 found in malignant tumors, which relates to chemoradiation-resistance and poor prognosis²³⁻²⁶. As such, it has been hypothesized that image-based quantification of tumor heterogeneity –through its relation with biologic tumor characteristics– may provide important information for staging, predicting response to treatment, and predicting prognosis in cancer patients^{21,22,27,28}. Indeed, growing evidence suggests that image analysis of tumor heterogeneity could be useful in several cancer types²⁹⁻³⁴.

The innovative field of radiomics could provide opportunities in the management of patients with esophageal cancer for improvements in staging, predicting treatment response, and predicting survival. The aim of this review is to outline the current evidence and future potential for the application of radiomics in patients with esophageal cancer.

TEXTURE FEATURES ANALYSIS

Both CT and ¹⁸F-FDG PET images are of particular interest when considering quantitative analysis in esophageal tumors, since these modalities are routinely used in clinical practice. CT images are mostly used to extract morphologic information of esophageal tumors, but recent studies suggest that quantitative image features can provide additional information^{22,35,36}. Most ¹⁸F-FDG PET studies in esophageal cancer quantify metabolic tumor activity solely by using the maximum standardized uptake value (SUV_{max})^{37,38}. However, extracted from a single voxel, SUV_{max} does not characterize the total activity nor heterogeneity of the ¹⁸F-FDG uptake for the entire tumor^{39,40}. Recent studies suggest that spatial image information, such as metabolic tumor volume (MTV), total lesion glycolysis (TLG), tumor shape, and texture features, provide more useful information than SUV_{max} ^{27,41-44}.

TEXTURE FEATURES

Among the studied CT and ¹⁸F-FDG PET quantitative image parameters, texture features are most informative on tumor heterogeneity, and thought to be most closely related to underlying physiologic processes such as vascularization, perfusion, cellular proliferation, and hypoxia^{36,45}. Texture is defined as a spatial arrangement of voxels allowing extraction of complex image properties^{27,45}. Different approaches can be used to quantify tumor texture, including model-based fractal analysis and statistic-based methods⁴⁶. Model-based fractal analysis methods describe the complexity of an object by identifying the property of self-

similarity and roughness of a surface at different levels, and have so far only been described twice in esophageal tumors^{47,48}. Statistic-based approaches have been most widely used for texture analysis in (esophageal) oncology, and are based on the distribution and spatial relationship of voxel intensity values within an image⁴⁶.

Within the statistic-based approaches, first-order statistics represent texture on a global scale calculated from the original voxel intensity values without taking the spatial relationship between voxels into account (e.g. mean, median, percentiles, quartiles, range, interquartile range, standard deviation [SD], coefficient of variation [COV], skewness, kurtosis)⁴⁸. Second-order statistics represent texture on a local scale and measure co-occurrence of voxel pairs using grey-level co-occurrence matrices (GLCM; e.g. entropy, energy, homogeneity, contrast/inertia, correlation, dissimilarity)²⁸. Higher-order statistics capture properties of three or more voxels occurring at specific locations relative to each other, and represent regional texture extracted from grey-level run length matrices (GLRLM; e.g. high/low grey-level run emphasis, run percentage), grey-level size zone matrices (GLSZM; e.g. high/low intensity zone emphasis, zone percentage), or local texture extracted from neighborhood gray-tone difference matrices (NGTDM; e.g. coarseness, busyness, texture strength, complexity)^{28,48,49}.

REPRODUCIBILITY

An overview of studies reporting on the reproducibility and precision of image texture features in esophageal cancer is provided in **Table 1**. Two studies (in ¹⁸F-FDG PET) have demonstrated that only a limited number of texture features are reproducible with respect to physiologic variability as assessed on double baseline scans^{45,49}. A French study acquired double baseline ¹⁸F-FDG PET scans within 2-7 days of each other on the same scanner in 16 esophageal cancer patients and reported that the most reproducible features were local entropy, local homogeneity, regional intensity variability, and regional size-zone variability⁴⁵. Similarly, a study from the US including 7 patients who underwent double baseline ¹⁸F-FDG PET scanning within 11-42 days of each other on scanners from different institutions found that the reproducibility was good for (local) second-order and regional higher-order features, but poor for local higher-order features⁴⁹. Although the two studies have small samples, these results suggest that only a certain amount of texture features may be used in further research, and other features with poor reproducibility should be abandoned as results will likely not be generalizable. Similar findings were observed in a study that found good reproducibility of some texture features but poor reproducibility for others when acquisition modes and

Table 1 Studies on robustness or reproducibility of image features analysis in esophageal cancer

| Study | n | Histology (AC/SCC) | Tumor stage | Treatment | Imaging modality | Imaging timing | Image parameters | Outcome |
|-----------------------------|----|--------------------|-------------|--|-------------------------|-----------------|--|--|
| CT | | | | | | | | |
| Ganeshan 2012 ²² | 21 | 14/7 | II-IV | NR | Un-enhanced CT | Baseline | - Entropy, uniformity - 6 smoothing scales | Influence of varying smoothing scales on entropy and uniformity |
| PET | | | | | | | | |
| Tixier 2011 ²⁷ | 41 | 10/31 | I-IV | dCRT | ¹⁸ F-FDG PET | Baseline | - 7 intensity and 31 texture features - 4 quantization levels | Influence of varying quantization levels on texture features |
| Tixier 2012 ⁴⁵ | 16 | NR | NR | NR | ¹⁸ F-FDG PET | Double baseline | - 8 global, 11 regional, and 6 local texture features - 5 quantization levels | Test-retest reproducibility of texture features |
| Hatt 2013 ⁵⁴ | 50 | 14/36 | I-IV | dCRT | ¹⁸ F-FDG PET | Baseline | - 10 texture features - 3 segmentation methods - With and without PVC | Influence of varying segmentation methods and PVC on texture features |
| Dong 2015 ⁴⁰ | 50 | 0/50 | I-IV | Surgery ± adjuvant ChTx/RT or dCRT or ChTx | ¹⁸ F-FDG PET | Baseline | - Visual heterogeneity score, coefficient of variation of SUV, and entropy - 4 segmentation methods | Influence of tumor heterogeneity on delineated tumor volume using different segmentation methods |
| Doumou 2015 ⁴⁷ | 64 | 64/0 | NR | NR | ¹⁸ F-FDG PET | Baseline | - 57 texture features - 5 smoothing values - 4 segmentation methods - 5 quantization levels | Influence of varying smoothing values, segmentation methods, and quantization levels on texture features |

Table 1 (continued)

| Study | n | Histology (AC/SCC) | Tumor stage | Treatment | Imaging modality | Imaging timing | Image parameters | Outcome |
|-------------------------------|-----|--------------------|-------------|---|-------------------------|--|--|--|
| Hatt 2015 ⁵¹ | 112 | 63/49 | I-III | dCRT (39%) or nCRT ^{18F} -FDG PET + Surgery (61%) | ^{18F} -FDG PET | Baseline | - MTV, entropy, dissimilarity, HILAE, and zone percentage - 2 calculation methods (for entropy, dissimilarity) - 7 quantization levels | Influence of varying calculation methods and quantization levels on correlation between MTV and texture features |
| van Rossum 2016 ⁴⁹ | 217 | 217/0 | II-III | nCRT + Surgery (36% ^{18F} -FDG PET ChTx before nCRT) | ^{18F} -FDG PET | Double baseline (in 7 of 217 patients) | - 69 texture and 12 geometry features - 2 baseline scans at different institutions | Test-retest reproducibility of texture and geometry features (in 7 of 217 patients) |
| Yip 2016 ⁵³ | 45 | 44/1 | I-IV | nCRT + Surgery | ^{18F} -FDG PET | Baseline + after nCRT | - MTV, entropy, SRHIE, and SZHIE - 3 quantization levels - 11 registration algorithms for propagated post-treatment contours | Influence of varying quantization levels and propagated post-treatment contours on MTV and texture |

^{18F}-FDG: ^{18F}-fluorodeoxyglucose. AC: adenocarcinoma. ChTx: chemotherapy. CT: computed tomography. dCRT: definitive chemoradiotherapy. HILAE: high-intensity large-area emphasis. MTV: metabolic tumor volume. nCRT: neoadjuvant chemoradiotherapy. NR: not reported. RT: radiotherapy. PET: positron emission tomography. PVC: partial volume correction. SCC: squamous cell carcinoma. SRHIE: short-run high-intensity emphasis. SUV: standardized uptake value. SZHIE: short-zone high-intensity emphasis.

4 reconstruction parameters were varied in ^{18}F -FDG PET scans of 20 solid tumors⁵⁰. To this regard, additional investigation of reproducibility should be encouraged to move this field forward.

INFLUENCE OF SMOOTHING

Besides reproducibility, it is also important that similar measurements from the scan data are obtained when changing parameters such as smoothing, quantization, and segmentation. The ability of texture features to stay similar across variation of these parameters is often referred to as the 'precision' of texture features⁴⁷. Particularly in CT images, different scales of smoothing (i.e. image filtration) using Laplacian of Gaussian spatial band-pass filters are of importance to be able to reduce image noise and highlight different anatomical spatial scales from fine to medium and coarse texture within the tumor^{22,35}. Commonly used filter values for smoothing are 1.0 (highlighting fine textures, which may enhance tissue parenchymal features), 1.5-2.0 (highlighting medium textures), and 2.5 (highlighting coarse textures, which may enhance vascular features)³⁵. A British study in 21 patients showed that CT-based texture features (entropy and uniformity) were influenced by the level of smoothing and significantly associated with tumor stage and survival only after smoothing²².

INFLUENCE OF QUANTIZATION

In both CT and ^{18}F -FDG PET image post-processing, quantization (i.e. resampling) refers to the important process of resampling the Hounsfield (HU) or SUV levels in the image to a certain number of bins. Choosing the number of bins is a trade-off between gaining texture information accuracy with reduced noise effects (using less bins) and gaining amount of texture information (using more bins). Hence, quantization may influence texture features measurements^{47,51}. A recent study in 35 lung cancer patients indeed found that the manner of SUV quantization had a crucial effect on the resulting texture features and their interpretation, emphasizing the importance of standardized methodology in texture analysis⁵². The most common quantization method includes the use of a fixed number of discrete bins (e.g. 8, 16, 32, 64, 128 bins) to divide the image SUV range into equally spaced intervals resulting in discretized images with varying bin sizes depending on the SUV range⁵². However, this method appeared less appropriate for inter- and intra-patient comparison of texture features in a clinical setting than an alternative method that resamples the SUVs with a fixed bin size in units of SUV (e.g. 0.1, 0.5), maintaining a constant intensity resolution across all images⁵².

A French group showed in 12 esophageal tumors that texture features describing local tumor heterogeneity were insensitive to 5 different quantization values using a fixed number of bins (i.e. 8, 16, 32, 64, or 128 bins), while several regional features were sensitive to the chosen quantization value⁴⁵. The same authors described a multi-center series of 555 patients with different types of cancer (including 112 esophageal cancer patients) in which they found that significant texture details are lost when using a quantization of less than 32 bins⁵¹. Also, a higher potential for providing complementary information of texture features (i.e. a lower correlation) with respect to MTV was found using 64 rather than 32 bins⁵¹. A study from the US reported in a series of 45 patients that the value of texture features for predicting response to nCRT was highest when a quantization level of 128 was chosen⁵³. A British study in 64 patients found that 51 of 57 studied texture features showed poor agreement across varying quantization levels with a fixed number of bins (i.e. 8, 16, 32, 64, 128 bins), which stresses the need for further evaluation and standardization of quantization in future studies⁴⁷. So far, no studies in esophageal cancer patients reported on the influence of varying quantization using a fixed bin size rather than a fixed number of bins.

INFLUENCE OF SEGMENTATION

Accurate segmentation (i.e. contouring) of the tumor volume is crucial for computing texture features^{40,47,54}. Many segmentation methods have been proposed including manual delineation, fixed or adaptive thresholding, and multiple (semi-)automatic algorithms, but no consensus seems to emerge^{55,56}. Most popular segmentation methods in esophageal cancer literature include manual contouring^{35,36,40,53,57}, thresholding methods capturing aligned voxels with SUV values of ≥ 2.5 ^{39,40,57-59} or with values $\geq 30\%$ - 60% of the maximum intensity or grey-level^{22,40,47,48,54}, semi-automatic gradient-based contouring⁴⁹, and an automatic fuzzy locally adaptive Bayesian (FLAB) method^{27,45,51,54}.

Tumor heterogeneity is one of the most important factors influencing the results of different segmentation methods⁴⁰. A group from China recently demonstrated in 50 patients with esophageal squamous cell carcinoma that in tumors with a large size and high ¹⁸F-FDG uptake heterogeneity, large differences in delineated tumor volume across various manual and thresholding segmentation methods existed⁴⁰. More specifically, these authors suggest that in large or highly heterogeneous tumors one must be cautious to use frequently applied and relatively simple threshold-based segmentation methods⁴⁰. Similarly, a French study (n=50) demonstrated that thresholding methods and automatic FLAB contouring led to substantially different

4 functional volumes, significantly affecting some texture features (e.g. dissimilarity, size-zone variability), while not affecting others (e.g. entropy, homogeneity, zone percentage)⁵⁴. A British study (n=64) found that varying the relative threshold (45%, 50%, 55%, or 60% of SUV_{max}) resulted in moderate agreement in second-order (regional) features, but in poor agreement in higher-order (regional and local) features⁴⁷. Besides the high sensitivity to tumor heterogeneity, thresholding techniques are also sensitive to motion artifacts, noise and contrast variations, leading to disappointing results for small and non-spherical tumors^{55,56}. Manual delineation is easy to apply, but time-consuming, susceptible to window-level settings, suffering from intra- and inter-observer variability, and results strongly depend on experience of the reader⁵⁵. In general, (semi-)automatic segmentation methods are able to provide superior accuracy, reproducibility, and robustness for tumor volume contouring compared with manual and thresholding methods, and should therefore be preferred^{60,61}.

INFLUENCE OF TUMOR VOLUME

Several texture features have appeared highly correlated with esophageal tumor volume suggesting a certain level of dependency^{49,51}. When high correlations between parameters exist, an added contribution over each other is unlikely. As such, the previously mentioned French series of 555 patients with different types of cancer (including 112 esophageal cancer patients) found that the complementary information of tumor volume and heterogeneity increased substantially with larger tumors⁵¹. In fact, added value of texture features over tumor volume alone for outcome prediction was found in tumors $\geq 10\text{cm}^3$ only⁵¹. However, instead of excluding tumors smaller than 10cm^3 in future texture studies, they recommended that the correlation of texture features and tumor volume should always be reported to show whether texture and volume provide independent or redundant information⁵¹.

STAGING

Accurate tumor staging is crucial for determining prognosis and treatment decision-making in individual patients. EUS is the current modality of choice for primary tumor staging, with reported accuracies for distinguishing T-stages of 53-94% (median, 83%) and better performance in advanced compared to early disease^{62,63}. Disadvantages of EUS include the invasiveness of the technique, a failure rate of 14-25% due to stenotic tumors preventing passage of the endoscope, and the strong dependence of diagnostic performance on the experience of

the endoscopist⁶⁴⁻⁶⁶. CT is inferior to EUS in the evaluation of T-stage, but CT is useful for predicting surgical resectability by excluding tumors that show ingrowth into surrounding structures^{65,67}. Regional lymph node involvement is generally evaluated using EUS (sensitivity 80%, specificity 70%), CT (sensitivity 50%, specificity 83%), and ¹⁸F-FDG PET (sensitivity 51%, specificity 84%)^{68,69}. For the detection of distant metastasis, ¹⁸F-FDG PET provides additional diagnostic information over CT in 5-28% of patients at initial presentation¹⁴. Clearly, current clinical staging is suboptimal and in need of improvement⁷⁰.

RADIOMICS

Three studies (1 using CT and 2 using ¹⁸F-FDG PET) reported on the potential value of texture features analysis for staging in esophageal cancer (**Table 2**)^{22,58,59}. A British study (n=21) related two tumor heterogeneity features on unenhanced CT (entropy and uniformity) on 6 different smoothing scales (fine to coarse details) to the clinical American Joint Committee on Cancer (AJCC) stage based on ¹⁸F-FDG PET, CT, and EUS²¹. They found that tumor heterogeneity was significantly greater in patients with clinical stage III-IV compared to stage II²¹. However, the potential additional value of texture features beyond conventional staging could not be studied as conventional staging was considered the reference standard and no comparison with pathologic tumor stage was performed.

A group from China (n=20) correlated ¹⁸F-FDG PET-based SUV_{max} , entropy, and energy before surgery with pathologic AJCC-stage, T-stage, and N-stage⁷¹. Most of the studied correlations were weak to moderate only, with the exception of two strong correlations (AJCC-stage and entropy, Spearman's $r=0.63$; T-stage and entropy, Spearman's $r=0.69$)⁵⁸. Similar to the British study²², higher clinical stage and node-positive tumors were associated with increased tumor heterogeneity (i.e. higher entropy)⁵⁸. In ROC curve analysis, an entropy value above 4.7 yielded a sensitivity of 78% and specificity of 73% for predicting pathologic AJCC-stage III as opposed to stage I-II⁵⁸. Unfortunately, a multivariable analysis to determine the potential incremental value of the entropy value to predict pathologic stage beyond conventional staging modalities (e.g. EUS, CT) was not performed⁵⁸.

Another Chinese study included 36 patients who underwent both ¹⁸F-FDG and ¹⁸F-fluorothymidine (¹⁸F-FLT) PET, and compared the performance of 2 intensity, 2 geometry, and 5 texture features of both modalities for staging with pathologic AJCC-stage, T-stage, and N-stage as reference⁵⁹. They found that ¹⁸F-FDG PET features showed more significant associations with pathologic AJCC-stage and

Table 2 Studies on the value of image features analysis for staging in esophageal cancer

| Study | n | Histology (AC/SCC) | Tumor stage | Treatment | Imaging modality | Imaging timing | Image parameters | Outcome |
|-----------------------------|----|--------------------|-------------|---------------|---|----------------|---|--|
| CT | | | | | | | | |
| Ganeshan 2012 ²² | 21 | 14/7 | II-IV | NR | Un-enhanced CT | Baseline | - Entropy, uniformity - 6 smoothing scales | Clinical AJCC stage (PET-, CT-, and EUS-based) |
| PET | | | | | | | | |
| Dong 2013 ⁵⁸ | 40 | 0/40 | I-III | Surgery alone | ¹⁸ F-FDG PET | Baseline | - SUV _{max} , entropy, energy | Pathologic AJCC stage, T-stage, and N-stage |
| Ma 2015 ⁵⁹ | 36 | 0/36 | I-III | Surgery alone | ¹⁸ F-FDG PET and ¹⁸ F-FLT PET | Baseline | - SUV _{max} , SUV _{mean} , entropy, angular second moment, contrast, correlation, inverse differential moment, tumor length, eccentricity | Pathologic AJCC stage, T-stage, and N-stage |

¹⁸F-FDG: ¹⁸F-fluorodeoxyglucose. ¹⁸F-FLT: ¹⁸F-fluorothymidine. AC: adenocarcinoma. AJCC: American Joint Committee on Cancer. CT: computed tomography. EUS: endoscopic ultrasound. NR: not reported. PET: positron emission tomography. SCC: squamous cell carcinoma. SUV: standardized uptake value.

TN-stage than ^{18}F -FLT PET features⁵⁹. Interestingly, SUV_{max} , tumor length, and eccentricity appeared more important than the studied texture features (e.g. entropy, correlation, contrast) for staging⁵⁹. Unfortunately, ROC curve analysis and multivariable analysis adjusting for conventional staging modalities were lacking, impairing proper interpretation of potential added value in clinical practice⁵⁹.

PREDICTION OF TREATMENT RESPONSE

Esophageal tumors tend to respond differently to neoadjuvant chemo(radio) therapy or definitive CRT. Adenocarcinomas demonstrate a pathologic complete response (pCR; i.e. complete disappearance of viable tumor cells) to chemotherapy or CRT in 8-9% or 23-28% of patients, respectively^{6,72,73}, whereas squamous cell carcinomas have a pCR rate of 49% after CRT⁶. A pCR is associated with favorable disease-free and overall survival rates, and it has been speculated that accurate identification of pCR prior to surgery could yield an organ-preserving approach avoiding unnecessary surgical morbidity⁷⁴⁻⁷⁶. On the other hand, it is likely that non-responders to CRT (18-25%) or to chemotherapy (44-58%) are harmed by the toxicity of these therapies without prognostic benefit^{6,8,77,78}. Early identification of non-responders before or during treatment would be beneficial for this group as ineffective therapy could be modified or discontinued (advancing surgery without detrimental delay in the curative setting)⁷⁹.

Several diagnostic strategies have been proposed to predict response to treatment in esophageal cancer. The Response Evaluation Criteria in Solid Tumors (RECIST) method is often used for pre- and post-treatment CT scanning in the evaluation of response, but yields a poor sensitivity (33-55%) and moderate specificity (50-71%) for pathologic response⁸⁰. In fact, RECIST did not demonstrate any correlation with treatment response nor prognosis in a recent study in patients with esophageal cancer⁸¹. Post-treatment endoscopic biopsy has a high specificity (91%), but poor sensitivity (35%) for detecting residual cancer, whereas EUS after treatment yields a high sensitivity (96%), but very low specificity (11%)⁸². Sequential ^{18}F -FDG PET-based SUV measurements are able to predict treatment response with a moderate sensitivity (67%) and specificity (68%)³⁷. In addition, some clinical parameters have been repeatedly found to yield minor –but independent– predictive ability for treatment response (i.e. gender, clinical T-stage, and histologic differentiation grade)^{49,76,83}. Unfortunately, so far even combinations of modalities and clinical parameters do not yield sufficient predictive ability for pathologic response to guide treatment decision-making in routine clinical practice, and a tool with improved accuracy is highly desired^{37,49,84}.

RADIOMICS

An overview of studies reporting on the value of radiomics for the prediction of treatment response in esophageal cancer is presented in **Table 3**. Studies that performed imaging before and after treatment reported that tumor heterogeneity generally decreased following treatment^{36,49}. It has been hypothesized that tumors could be rendered more homogeneous following treatment due to a reduction in cellular density and interstitial pressure, and normalization of the vasculature with improved intra-tumor perfusion and oxygenation³⁶.

A group from the UK studied the value of contrast-enhanced CT image features analysis before and after neoadjuvant chemotherapy in 31 patients for the prediction of good versus poor pathologic response (tumor regression grade [TRG] 1-3 vs. 4-5)³⁶. Statistical significance was not reached for any of the univariable associations between image features and pathologic response with the exception of pre- and post-treatment SD, which however disappeared after correction for multiple testing³⁶. The same group also studied the value of >100 baseline ¹⁸F-FDG PET texture features versus a three-slices convolutional neural network (3S-CNN; which is trained directly from scans rather than ‘manually’ calculated) for the prediction of good versus poor pathologic response (n=217)⁴⁸. They found that 3S-CNN outperformed texture features analysis resulting in a sensitivity of 81% and specificity of 82%⁴⁸, but this finding has not yet been validated in other studies.

In two studies, a French group determined the associations of tumor texture features on baseline ¹⁸F-FDG PET scans with clinical response to definitive CRT^{27,54}. In their first study (n=41), the authors reported superior univariable discriminatory ability (area-under-the-curves [AUCs] 0.82-0.89) of several texture features (i.e. homogeneity, entropy, intensity variability, and size-zone variability) over SUV_{max} and SUV_{mean} (AUCs 0.59-0.70) for the prediction of clinical complete response or non-response²⁷. Similarly, in their second study with a partly overlapping study population (n=50), good univariable discriminatory ability (AUCs 0.80-0.90) was achieved with several image features (i.e. MTV, entropy, homogeneity, dissimilarity, intensity variability, and zone percentage) for the prediction of clinical non-response⁵⁴. Important limitations of these studies^{27,54} include the suboptimal reference standard defined by the CT-based RECIST method - which is known to correlate poorly to true (pathologic) response and survival^{80,81} - and the lack of multivariable prediction modeling (adjusted for clinical parameters and other predictive modalities) impairing proper interpretation of potential incremental value in clinical practice.

Based on baseline and post-treatment ^{18}F -FDG PET scans, investigators from the US aimed to predict pathologic response (TRG 1-2 vs. 3-5) to nCRT in the same 20 patients with esophageal cancer in three separate articles^{39,57,85}. By extracting 34 intensity, texture, and geometry features at both time points, they found that changes of features over treatment (Δ features) appeared more predictive of response than pre- or post-treatment assessment alone⁵⁷. Baseline skewness, $\Delta\text{SUV}_{\text{mean}}$, post-treatment inertia (contrast), correlation, and cluster prominence were found to be significant predictors of pathologic response in univariable analysis (AUCs 0.76-0.85)⁵⁷. In a second study, cross-bin histogram distance features were studied (capturing both ^{18}F -FDG uptake distribution and longitudinal information), resulting in slightly higher prediction accuracies than texture features⁸⁵. This finding requires validation as to date no other studies have reported on cross-bin histogram distance features in esophageal cancer imaging. In a third study, multivariable support vector machine (SVM) and logistic regression models were constructed including 33 ^{18}F -FDG PET image features as well as 16 clinical parameters³⁹. SVM models achieved higher accuracy than logistic regression models, particularly in models combining many variables (maximum AUC 1.00 vs. 0.90)³⁹, but it is important to acknowledge that substantial model overfitting has likely occurred given the small sample size and large amount of predictors included in the modeling, resulting in overoptimistic results.

Another group from the US studied the value of clinical parameters along with subjective and quantitative parameters from baseline and post-treatment ^{18}F -FDG PET scans in 217 patients with esophageal adenocarcinoma for the prediction of pCR as opposed to residual cancer after nCRT⁴⁹. Similar to other studies, lower baseline heterogeneity and a greater change towards more homogeneous ^{18}F -FDG uptake after treatment were associated with better response⁴⁹. In multivariable analysis and after internal validation using bootstrapping techniques, both ^{18}F -FDG PET-based subjective assessment of response and texture features analysis provided incremental value beyond clinical predictors, but this discriminatory improvement did not translate into a clinically relevant benefit as determined by decision-curve analysis⁴⁹.

Another group in the US (n=45) addressed the time-consuming issue of contouring longitudinal scans and investigated the usefulness of 11 different registration algorithms for post-treatment contour propagation in relation to their ability to predict pathologic response⁵³. They showed that propagated contours could be constructed fast (<30 seconds) and that 3 texture features (e.g. entropy) resulting

Table 3 Studies on the value of image features analysis for the prediction of treatment response in esophageal cancer

| Study | n | Histology (AC/SCC/other) | Tumor stage | Treatment | Imaging modality | Imaging timing | Image parameters | Outcome |
|-------------------------------|-----|--------------------------|-------------|-----------------|-------------------------|------------------------|--|--|
| CT | | | | | | | | |
| Yip 2015 ³⁶ | 31 | 22/9/0 | I-IV | nChTx + Surgery | Contrast-enhanced CT | Baseline + after nChTx | - Entropy, uniformity, mean grey-level intensity, kurtosis, skewness, and SD - 4 smoothing scales | Pathologic response (TRG* 1-3 vs. 4-5) |
| PET | | | | | | | | |
| Tixier 2011 ²⁷ | 41 | 10/31/0 | I-IV | dCRT | ¹⁸ F-FDG PET | Baseline | - 7 intensity and 31 texture features - 4 quantization levels | Clinical response (based on CT; RECIST: CR vs. PR vs. non-R) |
| Hatt 2013 ⁵⁴ | 50 | 14/36/0 | I-IV | dCRT | ¹⁸ F-FDG PET | Baseline | - 10 texture features - 3 segmentation methods - With and without PVC | Clinical response (based on CT; RECIST: CR + PR vs. non-R) |
| Tan 2013-1 ⁵⁷ | 20 | 17/3/0 | II-III | nCRT + Surgery | ¹⁸ F-FDG PET | Baseline + after nCRT | - 34 intensity, texture, and geometry features | Pathologic response (TRG* 1-2 vs. 3-5) |
| Tan 2013-2 ⁸⁵ | 20 | NR | NR | nCRT + Surgery | ¹⁸ F-FDG PET | Baseline + after nCRT | - SUV _{max} , SUV _{peak} , TLG, 8 texture features, and 19 histogram distances | Pathologic response (TRG* 1-2 vs. 3-5) |
| Zhang 2014 ³⁹ | 20 | 17/3/0 | II-III | nCRT + Surgery | ¹⁸ F-FDG PET | Baseline + after nCRT | - 9 intensity, 8 texture, and 15 geometry features, TLG, and 16 clinical features | Pathologic response (TRG* 1-2 vs. 3-5) |
| Ypsilantis 2015 ⁴⁸ | 107 | 86/20/1 | II-IV | nChTx + Surgery | ¹⁸ F-FDG PET | Baseline | - More than 100 texture features vs. convolutional neural network (3S-CNN) trained directly from scans | Pathologic response (TRG* 1-3 vs. 4-5) |

Table 3 (continued)

| Study | n | Histology (AC/SCC/other) | Tumor stage | Treatment | Imaging modality | Imaging timing | Image parameters | Outcome |
|-------------------------------|-----|--------------------------|-------------|---------------------------------------|-------------------------|-----------------------|--|---|
| van Rossum 2016 ⁴⁹ | 217 | 217/0/0 | II-III | nCRT + Surgery (36% ChTx before nCRT) | ¹⁸ F-FDG PET | Baseline + after nCRT | - 69 texture and 12 geometry features - 2 baseline scans at different institutions | Pathologic response (TRG [†] 1 vs. 2-4) |
| Yip 2016 ⁵³ | 45 | 44/1/0 | I-IV | nCRT + Surgery | ¹⁸ F-FDG PET | Baseline + after nCRT | - MTV, entropy, SRHIE, SZHIE - 3 quantization levels - 11 registration algorithms for propagated post-treatment contours | Pathologic response (downstaged vs. upstaged or equal pathologic TN-stage compared to baseline clinical TN-stage) |

*: According to Mandard et al.⁹³; †: According to Chiriac et al.⁷⁵. ¹⁸F-FDG: ¹⁸F-fluorodeoxyglucose. 3S-CNN: three-slices convolutional neural network. AC: adenocarcinoma. ChTx: chemotherapy. CR: complete response. CT: computed tomography. dCRT: definitive chemoradiotherapy. MTV: metabolic tumor volume. nChTx: neoadjuvant chemotherapy. nCRT: neoadjuvant chemoradiotherapy. non-R: non-response. NR: not reported. RECIST: Response Evaluation Criteria in Solid Tumors. PET: positron emission tomography. PR: partial response. SCC: squamous cell carcinoma. SD: standard deviation. SRHIE: short-run high-intensity emphasis. SUV: standardized uptake value. SZHIE: short-zone high-intensity emphasis. TLG: total lesion glycolysis. TRG: tumor regression grade.

4 from most algorithms significantly predicted pathologic responders (AUCs 0.72-0.78), with the exception of fast-demons and fast-free-form deformable algorithms, and rigidly propagated contours, which should therefore not be used⁵³. An uncommon reference standard was used consisting of pathologic TN-downstaging (responders) versus TN-upstaging or no change in stage (non-responders) as compared to the baseline clinical TN-stage⁵³. This endpoint was likely suboptimal since it has not been validated as surrogate marker for long-term outcomes and clinical TN-staging is inaccurate in many cases.

PREDICTION OF SURVIVAL

Accurate stratification of patients according to their expected prognosis is crucial at the time of diagnosis as well as throughout treatment and follow-up. The most important prognostic factor before treatment is the clinical TNM-stage, and -to a lesser extent- the initial SUV_{max} value^{4,86}. Endoscopic biopsy, subjective ¹⁸F-FDG PET-based response, and SUV_{max} after chemo(radio)therapy are other parameters with some prognostic value^{38,86,87}. After surgery, pathologic TNM-staging, lymph node ratio, extracapsular lymph node involvement, radicality of resection, and pathologic response to neoadjuvant therapy have prognostic impact^{74,75,88-91}. Despite the availability of these prognostic factors, we are still failing our patients in terms of accurate individualized prediction of survival probability resulting in inaccurate patient selection for different treatment approaches, as for example can be seen from the high number of patients with very early progression (24-41% within 1 year) after treatment with curative intent⁹².

RADIOMICS

Studies on the value of radiomics for the prediction of survival in esophageal cancer are outlined in **Table 4**. Three studies from the UK have described predictive value for survival using texture features based on baseline unenhanced CT²² or pre- and post-treatment contrast-enhanced CT^{35,36}. The first investigation included 21 patients with esophageal cancer -for which the important prognostic factor of treatment was not reported- and studied tumor entropy and uniformity for 6 smoothing scales²². It was demonstrated that the CT-based coarse uniformity feature was superiorly predictive for overall survival, even resulting in redundancy of clinical TNM-stage and SUV_{max} in a stepwise forward Cox regression analysis, suggesting substantial overlap in information²². In the two other studies, tumor entropy, uniformity, mean grey-level intensity, kurtosis, skewness, and SD for 4 quantization levels on baseline and post-treatment contrast-enhanced CT were

Table 4 Studies on the value of image features analysis for the prediction of survival in esophageal cancer

| Study | n | Histology (AC/SCC/other) | Tumor stage | Treatment | Imaging modality | Imaging timing | Image parameters | Outcome |
|-----------------------------|-----|--------------------------|-------------|------------------------------------|-------------------------|------------------------|--|------------------|
| CT | | | | | | | | |
| Ganeshan 2012 ²² | 21 | 14/7 | II-IV | NR | Unenhanced CT | Baseline | - Entropy, uniformity - 6 smoothing scales | Overall survival |
| Yip 2014 ³⁵ | 36 | 9/26/1 | I-IV | dCRT (56% ChTx before dCRT) | Contrast-enhanced CT | Baseline + after dCRT | - Entropy, uniformity, mean grey-level intensity, kurtosis, skewness, and SD - 4 smoothing scales | Overall survival |
| Yip 2015 ³⁶ | 31 | 22/9/0 | I-IV | nChTx + Surgery | Contrast-enhanced CT | Baseline + after nChTx | - Entropy, uniformity, mean grey-level intensity, kurtosis, skewness, and SD - 4 smoothing scales | Overall survival |
| PET | | | | | | | | |
| Hatt 2015 ⁵¹ | 112 | 63/49 | I-III | dCRT (39%) or nCRT + Surgery (61%) | ¹⁸ F-FDG PET | Baseline | - MTV, entropy, dissimilarity, HILAE, and zone percentage - 2 calculation methods (for entropy, dissimilarity) - 7 quantization levels | Overall survival |

¹⁸F-FDG: ¹⁸F-fluorodeoxyglucose. 3S-CNN: three-slices convolutional neural network. AC: adenocarcinoma. ChTx: chemotherapy. CT: computed tomography. dCRT: definitive chemoradiotherapy. HILAE: high-intensity large-area emphasis. MTV: metabolic tumor volume. nChTx: neoadjuvant chemotherapy. nCRT: neoadjuvant chemoradiotherapy. NR: not reported. PET: positron emission tomography. SCC: squamous cell carcinoma. SD: standard deviation.

4 related to overall survival^{35,36}. After adjusting for tumor stage and age, post-treatment entropy and uniformity features on a medium to coarse scale remained significant prognostic factors in 36 patients who underwent definitive CRT³⁵. In the other study performed by the same group, a relative change in skewness on a fine smoothing scale was associated with survival in 31 patients who underwent neoadjuvant chemotherapy followed by surgery³⁶.

The French study that included baseline ¹⁸F-FDG PET scans of 555 cancer patients (of whom 112 had esophageal cancer and underwent definitive CRT or nCRT followed by surgery) assessed the value of MTV, entropy, dissimilarity, high-intensity large-area emphasis, and zone percentage for the prediction of overall survival⁵¹. Although MTV and heterogeneity (along with tumor stage) were independent prognostic factors in non-small cell lung cancer, these parameters had less complementary value in esophageal cancer which was attributed to smaller overall volumes⁵¹. The local dissimilarity parameter appeared most predictive for overall survival in the patients with esophageal cancer⁵¹.

CONCLUSION

Since the first publication on image texture feature analysis in esophageal cancer in the year 2011²⁷, the body of evidence on radiomics in this setting has been growing steadily suggesting potential incremental value for staging, prediction of response to chemo(radio)therapy, and predicting survival. As such, radiomics approaches may contribute to the ongoing movement towards more individualized treatment strategies for these patients. An advantage of this emerging field is that it can fit in within existing practice without imposing additional burden to patients, as it involves post-processing techniques on standard CT or ¹⁸F-FDG PET images which are performed as part of routine clinical practice. However, current evidence is still exploratory in nature and further validation in larger studies is required before implementation in clinical practice could be considered.

Acknowledgement and further evaluation of limitations with respect to reproducibility of image features and the substantial influence of varying smoothing scales, quantization levels, and contouring methods is of crucial importance to move this field forward. To this regard, parameters such as local entropy derived from GLCMs (and to a lesser extent uniformity, dissimilarity, or zone percentage) for tumor heterogeneity characterization should be preferred, as these appear most reproducible and robust, and have repeatedly shown high predictive ability for staging, prediction of response, and prediction of survival. Standardization of

imaging and radiomics approaches, multivariable prediction modeling focusing on incremental value of radiomics beyond conventional diagnostics and predictors, and validation of findings are key to successful future introduction of radiomics in the clinical management of esophageal cancer.

REFERENCES

1. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. *Lancet* 2013;381:400-12
2. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003;349:2241-52
3. Omloo JM, Lagarde SM, Hulscher JB, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. *Ann Surg* 2007;246:992-1000; discussion 1000-1
4. Rice TW, Rusch VW, Ishwaran H, et al. Cancer of the esophagus and esophagogastric junction: data-driven staging for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals. *Cancer* 2010;116:3763-73
5. Bhatt A, Abe S, Kumaravel A, et al. Indications and techniques for endoscopic submucosal dissection. *Am J Gastroenterol* 2015;110:784-91
6. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
7. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20
8. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011;12:681-92
9. Wong R, Malthaner R. Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus. *Cochrane Database Syst Rev* 2006;1:CD002092
10. Homs MY, van der Gaast A, Siersema PD, et al. Chemotherapy for metastatic carcinoma of the esophagus and gastro-esophageal junction. *Cochrane Database Syst Rev* 2006;4:CD004063
11. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;358:36-46
12. Diederich S. Staging of oesophageal cancer. *Cancer Imaging* 2007;7:S63-6
13. Jamil LH, Gill KR, Wallace MB. Staging and restaging of advanced esophageal cancer. *Curr Opin Gastroenterol* 2008;24:530-4
14. van Rossum PS, van Lier AL, Lips IM, et al. Imaging of oesophageal cancer with FDG-PET/CT and MRI. *Clin Radiol* 2015;70:81-95
15. Rasanen JV, Sihvo EI, Knuuti MJ, et al. Prospective analysis of accuracy of positron emission tomography, computed tomography, and endoscopic ultrasonography in staging of adenocarcinoma of the esophagus and the esophagogastric junction. *Ann Surg Oncol* 2003;10:954-60
16. Munden RE, Macapinlac HA, Erasmus JJ. Esophageal cancer: the role of integrated CT-PET in initial staging and response assessment after preoperative therapy. *J Thorac Imaging* 2006;21:137-45

17. Bruzzi JF, Swisher SG, Truong MT, et al. Detection of interval distant metastases: clinical utility of integrated CT-PET imaging in patients with esophageal carcinoma after neoadjuvant therapy. *Cancer* 2007;109:125-34
18. Monjazez AM, Riedlinger G, Aklilu M, et al. Outcomes of patients with esophageal cancer staged with ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET): can postchemoradiotherapy FDG-PET predict the utility of resection? *J Clin Oncol* 2010;28:4714-21
19. Blom RL, Schreurs WM, Belgers HJ, et al. The value of post-neoadjuvant therapy PET-CT in the detection of interval metastases in esophageal carcinoma. *Eur J Surg Oncol* 2011;37:774-8
20. Goense L, van Rossum PS, Reitsma JB, et al. Diagnostic performance of ¹⁸F-FDG PET and PET/CT for the detection of recurrent esophageal cancer after treatment with curative intent: a systematic review and meta-analysis. *J Nucl Med* 2015;56:995-1002
21. Lambin P, Rios-Velazquez E, Leijenaar R, et al. Radiomics: extracting more information from medical images using advanced feature analysis. *Eur J Cancer* 2012;48:441-6
22. Ganeshan B, Skogen K, Pressney I, et al. Tumour heterogeneity in oesophageal cancer assessed by CT texture analysis: preliminary evidence of an association with tumour metabolism, stage, and survival. *Clin Radiol* 2012;67:157-64
23. Maley CC, Galipeau PC, Finley JC, et al. Genetic clonal diversity predicts progression to esophageal adenocarcinoma. *Nat Genet* 2006;38:468-73
24. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med* 2012;366:883-92
25. Marusyk A, Almendro V, Polyak K. Intra-tumour heterogeneity: a looking glass for cancer? *Nat Rev Cancer* 2012;12:323-34
26. Fisher R, Pusztai L, Swanton C. Cancer heterogeneity: implications for targeted therapeutics. *Br J Cancer* 2013;108:479-85
27. Tixier F, Le Rest CC, Hatt M, et al. Intratumor heterogeneity characterized by textural features on baseline ¹⁸F-FDG PET images predicts response to concomitant radiochemotherapy in esophageal cancer. *J Nucl Med* 2011;52:369-78
28. Chicklore S, Goh V, Siddique M, et al. Quantifying tumour heterogeneity in ¹⁸F-FDG PET/CT imaging by texture analysis. *Eur J Nucl Med Mol Imaging* 2013;40:133-40
29. Goh V, Sanghera B, Wellsted DM, et al. Assessment of the spatial pattern of colorectal tumour perfusion estimated at perfusion CT using two-dimensional fractal analysis. *Eur Radiol* 2009;19:1358-65
30. Goh V, Ganeshan B, Nathan P, et al. Assessment of response to tyrosine kinase inhibitors in metastatic renal cell cancer: CT texture as a predictive biomarker. *Radiology* 2011;261:165-71
31. Mu W, Chen Z, Liang Y, et al. Staging of cervical cancer based on tumor heterogeneity characterized by texture features on ¹⁸F-FDG PET images. *Phys Med Biol* 2015;60:5123-39

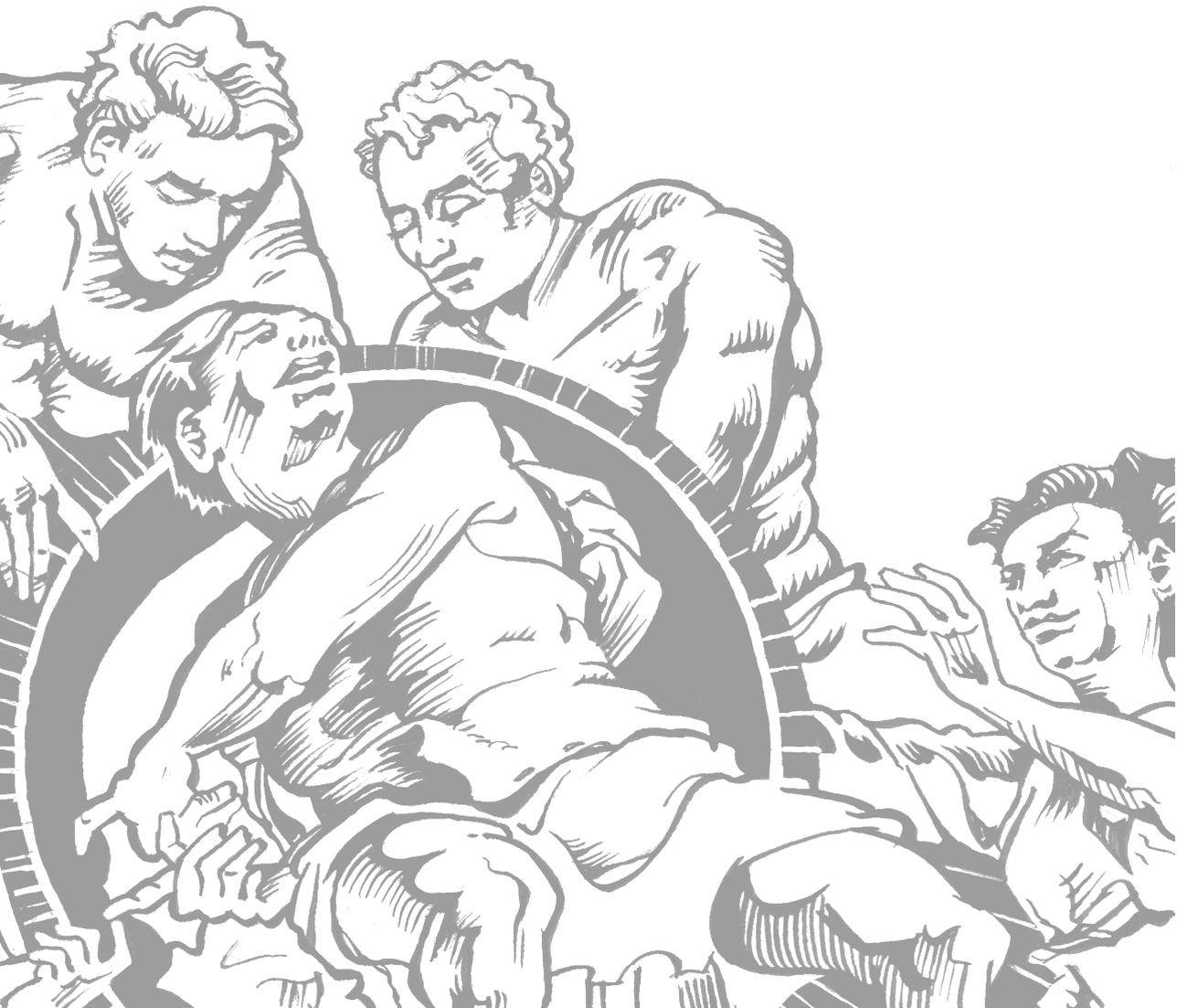
- 4
32. Fried DV, Tucker SL, Zhou S, et al. Prognostic value and reproducibility of pretreatment CT texture features in stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2014;90:834-42
 33. Fried DV, Mawlawi O, Zhang L, et al. Stage III non-small cell lung cancer: prognostic value of FDG PET quantitative imaging features combined with clinical prognostic factors. *Radiology* 2016;278:214-22
 34. Knogler T, El-Rabadi K, Weber M, et al. Three-dimensional texture analysis of contrast enhanced CT images for treatment response assessment in Hodgkin lymphoma: comparison with F-18-FDG PET. *Med Phys* 2014;41:121904
 35. Yip C, Landau D, Kozarski R, et al. Primary esophageal cancer: heterogeneity as potential prognostic biomarker in patients treated with definitive chemotherapy and radiation therapy. *Radiology* 2014;270:141-8
 36. Yip C, Davnall F, Kozarski R, et al. Assessment of changes in tumor heterogeneity following neoadjuvant chemotherapy in primary esophageal cancer. *Dis Esophagus* 2015;28:172-9
 37. Kwee RM. Prediction of tumor response to neoadjuvant therapy in patients with esophageal cancer with use of ¹⁸F FDG PET: a systematic review. *Radiology*. 2010;254:707-17
 38. Zhu W, Xing L, Yue J, et al. Prognostic significance of SUV on PET/CT in patients with localised oesophagogastric junction cancer receiving neoadjuvant chemotherapy/chemoradiation: a systematic review and meta-analysis. *Br J Radiol* 2012;85:e694-701
 39. Zhang H, Tan S, Chen W, et al. Modeling pathologic response of esophageal cancer to chemoradiation therapy using spatial-temporal ¹⁸F-FDG PET features, clinical parameters, and demographics. *Int J Radiat Oncol Biol Phys* 2014;88:195-203
 40. Dong X, Wu P, Sun X, et al. Intra-tumour ¹⁸F-FDG uptake heterogeneity decreases the reliability on target volume definition with positron emission tomography/computed tomography imaging. *J Med Imaging Radiat Oncol* 2015;59:338-45
 41. El Naqa I, Grigsby P, Apte A, et al. Exploring feature-based approaches in PET images for predicting cancer treatment outcomes. *Pattern Recognit* 2009;42:1162-71
 42. Roedl JB, Colen RR, Holalkere NS, et al. Adenocarcinomas of the esophagus: response to chemoradiotherapy is associated with decrease of metabolic tumor volume as measured on PET-CT. Comparison to histopathologic and clinical response evaluation. *Radiother Oncol* 2008;89:278-86
 43. Blom RL, Steenbakkers IR, Lammering G, et al. PET/CT-based metabolic tumour volume for response prediction of neoadjuvant chemoradiotherapy in oesophageal carcinoma. *Eur J Nucl Med Mol Imaging* 2013;40:1500-6
 44. Hatt M, Visvikis D, Pradier O, et al. Baseline ¹⁸F-FDG PET image-derived parameters for therapy response prediction in oesophageal cancer. *Eur J Nucl Med Mol Imaging* 2011;38:1595-1606
 45. Tixier F, Hatt M, Le Rest CC, et al. Reproducibility of tumor uptake heterogeneity characterization through textural feature analysis in ¹⁸F-FDG PET. *J Nucl Med* 2012;53:693-700
 46. Castellano G, Bonilha L, Li LM, et al. Texture analysis of medical images. *Clin Radiol* 2004;59:1061-9

47. Doumou G, Siddique M, Tsoumpas C, et al. The precision of textural analysis in ^{18}F -FDG-PET scans of oesophageal cancer. *Eur Radiol* 2015;25:2805-12
48. Ypsilantis PP, Siddique M, Sohn HM, et al. Predicting response to neoadjuvant chemotherapy with PET imaging using convolutional neural networks. *PLoS One* 2015;10:e0137036
49. van Rossum PS, Fried DV, Zhang L, et al. The incremental value of subjective and quantitative assessment of ^{18}F -FDG PET for the prediction of pathologic complete response to preoperative chemoradiotherapy in esophageal cancer. *J Nucl Med* 2016;57:691-700
50. Galavis PE, Hollensen C, Jallow N, et al. Variability of textural features in FDG PET images due to different acquisition modes and reconstruction parameters. *Acta Oncol* 2010;49:1012-6
51. Hatt M, Majdoub M, Vallieres M, et al. ^{18}F -FDG PET uptake characterization through texture analysis: investigating the complementary nature of heterogeneity and functional tumor volume in a multi-cancer site patient cohort. *J Nucl Med* 2015;56:38-44
52. Leijenaar RT, Nalbantov G, Carvalho S, et al. The effect of SUV discretization in quantitative FDG-PET Radiomics: the need for standardized methodology in tumor texture analysis. *Sci Rep* 2015;5:11075
53. Yip SS, Coroller TP, Sanford NN, et al. Use of registration-based contour propagation in texture analysis for esophageal cancer pathologic response prediction. *Phys Med Biol* 2016;61:906-22
54. Hatt M, Tixier F, Cheze Le Rest C, et al. Robustness of intratumour ^{18}F -FDG PET uptake heterogeneity quantification for therapy response prediction in oesophageal carcinoma. *Eur J Nucl Med Mol Imaging* 2013;40:1662-71
55. Zaidi H, El Naqa I. PET-guided delineation of radiation therapy treatment volumes: a survey of image segmentation techniques. *Eur J Nucl Med Mol Imaging* 2010;37:2165-87
56. Lee JA. Segmentation of positron emission tomography images: some recommendations for target delineation in radiation oncology. *Radiother Oncol* 2010;96:302-7
57. Tan S, Kligerman S, Chen W, et al. Spatial-temporal [^{18}F]FDG-PET features for predicting pathologic response of esophageal cancer to neoadjuvant chemoradiation therapy. *Int J Radiat Oncol Biol Phys* 2013;85:1375-82
58. Dong X, Xing L, Wu P, et al. Three-dimensional positron emission tomography image texture analysis of esophageal squamous cell carcinoma: relationship between tumor ^{18}F -fluorodeoxyglucose uptake heterogeneity, maximum standardized uptake value, and tumor stage. *Nucl Med Commun* 2013;34:40-6
59. Ma C, Li D, Yin Y, et al. Comparison of characteristics of ^{18}F -fluorodeoxyglucose and ^{18}F -fluorothymidine PET during staging of esophageal squamous cell carcinoma. *Nucl Med Commun* 2015;36:1181-6
60. Werner-Wasik M, Nelson AD, Choi W, et al. What is the best way to contour lung tumors on PET scans? Multiobserver validation of a gradient-based method using a NSCLC digital PET phantom. *Int J Radiat Oncol Biol Phys* 2012;82:1164-71

- 4
61. Hatt M, Cheze le Rest C, Turzo A, et al. A fuzzy locally adaptive Bayesian segmentation approach for volume determination in PET. *IEEE Trans Med Imaging* 2009;28:881-93
 62. Puli SR, Reddy JB, Bechtold ML, et al. Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. *World J Gastroenterol* 2008;14:1479-90
 63. van Vliet EP, Eijkemans MJ, Kuipers EJ, et al. Publication bias does not play a role in the reporting of the results of endoscopic ultrasound staging of upper gastrointestinal cancers. *Endoscopy* 2007;39:325-32
 64. Preston SR, Clark GW, Martin IG, et al. Effect of endoscopic ultrasonography on the management of 100 consecutive patients with oesophageal and junctional carcinoma. *Br J Surg* 2003;90:1220-4
 65. Wakelin SJ, Deans C, Crofts TJ, et al. A comparison of computerised tomography, laparoscopic ultrasound and endoscopic ultrasound in the preoperative staging of oesophago-gastric carcinoma. *Eur J Radiol* 2002;41:161-7
 66. van Vliet EP, Eijkemans MJ, Poley JW, et al. Staging of esophageal carcinoma in a low-volume EUS center compared with reported results from high-volume centers. *Gastrointest Endosc* 2006;63:938-47
 67. van Zoonen M, van Oijen MG, van Leeuwen MS, et al. Low impact of staging EUS for determining surgical resectability in esophageal cancer. *Surg Endosc* 2012;26:2828-34
 68. van Vliet EP, Heijenbrok-Kal MH, Hunink MG, et al. Staging investigations for esophageal cancer: a meta-analysis. *Br J Cancer* 2008;98:547-57
 69. van Westreenen HL, Westerterp M, Bossuyt PM, et al. Systematic review of the staging performance of ¹⁸F-fluorodeoxyglucose positron emission tomography in esophageal cancer. *J Clin Oncol* 2004;22:3805-12
 70. Hofstetter WL. Preoperative chemoradiation in an era of suboptimal clinical staging. *JAMA Surg* 2016;151:245-6
 71. Dong X, Xing L, Wu P, et al. Three-dimensional positron emission tomography image texture analysis of esophageal squamous cell carcinoma: Relationship between tumor ¹⁸F-fluorodeoxyglucose uptake heterogeneity, maximum standardized uptake value, and tumor stage. *Nucl Med Commun* 2013;34:40-6
 72. van der Sluis PC, Ubink I, van der Horst S, et al. Safety, efficacy, and long-term follow-up evaluation of perioperative epirubicin, cisplatin, and capecitabine chemotherapy in esophageal resection for adenocarcinoma. *Ann Surg Oncol* 2015;22:1555-63
 73. Klevebro F, Alexandersson von Döbeln G, Wang N, et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. *Ann Oncol* 2016;27:660-7
 74. Donahue JM, Nichols FC, Li Z, et al. Complete pathologic response after neoadjuvant chemoradiotherapy for esophageal cancer is associated with enhanced survival. *Ann Thorac Surg* 2009;87:392-8; discussion 398-9
 75. Chirieac LR, Swisher SG, Ajani JA, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. *Cancer* 2005;103:1347-55

76. Ajani JA, Correa AM, Hofstetter WL, et al. Clinical parameters model for predicting pathologic complete response following preoperative chemoradiation in patients with esophageal cancer. *Ann Oncol* 2012;23:2638-42
77. Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997;15:261-7
78. Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. *J Clin Oncol* 2002;20:1996-2004
79. van Rossum PS, van Lier AL, van Vulpen M, et al. Diffusion-weighted magnetic resonance imaging for the prediction of pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer. *Radiother Oncol* 2015;115:163-70
80. Westerterp M, van Westreenen HL, Reitsma JB, et al. Esophageal cancer: CT, endoscopic US, and FDG PET for assessment of response to neoadjuvant therapy--systematic review. *Radiology* 2005;236:841-51
81. Yanagawa M, Tatsumi M, Miyata H, et al. Evaluation of response to neoadjuvant chemotherapy for esophageal cancer: PET Response Criteria In Solid Tumors versus Response Evaluation Criteria In Solid Tumors. *J Nucl Med* 2012;53:872-80
82. van Rossum PS, Goense L, Meziari J, et al. Endoscopic biopsy and EUS for the detection of pathologic complete response after neoadjuvant chemoradiotherapy in esophageal cancer: a systematic review and meta-analysis. *Gastrointest Endosc* 2016;83:866-79
83. Toxopeus EL, Nieboer D, Shapiro J, et al. Nomogram for predicting pathologically complete response after neoadjuvant chemoradiotherapy for oesophageal cancer. *Radiother Oncol* 2015;115:392-8
84. Cheedella NK, Suzuki A, Xiao L, et al. Association between clinical complete response and pathological complete response after preoperative chemoradiation in patients with gastroesophageal cancer: analysis in a large cohort. *Ann Oncol* 2013;24:1262-6
85. Tan S, Zhang H, Zhang Y, et al. Predicting pathologic tumor response to chemoradiotherapy with histogram distances characterizing longitudinal changes in ¹⁸F-FDG uptake patterns. *Med Phys* 2013;40:101707
86. Suzuki A, Xiao L, Hayashi Y, et al. Nomograms for prognostication of outcome in patients with esophageal and gastroesophageal carcinoma undergoing definitive chemoradiotherapy. *Oncology* 2012;82:108-13
87. Lin SH, Wang J, Allen PK, et al. A nomogram that predicts pathologic complete response to neoadjuvant chemoradiation also predicts survival outcomes after definitive chemoradiation for esophageal cancer. *J Gastrointest Oncol* 2015;6:45-52
88. Verhage RJ, Zandvoort HJ, ten Kate FJ, et al. How to define a positive circumferential resection margin in T3 adenocarcinoma of the esophagus. *Am J Surg Pathol* 2011;35:919-26
89. Lagarde SM, Reitsma JB, de Castro SM, et al. Prognostic nomogram for patients undergoing oesophagectomy for adenocarcinoma of the oesophagus or gastro-oesophageal junction. *Br J Surg* 2007;94:1361-8

- 4
90. Lagarde SM, Reitsma JB, Ten Kate FJ, et al. Predicting individual survival after potentially curative esophagectomy for adenocarcinoma of the esophagus or gastroesophageal junction. *Ann Surg* 2008;248:1006-13
 91. Nafteux PR, Lerut AM, Moons J, et al. International multicenter study on the impact of extracapsular lymph node involvement in primary surgery adenocarcinoma of the esophagus on overall survival and staging systems. *Ann Surg* 2015;262:809-16
 92. Shapiro J, van Lanschot JJ, Hulshof MC, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol* 2015;16:1090-8
 93. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer* 1994;73:2680-6



Chapter 5

Diagnostic performance of ^{18}F -FDG PET and PET/CT for the detection of recurrent esophageal cancer after treatment with curative intent: a systematic review and meta-analysis

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Journal of Nuclear Medicine 2015;56:995-1002

ABSTRACT

The aim of this study was to assess the diagnostic performance of ^{18}F -FDG PET and integrated ^{18}F -FDG PET/CT for diagnosing recurrent esophageal cancer after initial treatment with curative intent.

METHODS

The PubMed, Embase, and Cochrane library were systematically searched for all relevant literature using the key words “ ^{18}F -FDG PET” and “esophageal cancer” and synonyms. Studies examining the diagnostic value of ^{18}F -FDG PET or integrated ^{18}F -FDG PET/CT, either in routine clinical follow-up or in symptomatic patients in whom recurrence of esophageal cancer was suspected, were deemed eligible for inclusion. The primary outcome was the presence of recurrent esophageal cancer as determined by histopathologic biopsy or clinical follow-up. Risk of bias and applicability concerns were assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. Sensitivities and specificities of individual studies were meta-analyzed using bivariate random-effects models.

RESULTS

Eight eligible studies were included for meta-analysis, comprising 486 patients with esophageal cancer who underwent ^{18}F -FDG PET or PET/CT after previous treatment with curative intent. The quality of the included studies assessed by the QUADAS-2 tool was considered reasonable; there were few concerns with regard to the risk of bias and applicability. Integrated ^{18}F -FDG PET/CT and standalone ^{18}F -FDG PET were used in 4 and 3 studies, respectively. One other study analyzed both modalities separately. In 4 studies, ^{18}F -FDG PET or PET/CT was performed as part of routine follow-up, whereas in 4 other studies the diagnostic test was performed on indication during clinical follow-up. Pooled estimates of sensitivity and specificity for ^{18}F -FDG PET and PET/CT in diagnosing recurrent esophageal cancer were 96% (95% confidence interval, 93–97%) and 78% (95% confidence interval, 66–86%), respectively. Subgroup analysis revealed no statistically significant difference in diagnostic accuracy according to type of PET scanner (standalone PET vs. integrated PET/CT) or indication of scanning (routine follow-up vs. on indication).

CONCLUSION

¹⁸F-FDG PET and PET/CT are reliable imaging modalities with a high sensitivity and moderate specificity for detecting recurrent esophageal cancer after treatment with curative intent. The use of ¹⁸F-FDG PET or PET/CT particularly allows for a minimal false-negative rate. However, histopathologic confirmation of ¹⁸F-FDG PET- or ¹⁸F-FDG PET/CT-based suspected lesions remains required, because a considerable false-positive rate is noticed.

INTRODUCTION

5

Surgical resection of the esophagus with en-bloc lymphadenectomy remains the cornerstone of treatment with curative intent for patients with localized esophageal cancer¹. A multimodal approach is increasingly applied as strong evidence exists for a survival benefit of 7-13% with neoadjuvant chemo(radio)therapy over surgery alone^{2,3}. Overall 5-year survival rates of patients with esophageal cancer who are treated with curative intent remain relatively poor (34-47%)^{3,4}. This is mainly attributable to the high incidence of recurrent disease early after treatment ranging from 45% to 53%⁵⁻⁷. Most recurrences occur within the first two years after surgery with median time to recurrence of 10 to 12 months^{6,7}. About half of these patients (51%) are diagnosed with isolated distant systemic recurrence. This affects liver, bone and lung mainly⁵⁻⁷. Locoregional recurrence or a combination of locoregional and distant recurrence occur less frequent (14% and 35%, respectively)⁷. After diagnosing recurrent esophageal cancer, poor median survival rates of 3 to 8 months have been reported⁸.

Currently, most institutes use conventional imaging modalities such as computed tomography (CT) and endoscopy with or without endoscopic ultrasound (EUS) for the detection of recurrent esophageal cancer. However, the interpretation of these imaging techniques after prior treatment is difficult due to local anatomic changes caused by surgery⁹. In addition, distant recurrent esophageal cancer may be radiologically occult on CT or may occur in unusual and unexpected locations outside the conventional field coverage of CT¹⁰.

Whole-body ¹⁸F fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) and integrated ¹⁸F-FDG PET/CT have emerged as useful adjuncts to conventional staging modalities in the pre-treatment staging of esophageal cancer. In particular, baseline ¹⁸F-FDG PET/CT has gained ground by outperforming CT alone in the detection of unexpected distant metastases¹¹. Accordingly, ¹⁸F-FDG PET or PET/CT may also be a very useful method for detecting recurrent disease in the postoperative follow-up of esophageal cancer patients as recurrences predominantly tend to occur at distant sites⁷. In the past years, several studies have been published on the utility of ¹⁸F-FDG PET or PET/CT in the detection of esophageal cancer recurrence. However, it is difficult to draw conclusions based on the individual studies because methodological quality may vary, sample sizes are generally small and differences in study design and patient populations may cause heterogeneity in reported outcomes.

In order to critically appraise and potentially overcome shortcomings of individual studies the aim of this study was to systematically review and meta-analyze the diagnostic performance of ¹⁸F-FDG PET and PET/CT for diagnosing recurrent esophageal cancer after initial treatment with curative intent.

MATERIAL AND METHODS

The study protocol has been registered in the PROSPERO international prospective register of systematic reviews and accessible at <http://www.crd.york.ac.uk/prospero/> (Registration number: CRD42014009615).

SEARCH STRATEGY

On the 16th of December 2014 a systematic search was performed in the databases Medline (via Pubmed), Embase and the Cochrane library. The full search strategy is presented in **Table 1**.

Table 1 Search strategy and results as on 16 December 2014

| No. | Search query | Pubmed | Embase | Cochrane |
|-----|--|-----------|-----------|----------|
| 1 | pet OR pet-ct OR fluorodeoxyglucose OR "2 fluoro 2 deoxy" OR FDG OR positron emission tomography OR positron-emission tomography OR "18fdg" | 73.205 | 94.057 | 3.121 |
| 2 | esophageal OR esophagus OR oesophageal OR oesophagus OR gastro- esophageal OR gastro-oesophageal OR gastroesophageal OR oesophagogastric OR esophagogastric | 128.173 | 127.316 | 8.707 |
| 3 | cancer OR cancers OR tumor OR tumour OR tumors OR tumours OR neoplasm OR neoplasms OR malignancy OR malignancies OR adenocarcinoma OR adenocarcinomas OR carcinoma OR carcinomas | 2.206.283 | 2.270.954 | 90.252 |
| 4 | #1 AND #2 AND #3 | 948 | 1.684 | 60 |

STUDY SELECTION

After removing duplicates of the retrieved articles, titles and abstracts were screened for eligibility by two authors independently (L.G. and P.S.N.v.R.). The full text of potentially relevant articles was retrieved and independently assessed by two authors for inclusion (L.G. and P.S.N.v.R.).

5

Studies examining the test accuracy of ^{18}F -FDG PET or integrated ^{18}F -FDG PET/CT, in either routine clinical follow-up with a fixed time interval irrespective of physical complaints, or in symptomatic patients suspected of recurrent esophageal cancer were deemed eligible for inclusion. Only studies that included patients who were previously treated with curative intent for esophageal cancer, and that reported on the diagnostic accuracy of ^{18}F -FDG PET or PET/CT for the detection of disease recurrence were included. Treatment with curative intent should have had at least included surgery, either or not combined with (neo)adjuvant chemo(radio)therapy. The reference standard was recurrent esophageal cancer as confirmed by histopathologic biopsy or clinical follow-up.

Case reports, studies with less than 10 included patients, reviews, poster abstracts and animal studies were excluded. Also publications written in another language than Dutch, English or German were excluded from this review. Missing data of possible eligible studies were requested from study authors. References of the included studies and of related review studies were also screened for inclusion. Disagreements regarding the eligibility of a study were resolved by consensus.

DATA EXTRACTION AND QUALITY ASSESSMENT

Study and patient characteristics along with ^{18}F -FDG PET or PET/CT parameters were extracted from each study. The quality of the included studies was critically appraised by two authors independently (L.G. and P.S.N.v.R.), according to the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool¹². QUADAS-2 assesses risk of bias and applicability concerns on four key domains including, patient selection, index test, reference standard and flow and timing, respectively. To reach a judgment on the risk of bias the provided signaling questions of the QUADAS-2 tool were used. Risk of bias and applicability concerns were judged as 'low', 'high', or 'unclear' risk or concern for the various QUADAS domains.

STATISTICAL ANALYSIS

The target condition consisted of the presence of recurrent esophageal cancer as determined by histopathologic biopsy or clinical follow-up. From each included study the number of true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN) were obtained on a 'per-patient' basis if available. From studies reporting on a 'per-lesion' or 'per-scan' basis the reported sensitivities and specificities were used, but the absolute numbers leading to these estimates according to the total number of patients with and without recurrent disease were

recalculated to prevent overestimation of the weight of the results. Subsequently, for each study the sensitivity and specificity along with 95% confidence intervals (95% CIs) were calculated and depicted in Forest plots.

A bivariate random effects model was used to obtain pooled estimates of sensitivity and specificity with their corresponding 95% CIs from the individual studies. The bivariate model uses a random effects approach to incorporate heterogeneity beyond chance as a result of clinical and methodological differences between studies¹³. The bivariate model also estimates whether sensitivities and specificities are (negatively) correlated across studies due to implicit differences in threshold to consider a ¹⁸F-FDG PET or PET/CT scan suspected for recurrence (positive index test result). The pooled estimate of sensitivity and specificity and the corresponding 95% confidence ellipse is shown in ROC space¹⁴.

Subgroup analyses were performed by adding the following study characteristics (covariates) to the bivariate model: 'standalone ¹⁸F-FDG PET' versus 'integrated ¹⁸F-FDG PET/CT', 'index test performed on indication' versus 'index test performed as part of routine follow-up', and 'Asian studies' versus 'non-Asian studies'. A p-value of <0.05 was considered statistically significant. The non-linear mixed model procedure of SAS (version 9.2, SAS Institute, Cary, N.C., USA) was used to estimate the parameters of the bivariate model.

RESULTS

ELIGIBLE STUDIES

The systematic search yielded 948 articles from Medline, 1684 from Embase and 60 from the Cochrane library (**Table 1**). After removing duplicates, 1867 articles remained of which title and abstract were reviewed. Forty-three articles were deemed potentially relevant for this study. After reading the full text of the remaining studies, 35 articles were excluded because these concerned review studies (n=13), non-diagnostic studies (n=8), poster abstracts (n=5), publications in other than pre-specified languages (n=4), case reports (n=2), a study that included less than 10 patients (n=1) or studies in which insufficient data was available (n=2). Missing data of these latter two studies were requested from study authors without satisfying result^{15,16}. Screening of references of these eligible articles and related review studies did not yield additional relevant publications. Consequently, eight studies met our inclusion and exclusion criteria comprising a total of 486 patients with esophageal cancer that underwent ¹⁸F-FDG PET or PET/CT after previous treatment with curative intent. The described process of study selection is summarized in **Figure 1**.

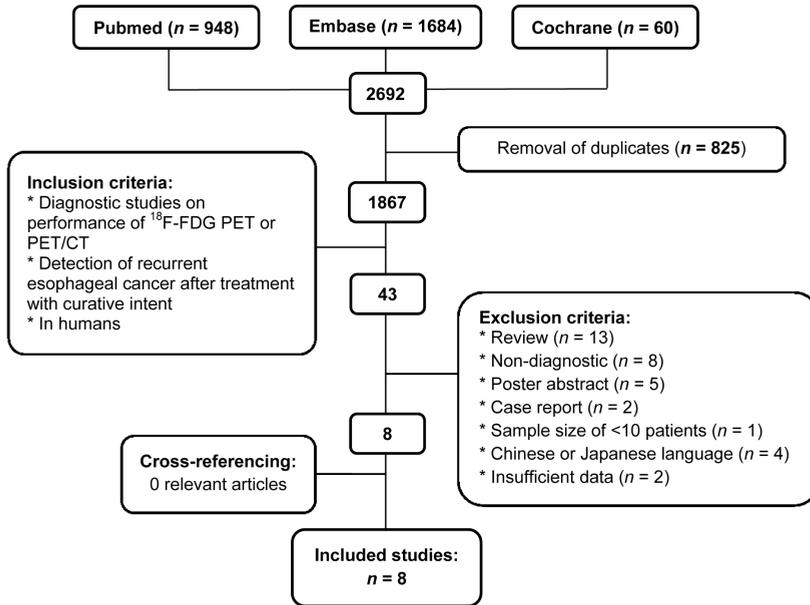


Figure 1 Flowchart summarizing search results and study selection.

The general characteristics of the included studies are presented in **Table 2**¹⁷⁻²⁴. **Table 3** outlines the used ¹⁸F-FDG PET or PET/CT parameters and reference standards. Only one of the 8 studies was prospectively designed to answer this research question²². The duration of clinical follow-up after acquisition of a ¹⁸F-FDG PET or PET/CT scan was less than 6 months in one of the included studies²³, at least 6 months or longer in five studies^{17,18,20,21,24}, and not described in two other studies^{19,22}. In four studies the diagnostic value of integrated ¹⁸F-FDG PET/CT was analyzed^{17,18,20,21}, and three studies analyzed the diagnostic value of standalone ¹⁸F-FDG PET²²⁻²⁴. In one study the value of integrated ¹⁸F-FDG PET with CT versus ¹⁸F-FDG PET alone was analyzed separately; hereafter the data from this study is referred to as ‘Roedl [1]’ and ‘Roedl [2]’, respectively¹⁹. In four studies the diagnostic test was performed on routine basis^{19,21-23}, whereas in the other studies the diagnostic test was performed on indication during clinical follow-up^{17,18,20,24}. In six studies ¹⁸F-FDG PET or PET/CT positive results were analyzed on a ‘per-patient’ basis, whereas in two studies the results were either assessed on a ‘per-scan’¹⁷ or ‘per-lesion’²⁴ basis.

Table 2 Characteristics of the 8 included studies

| First author, year | Country | Type of study | n | Mean age (range) | Gender (M/F) | Histology (SCC/ AC/ other) | Initial treatment | Type of scanner, slice thickness of CT, acquisition mode and reconstruction method | Reason for imaging |
|---------------------------|---------|---------------|-----|------------------|--------------|----------------------------|------------------------------|--|--------------------|
| Sharma 2014 ¹⁷ | India | Retro | 180 | 56 (26-81) | 126/54 | 115/59/6 | S, C, SC, CR, SR, nCRT and S | Integrated PET/CT, 4mm, 3D, IR | On indication |
| Sun 2009 ¹⁸ | China | Retro | 20 | 55 (39-68) | 15/5 | NR | S and adj R | Integrated PET/CT, 3.3mm, IR, NR | On indication |
| Roedl 2008 ¹⁹ | USA | Retro | 47 | NR (NR) | 35/12 | 11/36/0 | S, R | Standalone PET and integrated PET/CT, 2mm, NR, NR | Routine |
| Guo 2007 ²⁰ | China | Retro | 56 | NR (38-77) | 47/9 | NR | nCRT and S | Integrated PET/CT, 4.24mm, NR, IR | On indication |
| Jadvar 2006 ²¹ | USA | Retro | 46 | NR (47-84) | 50/10 | NR | S, SC, R, C, SCR | Integrated PET/CT, 3.4mm, NR, IR | Routine |
| Teyton 2009 ²² | France | Prosp | 41 | 59 (43-83) | 38/3 | 31/10/0 | S, SC | Standalone PET, NR, 3D, IR | Routine |
| Kato 2004 ²³ | Japan | Retro | 55 | 61 (36-74) | 48/7 | 50/3/2 | S | Standalone PET, 3.1mm, NR, IR | Routine |
| Flamen 2000 ²⁴ | Belgium | Retro | 41 | 62 (NR) | 36/5 | 14/27/0 | S | Standalone PET, NR, NR, IR | On indication |

AC: adenocarcinoma. adj: adjuvant. C: chemotherapy. CR: chemoradiotherapy. IR: iterative reconstruction. nCRT: neoadjuvant chemoradiotherapy. NR: not reported. Prosp: prospective. R: radiotherapy. Retro: retrospective. S: surgery. SC: squamous cell carcinoma. SCC: squamous cell carcinoma. SR: surgery and radiotherapy. 2D: two-dimensional. 3D: three-dimensional.

Table 3 ¹⁸F-FDG PET or PET/CT parameters, methods of image interpretation, and reference standard of included studies

| First author, year | FDG dose | Time ¹⁸ F-FDG administration to scanning | Criteria for positive scan |
|---------------------------|---------------------------------|---|--|
| Sharma 2014 ¹⁷ | 370 MBq | 45-60 minutes | -Suspicious CT lesions with ¹⁸ F-FDG uptake -Suspicious CT lung lesion -FDG hotspot liver |
| Sun 2009 ¹⁸ | 60 MBq | 60 minutes | Markedly to moderately increased uptake of ¹⁸ F-FDG |
| Roedl 2008 ¹⁹ | 555 MBq | 60 minutes | Focal and eccentric uptake of ¹⁸ F-FDG |
| Guo 2007 ²⁰ | 370 MBq | 60 minutes | Focal uptake of ¹⁸ F-FDG |
| Jadvar 2006 ²¹ | 555 MBq | 60 minutes | Focal uptake of ¹⁸ F-FDG |
| Teyton 2008 ²² | 355 MBq | 60 minutes | Focal uptake of ¹⁸ F-FDG |
| Kato 2004 ²³ | 275-370 MBq | 40 minutes | NR |
| Flamen 2000 ²⁴ | 6.5 MBq/kg (maximum 555 MBq) | 60 minutes | NR |

NR: not reported.

QUALITY ASSESSMENT

The results of the quality assessment using the QUADAS-2 tool are presented in **Table 4**. The risk of bias concerning patient selection was low in 7 of the included studies; one study deemed at high risk of bias because it did not include a consecutive sample of patients²⁰. Risk of bias with regard to the index test was low in all studies since the index test results were consistently interpreted without knowledge of the outcome of the reference test. However, the risk of bias for the reference test was deemed unclear for most studies because these articles lack to report whether or not the reference standard was interpreted without knowledge of the index test result. Furthermore, applicability concerns for patient selection were found in 4 studies because the study population consisted of patients that underwent a variety

| Interpreters | Reference standard | Duration of clinical follow-up | Patients with recurrence (%) |
|--|--|--------------------------------|------------------------------|
| Two nuclear medicine physicians | Histology and/or clinical follow-up with imaging | Minimally 6 months | NR |
| Two nuclear medicine physicians | Histology and/or clinical follow-up | Minimally 10 months | 55.0 |
| Nuclear medicine physicians and radiologists | Histology and/or clinical follow-up with imaging | NR | 57.4 |
| Three nuclear medical physicians | Histology and/or clinical follow-up with imaging | Minimally 6 months | 80.4 |
| NR | Histology and/or clinical follow-up with imaging | Up to 18 months | 60.9 |
| Two nuclear medicine physicians | Histology and/or clinical follow-up with imaging | NR | 56.1 |
| Two nuclear medicine physicians | Histology and/or clinical follow-up with imaging | Within 6 months | 49.1 |
| Two nuclear medicine physicians | Histology and/or clinical follow-up with imaging | Minimally 6 months | 80.5 |

of treatment regimens. In general, there were only few high concerns with regard to the risk of bias and applicability, the quality of the currently available literature was considered reasonable.

DIAGNOSTIC ACCURACY

The results of two studies that assessed the diagnostic value of ¹⁸F-FDG PET or PET/CT on a 'per-lesion' or 'per-scan' basis were adjusted according to their sample size^{17,24}. The paired Forest plots of sensitivity and specificity of the eight individual studies are presented in **Figure 2**. The reported sensitivities ranged from 89% to 100% and specificities from 55% to 94%. For the calculation of the overall pooled estimates only the data of Roedl [1] - and not of Roedl [2] - was used to

Table 4 Quality assessment of included studies

| First author, year | Risk of bias | | | | Applicability concerns | | |
|---------------------------|-------------------|------------|--------------------|-----------------|------------------------|------------|--------------------|
| | Patient selection | Index test | Reference standard | Flow and timing | Patient selection | Index test | Reference standard |
| Sharma 2014 ¹⁷ | L | L | U | L | H | L | L |
| Sun 2009 ¹⁸ | L | L | U | L | H | L | L |
| Roedl 2008 ¹⁹ | L | L | U | U | L | L | L |
| Guo 2007 ²⁰ | H | L | U | L | H | L | L |
| Jadvar 2006 ²¹ | U | L | H | U | H | L | L |
| Teyton 2009 ²² | L | L | U | U | L | L | L |
| Kato 2004 ²³ | L | L | U | H | L | L | L |
| Flamen 2000 ²⁴ | L | L | U | L | L | L | L |

H: high. L: low. U: unclear.

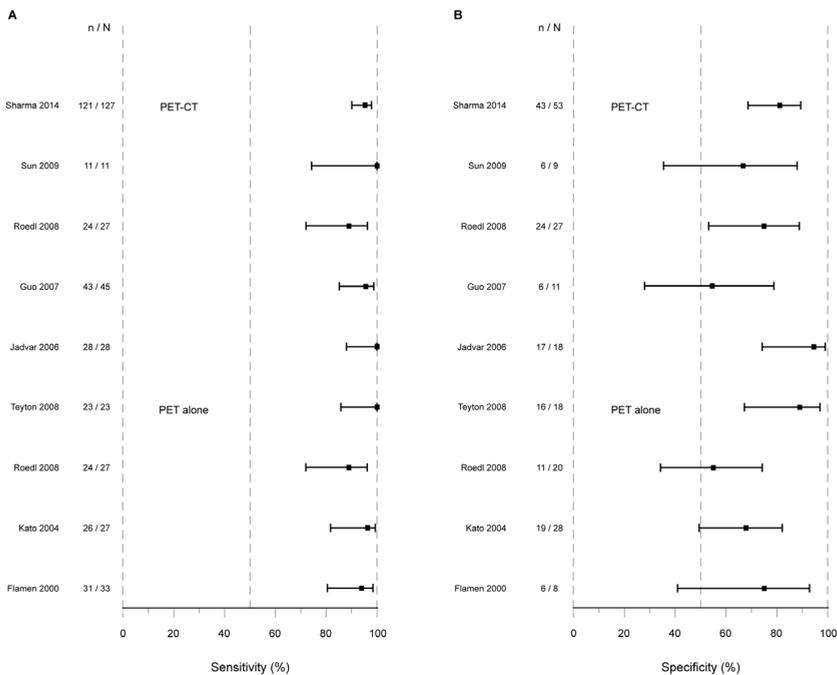


Figure 2 A) Forest plot of sensitivity of integrated ¹⁸F-FDG PET/CT and PET alone for the detection of recurrent esophageal cancer after treatment with curative intent; n: number of true-positives; N: number of true-positives + false-negatives. B) Forest plot of specificity of integrated ¹⁸F-FDG PET/CT and PET alone for the detection of recurrent esophageal cancer after treatment with curative intent; n: number of true-negatives; N: number of true-negatives + false-positives.

prevent using the data from this study twice¹⁹. Sensitivity was eventually pooled with a fixed effect model as the between-study variation was not larger than could be expected by chance. More variation than expected by chance was observed for specificity, therefore a random effects pooling was used for specificity. Pooled estimates of sensitivity and specificity were 96% (95% CI: 93% to 97%) and 78% (95% CI: 66% to 86%), respectively. The estimates from the individual studies, and the pooled estimates of sensitivity and specificity together with the 95% confidence ellipse are shown in **Figure 3**.

The planned subgroup analysis was restricted to specificity alone as there was no real heterogeneity in sensitivity. The subgroup analysis revealed no statistically significant difference in specificity according to type of PET-scanner (standalone PET versus integrated PET/CT), indication of scanning (part of routine follow-up versus on indication), and country of origin (Asian versus non-Asian) (**Table 5**).

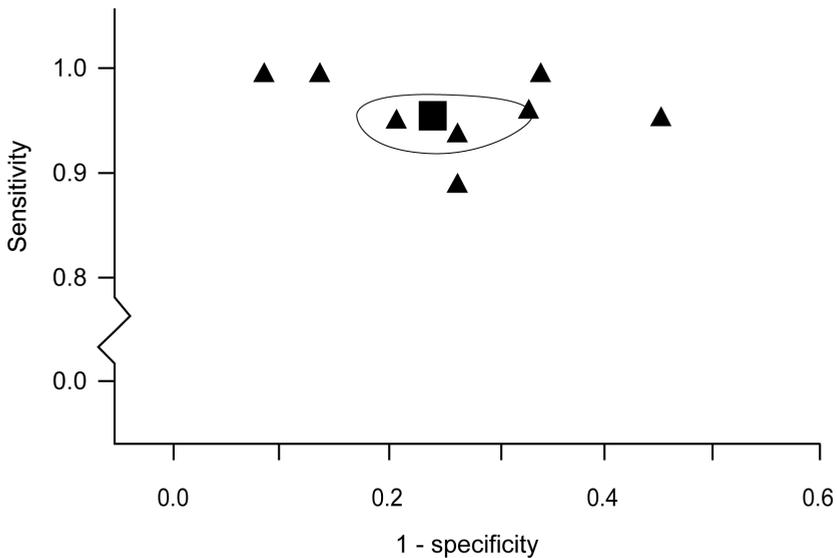


Figure 3 Pooled estimate of sensitivity and specificity (square) and corresponding 95% confidence ellipse along with the estimates from the individual studies (triangles) in ROC space.

Table 5 Results from subgroup analyses for specificity

| Factor | No. of studies | Specificity (95% CI) | p-value |
|----------------------------|----------------|----------------------|---------|
| Type of scan | | | 0.213 |
| ¹⁸ F-FDG PET/CT | 5 | 78% (70 - 85) | |
| ¹⁸ F-FDG PET | 4 | 70% (59 - 80) | |
| Indication of test | | | 0.748 |
| Routine imaging | 4 | 78% (69 - 86) | |
| Clinical suspicion | 4 | 76% (65 - 85) | |
| Country of origin | | | 0.099 |
| Asian | 4 | 73% (64 - 81) | |
| Non-Asian | 4 | 84% (73 - 91) | |

Note. Subgroup analysis was only performed for specificity, because there was no variation beyond chance for sensitivity.

DISCUSSION

This study is the first study to systematically review and summarize the currently available evidence on the accuracy of ¹⁸F-FDG PET and PET/CT for diagnosing recurrent esophageal cancer after primary treatment with curative intent. The methodological quality of the eight included studies analyzed by the QUADAS-2 tool concerning risk of bias was low in most studies. Pooled estimates for ¹⁸F-FDG PET and PET/CT yielded a high sensitivity and moderate specificity of 96% and 78% respectively. Sensitivity was consistently high in all studies, but variation was present in specificity. Subgroup analysis could not link specific study characteristics to systematically higher or lower specificity. Current evidence indicates that ¹⁸F-FDG PET and PET/CT are valuable tests for clinical practice in the follow-up of patients with esophageal cancer after primary treatment.

Certain limitations apply to this meta-analysis. Methodological concerns that may have influenced the results of the various studies include absence of blinding the index test from the reference test, and inclusion of heterogeneous treatment modalities among individual studies. Another limitation is the limited number of included studies in this meta-analysis. Also, in this meta-analysis three of eight studies only included patients with a clinical suspicion of recurrence. This may have led to an overestimation of the diagnostic value of ¹⁸F-FDG PET or PET/CT, as these patients have an increased pre-test probability compared to patients without suspicion of recurrence. However, subgroup analysis could not confirm

this potential difference in diagnostic accuracy of ¹⁸F-FDG PET or PET/CT on clinical indication or as part of routine follow-up (specificity 78% [95% CI: 69% to 86%] versus 76% [95% CI: 65% to 85%], respectively; $p=0.748$). In addition, the country of origin did not seem to have influenced the results of the different studies significantly. Last, differential verification bias was of concern in most included studies as different reference standards were used for confirmation of the diagnosis. Most negative ¹⁸F-FDG PET or PET/CT cases were verified by a potentially less reliable and second best reference test (clinical follow-up instead of histopathologic biopsy), which may have resulted in a slight overestimation of sensitivity and underestimation of specificity²⁵. None of the included studies applied a correction method to their results for this potential bias.

Conventional imaging modalities for recurrent esophageal cancer include, endoscopy with or without EUS and CT of thorax and abdomen. EUS has proven to be effective for the detection of locoregional recurrence (sensitivity >90%), but both endoscopy and EUS fail to detect distant metastases²⁶. Currently, distant metastases are of particular interest since the incidence of locoregional recurrence is substantially reduced by new treatment algorithms, including neoadjuvant chemo(radio)therapy⁷. CT scans are commonly used for detection of distant metastases, although the diagnostic value of CT for local recurrence is limited at the site of resection due to anatomic distortion caused by surgery and radiotherapy⁹. Furthermore, only limited data on the diagnostic value of CT for detecting recurrent esophageal cancer is available with reported sensitivities ranging from 65% to 89%^{22,23}. The pooled sensitivity estimate for ¹⁸F-FDG PET and PET/CT of 96% from this meta-analysis indicates that ¹⁸F-FDG PET and PET/CT is likely to outperform CT to this regard, which is confirmed by direct comparison in two studies^{22,23}.

Comparison of reported specificities for CT and the current pooled specificity estimate for ¹⁸F-FDG PET and PET/CT suggests an inferior specificity for ¹⁸F-FDG PET and PET/CT compared to standalone CT (78% versus 79%-91%, respectively)^{22,23}. The lower specificity of ¹⁸F-FDG PET is a common problem in oncologic patients and is mainly caused by false positive findings due to chronic inflammation after surgery, chronic respiratory tract disease, radiation pneumonitis or dilation of anastomotic strictures^{20,27,28}. A combination of metabolic imaging (¹⁸F-FDG PET) with anatomic imaging (CT) has been reported to improve diagnostic accuracy compared to PET alone, especially in diagnosing locoregional recurrence^{15,17,19}. To this regard, the only direct comparative study in esophageal cancer recurrence diagnosis found a higher specificity in favor of

PET/CT compared to PET alone (75% versus 55%, respectively)¹⁹. However, this potential benefit of ¹⁸F-FDG PET/CT as opposed to standalone ¹⁸F-FDG PET for diagnosing recurrent esophageal cancer did not reach statistical significance by subgroup analysis in this meta-analysis (specificity 78% [95% CI: 70% to 85%] versus 70% [95% CI: 59% to 80%], respectively; $p=0.213$).

The specificities used in this meta-analysis were derived from analysis on a per-patient basis and the pooled results can therefore not exclude the possibility of superiority of ¹⁸F-FDG PET/CT over PET for specific anatomic sites. Anatomic site-specific TP and FP numbers were reported on a per-lesion basis in 5 of 8 studies^{17,19,20,23,24} and suggested a difference in the positive predictive values (e.g. $TP / [TP + FP]$) for diagnosing locoregional recurrence using ¹⁸F-FDG PET/CT (range 79%-95%)^{17,19,20} compared with ¹⁸F-FDG PET (range 59%-68%)^{19,23,24}. The difference between positive predictive values for diagnosing distant recurrence of PET/CT (range 89%-95%)^{17,19,20} and PET (84%-90%) studies were minor^{19,23,24}. However, in contrast to specificities, the pooling of positive predictive values is questionable due to their strong dependency on the pre-test probability (e.g. prevalence of true recurrences), which varies among the included studies with different clinical settings. To this regard, another subject of note is the continuous technological progress of ¹⁸F-FDG PET/CT image generation and reconstruction algorithms, and ¹⁸F-FDG PET with integrated magnetic resonance imaging (MRI) is now clinically introduced²⁹. These developments may prove to further increase the accuracy in diagnosing recurrent esophageal cancer.

In the current guidelines of the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) there is no room for routine imaging or endoscopy with biopsies after initial treatment for esophageal cancer^{30,31}. The key reason to refrain from routine imaging is the limited amount of adequate therapeutic options when recurrence is detected. Current treatment options for recurrent disease consist of salvage chemo(radio)therapy which is associated with symptomatic relief and improved survival rates^{32,33}. Furthermore, recent experimental studies have demonstrated that re-operation for selected cases of localized recurrence or solitary recurrence in lymph nodes, lungs and subcutaneous lesions is safe and may improve survival³⁴⁻³⁸. This is supported by a recent study that demonstrated a significant survival benefit for patients treated with salvage lymphadenectomy compared to chemo(radio)therapy in patients with cervical lymph node recurrence³⁷.

Future clinical decision-making with regard to treatment strategy for recurrent disease will depend on the extent and location of the recurrence. Routine imaging with CT and PET has been shown to possess the ability to detect recurrent esophageal cancer in a pre-symptomatic phase^{8,39}. However, so far no studies combining routine imaging with aggressive treatment strategies are available. Also, very little is known about cost-effectiveness of routine imaging and gain of quality of life after early detection of recurrent esophageal disease. Therefore, with the limited evidence available for routine imaging in recurrent esophageal cancer, at this moment routine imaging is not recommended. In case recurrent disease is clinically suspected, the method of choice is ¹⁸F-FDG PET/CT.

In conclusion, this meta-analysis demonstrates that ¹⁸F-FDG PET and PET/CT are reliable imaging modalities with a high sensitivity and moderate specificity for detecting recurrent esophageal cancer. The use of ¹⁸F-FDG PET or PET/CT particularly allows for a minimal false negative rate. However, histopathologic confirmation of ¹⁸F-FDG PET and PET/CT suspected lesions remains required, since a considerable false positive rate is noticed. The benefit of ¹⁸F-FDG PET and PET/CT over conventional imaging techniques, in terms of cost-effectiveness and improving clinical outcome, remains subject of debate. Future studies are warranted to analyze whether earlier detection of recurrent esophageal cancer along with more aggressive therapeutic approaches will improve survival and quality of life.

ACKNOWLEDGEMENTS

The authors thank Professor Rob J.P.M. Scholten - director of The Dutch Cochrane Centre hosted by the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands - for critically reviewing the manuscript and providing methodological support.

REFERENCES

1. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. *Lancet* 2013;381:400-12
2. Gebski V, Burmeister B, Smithers BM, et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: A meta-analysis. *Lancet Oncol* 2007;8:226-34
3. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
4. Omloo JM, Lagarde SM, Hulscher JB, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: Five-year survival of a randomized clinical trial. *Ann Surg* 2007;246:992-1000; discussion 1000-1
5. Hulscher JB, van Sandick JW, Tijssen JG, et al. The recurrence pattern of esophageal carcinoma after transhiatal resection. *J Am Coll Surg* 2000;191:143-8
6. Mariette C, Balon JM, Piessen G, et al. Pattern of recurrence following complete resection of esophageal carcinoma and factors predictive of recurrent disease. *Cancer* 2003;97:1616-23
7. Blom RL, Lagarde SM, van Oudenaarde K, et al. Survival after recurrent esophageal carcinoma has not improved over the past 18 years. *Ann Surg Oncol* 2013;20:2693-8
8. Abate E, DeMeester SR, Zehetner J, et al. Recurrence after esophagectomy for adenocarcinoma: Defining optimal follow-up intervals and testing. *J Am Coll Surg* 2010;210:428-35
9. Carlisle JG, Quint LE, Francis IR, et al. Recurrent esophageal carcinoma: CT evaluation after esophagectomy. *Radiology* 1993;189:271-5
10. Bruzzi JF, Swisher SG, Truong MT, et al. Detection of interval distant metastases: Clinical utility of integrated CT-PET imaging in patients with esophageal carcinoma after neoadjuvant therapy. *Cancer* 2007;109:125-34
11. Heeren PA, Jager PL, Bongaerts F, et al. Detection of distant metastases in esophageal cancer with ¹⁸F-FDG PET. *J Nucl Med* 2004;45:980-7
12. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529-36
13. Reitsma JB, Rutjes AW, Whiting P, et al. Chapter 9: Assessing methodological quality. In: Deeks JJ, Bossuyt PM, Gatsonis C (editors). *Cochrane handbook for systematic reviews of diagnostic test accuracy*. Version 1.0.0. The Cochrane Collaboration, 2009. Available from: <http://srdta.cochrane.org/>
14. Reitsma JB, Glas AS, Rutjes AW, et al. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005;58:982-90
15. Bar-Shalom R, Guralnik L, Tsalic M, et al. The additional value of PET/CT over PET in FDG imaging of oesophageal cancer. *Eur J Nucl Med Mol Imaging* 2005;32:918-24
16. Wang F, Shen LY, Ma SH, et al. Advantages of positron emission tomography-computed tomography imaging in esophageal squamous cell carcinoma. *Dis Esophagus* 2013;26:832-7

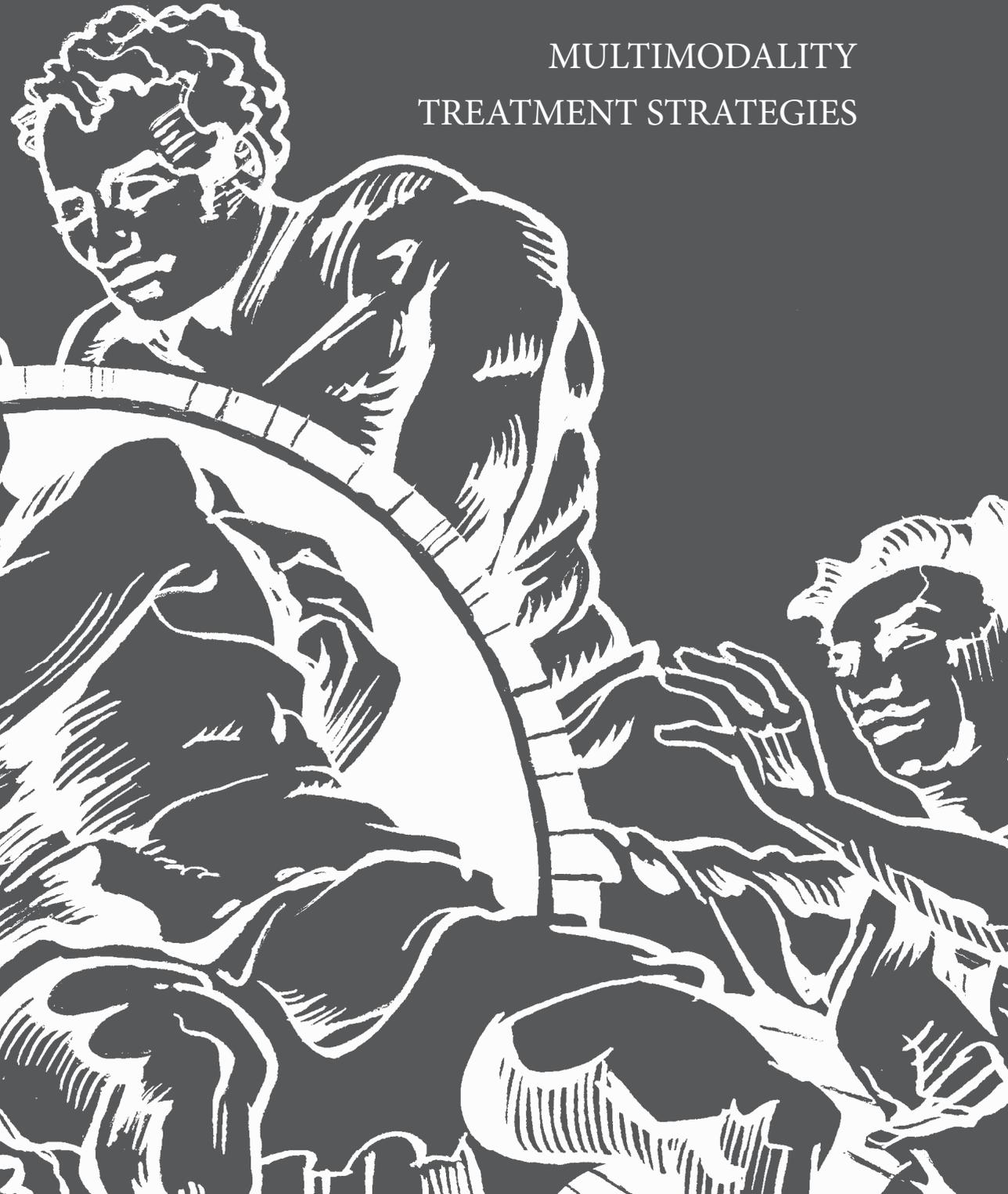
17. Sharma P, Jain S, Karunanithi S, et al. Diagnostic accuracy of ¹⁸F-FDG PET/CT for detection of suspected recurrence in patients with oesophageal carcinoma. *Eur J Nucl Med Mol Imaging* 2014;41:1084-92
18. Sun L, Su X, Guan Y, et al. Clinical usefulness of ¹⁸F-FDG PET/CT in the restaging of esophageal cancer after surgical resection and radiotherapy. *World J Gastroenterol* 2009;15:1836-42
19. Roedel JB, Harisinghani MG, Colen RR, et al. Assessment of treatment response and recurrence in esophageal carcinoma based on tumor length and standardized uptake value on positron emission tomography-computed tomography. *Ann Thorac Surg* 2008;86:1131-8
20. Guo H, Zhu H, Xi Y, et al. Diagnostic and prognostic value of ¹⁸F-FDG PET/CT for patients with suspected recurrence from squamous cell carcinoma of the esophagus. *J Nucl Med* 2007;48:1251-8
21. Jadvar H, Henderson RW, Conti PS. 2-deoxy-2-[F-18]fluoro-D-glucose - positron emission tomography/computed tomography imaging evaluation of esophageal cancer. *Mol Imaging Biol* 2006;8:193-200
22. Teyton P, Metges JP, Atmani A, et al. Use of positron emission tomography in surgery follow-up of esophageal cancer. *J Gastrointest Surg* 2009;13:451-8
23. Kato H, Miyazaki T, Nakajima M, et al. Value of positron emission tomography in the diagnosis of recurrent oesophageal carcinoma. *Br J Surg* 2004;91:1004-9
24. Flamen P, Lerut A, van Cutsem E, et al. The utility of positron emission tomography for the diagnosis and staging of recurrent esophageal cancer. *J Thorac Cardiovasc Surg* 2000;120:1085-92
25. Lijmer JG, Mol BW, Heisterkamp S, et al. Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA* 1999;282:1061-6
26. Muller C, Kahler G, Scheele J. Endosonographic examination of gastrointestinal anastomoses with suspected locoregional tumor recurrence. *Surg Endosc* 2000;14:45-50
27. Strauss LG. Fluorine-18 deoxyglucose and false-positive results: A major problem in the diagnostics of oncological patients. *Eur J Nucl Med* 1996;23:1409-15
28. van Westreenen HL, Heeren PA, Jager PL, et al. Pitfalls of positive findings in staging esophageal cancer with F-18-fluorodeoxyglucose positron emission tomography. *Ann Surg Oncol* 2003;10:1100-5
29. Gallamini A, Zwarthoed C, Borra A. Positron emission tomography (PET) in oncology. *Cancers (Basel)*. 2014;6:1821-89
30. NCCN Clinical practice guidelines in oncology (NCCN guidelines)—Esophageal and esophagogastric junction cancers. Version 1, 2014. Available from: http://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf
31. Stahl M, Mariette C, Haustermans K, et al. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24 Suppl 6:vi51-6
32. Raoul JL, Le Prise E, Meunier B, et al. Combined radiochemotherapy for postoperative recurrence of oesophageal cancer. *Gut* 1995;37:174-6
33. Zhang J, Peng F, Li N, et al. Salvage concurrent radio-chemotherapy for post-operative local recurrence of squamous-cell esophageal cancer. *Radiat Oncol* 2012;7:93

- 5
34. Kubota K, Kuroda J, Yoshida M, et al. Surgical therapy and chemoradiotherapy for postoperative recurrent esophageal cancer. *Hepatogastroenterology* 2013;60:1961-5
 35. Nakamura T, Ota M, Narumiya K, et al. Multimodal treatment for lymph node recurrence of esophageal carcinoma after curative resection. *Ann Surg Oncol* 2008;15:2451-7
 36. Hiyoshi Y, Morita M, Kawano H, et al. Clinical significance of surgical resection for the recurrence of esophageal cancer after radical esophagectomy. *Ann Surg Oncol* 2015;22:240-6
 37. Ma X, Zhao K, Guo W, et al. Salvage lymphadenectomy versus salvage radiotherapy/chemoradiotherapy for recurrence in cervical lymph node after curative resection of esophageal squamous cell carcinoma. *Ann Surg Oncol* 2015;22:624-9
 38. van der Sluis PC, Verhage RJ, van der Horst S, et al. Gastric conduit resection and jejunal interposition for recurrent esophageal cancer. *Ann Thorac Surg* 2012;93:1727-9
 39. Barbier PA, Luder PJ, Schupfer G, et al. Quality of life and patterns of recurrence following transhiatal esophagectomy for cancer: Results of a prospective follow-up in 50 patients. *World J Surg* 1988;12:270-6



PART II

MULTIMODALITY TREATMENT STRATEGIES





Chapter 6

Perioperative chemotherapy versus neoadjuvant chemoradiotherapy for esophageal or gastroesophageal junction adenocarcinoma: a propensity score-matched analysis comparing toxicity, pathologic outcome, and survival

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ABSTRACT

OBJECTIVES

To evaluate toxicity, pathologic outcome, and survival after perioperative chemotherapy (pCT) compared to neoadjuvant chemoradiotherapy (nCRT) followed by surgery for patients with resectable esophageal or gastroesophageal junction (GEJ) adenocarcinoma.

BACKGROUND

The optimal multimodality treatment strategy for resectable esophageal or GEJ adenocarcinoma has not been established.

METHODS

Consecutive patients with resectable esophageal or GEJ adenocarcinoma who underwent pCT (epirubicin, cisplatin and capecitabine) or nCRT (paclitaxel, carboplatin, and 41.4 Gy) followed by surgery were compared. Propensity score matching (PSM) was applied to create comparable groups.

RESULTS

Of 193 eligible patients, 21 were discarded after PSM; 86 and 86 patients who underwent pCT and nCRT, respectively, remained. Grade ≥ 3 thromboembolic events occurred only in the pCT group (19% vs. 0%, $p < 0.001$), whereas grade ≥ 3 leukopenia occurred more frequently in the nCRT group (14% vs. 4%, $p = 0.015$). No significant differences regarding postoperative morbidity and mortality were found. Pathologic complete response was more frequently observed with nCRT (18% vs. 11%, $p < 0.001$), without significantly improving radicality rates (95% vs. 89%, $p = 0.149$). Both strategies resulted in comparable 3-year progression-free survival (pCT vs. nCRT: 46% vs. 55%, $p = 0.373$) and overall survival rates (49% vs. 52%, $p = 0.918$). At 3-year follow-up, fewer locoregional recurrences occurred in the nCRT group (15% vs. 37%, $p = 0.018$).

CONCLUSIONS

Perioperative chemotherapy and neoadjuvant chemoradiotherapy in patients with resectable esophageal or gastroesophageal junction adenocarcinoma are both associated with substantial regimen-specific adverse events. Compared to perioperative chemotherapy, neoadjuvant chemoradiotherapy achieves higher pathologic response rates and a lower risk of locoregional recurrence, without improving survival.

INTRODUCTION

Esophageal cancer is the sixth most common cause of cancer-related mortality worldwide, and the incidence of esophageal adenocarcinoma is rapidly increasing^{1,2}. Resection of the esophagus with en-bloc lymphadenectomy is the mainstay of curative treatment for patients with esophageal cancer³. However, a multimodality treatment approach is increasingly utilized since both perioperative chemotherapy (pCT) and neoadjuvant chemoradiotherapy (nCRT) have shown a survival benefit over surgery alone⁴⁻⁷. Response to neoadjuvant treatment has been associated with a higher percentage of radical surgical resection rates (R0), a reduced risk of tumor recurrence, and improved overall survival rates⁸⁻¹⁰. Currently, the optimal multimodality treatment strategy for resectable esophageal or gastroesophageal junction (GEJ) adenocarcinoma has not been established^{5,11}.

The use of perioperative chemotherapy for esophageal cancer has yielded varying outcomes in terms of toxicity, pathologic outcome, and survival¹²⁻¹⁴. The MAGIC-trial showed a significant benefit of perioperative epirubicin, cisplatin, and fluorouracil chemotherapy over surgery alone with regard to R0 resection rates and survival⁴. Consecutive studies found that oral capecitabine was as effective as fluorouracil in this group of patients^{15,16}. Nevertheless, these treatment regimens are associated with a high toxicity profile, mainly consisting of thromboembolic events^{4,17}. In the recent CROSS trial, chemoradiotherapy followed by surgery was compared to surgery alone for patients with resectable esophageal cancer¹⁰. This trial recorded significantly increased R0 and survival rates, and achieved a significant rate of pathologic complete response (pathCR), favoring the multimodality group. This improvement was found to be clinically relevant for both squamous cell carcinoma and adenocarcinoma⁶. Due to the relatively low percentage of adverse events in combination with improved oncologic results, neoadjuvant chemoradiotherapy followed by surgery is now the preferred treatment strategy in the U.S. National Comprehensive Cancer Network (NCCN) guidelines and the European Society of Medical Oncology (ESMO) clinical practice guidelines^{18,19}. Meanwhile, perioperative chemotherapy remains the preferred treatment option for resectable esophageal or GEJ adenocarcinoma according to the British Society of Gastroenterology guidelines²⁰.

Currently, direct comparisons between perioperative chemotherapy with epirubicin, cisplatin and capecitabine (ECC) and neoadjuvant chemoradiotherapy consisting of paclitaxel, carboplatin and concurrent radiotherapy (CROSS) for patients with esophageal or GEJ adenocarcinoma are limited. Therefore, the current study aimed to compare these two treatment regimens with regard to toxicity, pathologic outcome, and survival.

PATIENTS AND METHODS

PATIENT POPULATION

From a prospectively acquired database consecutive patients treated with perioperative ECC or preoperative nCRT according to CROSS with the intention to receive surgery for resectable esophageal or GEJ adenocarcinoma (Siewert type I and II) were analyzed. Patients were treated between October 2006 and September 2015 at our tertiary referral center. In May 2012 the standard treatment with curative intent was switched from perioperative chemotherapy to neoadjuvant chemoradiotherapy. Diagnostic work-up consisted of endoscopy with biopsy, endoscopic ultrasound (EUS), ultrasonography of the neck, and either standalone computed tomography (CT) or integrated ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET)/CT scanning for clinical staging. From 2013 onwards, ^{18}F -FDG PET/CT was introduced as routine part of initial staging at our hospital. All patients had a WHO performance status of 0-2 and biopsy-proven resectable adenocarcinoma (clinical stage T1N1-3 or T2-4aN0-3) with no evidence of distant metastases at initial staging.

TREATMENT PROTOCOLS

Chemotherapy consisted of pre- and postoperative three-week cycles of an intravenous bolus of epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2), followed by 625 mg/m^2 of capecitabine twice daily for 21 days¹⁷. The chemoradiotherapy regimen consisted of a total radiation dose of 41.4 Gy in 23 fractions of 1.8 Gy in 5 weeks with concurrent weekly administration of carboplatin (targeted at an area under the curve of 2 mg/ml per minute) and paclitaxel (50 mg/m^2 of body-surface area)¹⁰. After completion of neoadjuvant treatment, patients were scheduled for transthoracic esophagectomy with en-bloc two-field lymphadenectomy followed by gastric conduit reconstruction with cervical anastomosis end-to-side with hand-sewn continuous sutures in monolayer²¹. Patients with severe cardiopulmonary co-morbidity were scheduled for a transhiatal esophagectomy as the risk of complications associated with a transthoracic resection was considered too high.

DATA COLLECTION AND FOLLOW-UP

Clinical patient characteristics, treatment details (e.g. chemotherapy regimens, surgical approach) and surgical outcome data (e.g. anastomotic leakage, hospital stay) were collected from the prospectively maintained database. Grading of toxicity was performed retrospectively by two independent observers according

to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0²². After esophagectomy, patients were routinely followed with an interval of 3 months in the first year, 6 months during the second year, and 12 months until 5 years after surgery. Diagnostic imaging was only performed in case of clinically suspected tumor recurrence. Recurrence was confirmed by histology or by clinical follow-up. Locoregional recurrence was defined as recurrence at the anastomotic site, mediastinum or upper abdomen, while distant recurrence was defined as recurrence in distant organs or distant lymph nodes. Progression-free survival (PFS) and overall survival (OS) were calculated from the date of first chemotherapy infusion to either the date of recurrence or last follow-up, or the date of death or last follow-up, respectively. Death from non-disease-related causes (e.g. myocardial infarction) were censored in the PFS analysis.

POSTOPERATIVE COURSE

Postoperative complications were graded according to the Clavien-Dindo classification^{23,24}. Postoperative complications were prospectively registered and discussed weekly.

PATHOLOGIC ANALYSIS

The resected specimens were processed according to a standardized protocol in accordance with the 7th edition of the International Union Against Cancer for ypTNM-classification²⁵. The (circumferential) resection margin was evaluated using the College of American Pathologist criteria²⁶. The degree of histopathologic tumor regression was graded according to the system proposed by Mandard et al²⁷.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY) and R 3.1.2 open-source software (<http://www.R-project.org>; 'MatchIt' and 'optmatch' packages). To evaluate significance of differences between the two groups, the chi-square test was used for categorical variables, and the Student's T-test and Mann-Whitney U-test were used for parametric and non-parametric continuous variables, respectively. Overall survival and PFS were assessed using the Kaplan-Meier method, with the log-rank test to determine significance. A p-value of <0.05 was considered statistically significant.

To reduce the effect of confounding influences of covariates on the assessed outcome between the two study groups (pCT versus nCRT), propensity score matching was used to build comparable groups. First, a propensity score (the

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probability [ranging from 0 to 1] that a patient was assigned to the chemotherapy or chemoradiotherapy group given the individual profile of potential confounders) was calculated for each patient using logistic regression, based on all covariates (n=10) marked in **Table 1**. Next, propensity score matching with the 'optimal matching' technique was used to generate matched pairs of cases (1:1) in which the average within-pair difference in propensity scores was minimized²⁸. Patients who fell outside the joint range of propensity scores (i.e. range of common support) were discarded. Due to the introduction of a randomized surgical trial in our center halfway through the study period²⁹, it appeared impossible to balance the groups for type of surgery (open vs. minimally invasive) without compromising the sample size of the nCRT group. Because the type of surgery may have influenced the postoperative course (including complications, hospital stay, and mortality) and R0 resections rates, additional analyses were performed. In the additional analyses the studied associations of the treatment arm (pCT vs. nCRT) with postoperative course parameters and R0 resection rate was adjusted for the type of surgery using multivariable logistic regression analysis.

RESULTS

PATIENT CHARACTERISTICS

In the study period a total of 106 patients underwent pCT and 87 underwent nCRT. In the original cohort significant differences were observed regarding surgical approach, type of surgery and clinical N-stage. Using propensity score matching, 86 chemotherapy and 86 chemoradiotherapy patients could be matched without large imbalances of the used covariates. Besides a remaining observed difference in type of surgery ($p=0.013$), balance among the two treatment arms improved substantially (**Table 1**). The results of the propensity score-matched cohort will be discussed here in further detail as this cohort consisted of groups with improved comparability.

TOXICITY

A total of 66 out of 86 patients (79%) received the complete treatment regimen of three preoperative chemotherapy cycles. Postoperative continuation of chemotherapy was administered in 34 patients (40%). The 5 cycles of chemotherapy within the nCRT group were completed in 63 of 86 patients (73%), whereas 85 (99%) received all 23 fractions of radiotherapy. The main reason for not completing all chemotherapy cycles in the nCRT group was leukopenia. Grade ≥ 3 adverse events in the pCT group mainly consisted of clinically relevant thromboembolic

Table 1 Comparison of baseline characteristics according to treatment protocol, before and after propensity score matching

| Variables | Original cohort | | | Propensity score matched cohort | | |
|---------------------------------|-----------------|----------------|---------|---------------------------------|----------------|---------|
| | pCT (n=106) | nCRT (n=87) | p value | pCT (n=86) | nCRT (n=86) | p value |
| Male gender* | 87 (82.1) | 77 (88.5) | 0.214 | 73 (84.9) | 76 (88.4) | 0.502 |
| Age (years)* | 62.5 ± 8.8 | 64.6 ± 8.1 | 0.099 | 62.9 ± 8.9 | 64.5 ± 8.1 | 0.232 |
| BMI (kg/m ²)*† | 26.3 ± 3.8 | 26.3 ± 4.1 | 0.873 | 26.4 ± 3.9 | 26.2 ± 4.1 | 0.744 |
| ASA score* | | | 0.183 | | | 0.445 |
| I | 30 (28.3) | 16 (18.4) | | 21 (24.4) | 16 (18.6) | |
| II | 68 (64.2) | 60 (69.0) | | 58 (67.4) | 59 (68.6) | |
| III | 8 (7.5) | 11 (12.6) | | 7 (8.1) | 11 (12.8) | |
| WHO performance status* | | | 0.086 | | | 0.169 |
| 0 | 57 (53.8) | 36 (41.4) | | 45 (52.3) | 36 (41.9) | |
| 1 | 49 (46.2) | 51 (58.6) | | 41 (47.7) | 50 (58.1) | |
| COPD | 11 (10.4) | 10 (11.5) | 0.804 | 8 (9.3) | 10 (11.6) | 0.618 |
| Cardiac co-morbidity | 25 (23.6) | 30 (34.5) | 0.095 | 20 (23.3) | 30 (34.9) | 0.093 |
| Diabetes mellitus | 11 (10.4) | 13 (14.9) | 0.339 | 10 (11.6) | 13 (15.1) | 0.502 |
| History of smoking* | 59 (55.7) | 60 (69.0) | 0.059 | 47 (54.7) | 59 (68.6) | 0.060 |
| Surgical approach* | | | 0.035 | | | 0.485 |
| Transhiatal | 23 (21.7) | 9 (10.3) | | 12 (14.0) | 9 (10.5) | |
| Trans thoracic | 83 (78.3) | 76 (89.7) | | 74 (86.0) | 77 (89.5) | |
| Type of surgery* | | | 0.008 | | | 0.013 |
| Open | 18 (17.0) | 29 (33.3) | | 14 (16.3) | 28 (32.6) | |
| Minimally invasive | 88 (83.0) | 58 (66.7) | | 72 (83.7) | 58 (67.4) | |
| Tumor length on endoscopy (cm)† | 5.3 ± 2.5 | 4.8 ± 2.3 | 0.219 | 5.3 ± 2.6 | 4.8 ± 2.3 | 0.191 |
| Clinical T-stage** | | | 0.301 | | | 0.514 |
| T1 | 2 (1.9) | 2 (2.3) | | 1 (1.2) | 2 (2.3) | |
| T2 | 9 (8.5) | 15 (17.2) | | 9 (10.5) | 15 (17.4) | |
| T3 | 91 (85.8) | 68 (78.2) | | 73 (84.9) | 67 (77.9) | |
| T4 | 4 (3.8) | 2 (2.3) | | 3 (3.5) | 2 (2.3) | |
| Clinical N-stage*§ | | | 0.019 | | | 0.110 |
| N0 | 25 (23.6) | 26 (29.9) | | 24 (27.9) | 25 (29.1) | |
| N1 | 29 (27.4) | 36 (41.4) | | 23 (26.7) | 36 (41.9) | |
| N2 | 34 (32.1) | 20 (23.0) | | 30 (34.9) | 20 (23.3) | |
| N3 | 18 (17.0) | 5 (5.7) | | 9 (10.5) | 5 (5.8) | |

Note. Data are numbers of patients with percentages in parentheses. *: variables used for propensity score matching. †: data are mean ± standard deviation. ‡: clinical tumor stage (cT) classified according to the 7th edition of the International Union Against Cancer (UICC) tumor-node-metastasis (TNM) classification²⁵. §: clinical lymph-node (cN) stage classified according to the 7th edition of the UICC TNM classification²⁵. ASA: American Society of Anesthesiologists. BMI: body mass index. COPD: chronic obstructive pulmonary disease. WHO: World Health Organization.

events, which occurred only in the pCT group and not in the nCRT group (19 vs. 0%, $p<0.001$), 9 of which were symptomatic pulmonary emboli. The remaining 7 thromboembolic events were asymptomatic (aortic or pulmonary emboli) and were detected during follow-up CT scans. Also grade ≥ 3 diarrhea occurred only in the chemotherapy group (8 vs. 0%, $p=0.014$). On the contrary, the incidence of grade ≥ 3 leukopenia in the nCRT group was significantly higher than observed in the chemotherapy group (14 vs. 4%, $p=0.015$). Other preoperative grade ≥ 3 adverse events did not differ significantly between the chemotherapy and chemoradiotherapy group (**Table 2**).

Table 2 Comparative analysis of toxicity (grade 3 or higher)* during neoadjuvant treatment

| Toxicity | pCT (n=86) | nCRT (n=86) | <i>p</i> value |
|---|---------------|----------------|----------------|
| Thromboembolic event (grade ≥ 3) | 16 (18.6) | 0 (0.0) | <0.001 |
| Neutropenia (grade ≥ 3) | 2 (2.3) | 7 (8.1) | 0.168 |
| Febrile neutropenia (grade ≥ 3) | 5 (5.8) | 2 (2.3) | 0.443 |
| Leukopenia (grade ≥ 3) | 3 (3.5) | 12 (14.0) | 0.015 |
| Thrombocytopenia (grade ≥ 3) | 1 (1.2) | 5 (5.8) | 0.210 |
| Anemia (grade ≥ 3) | 1 (1.2) | 0 (0.0) | 1.000 |
| Nausea (grade ≥ 3) | 7 (8.1) | 5 (5.8) | 0.549 |
| Vomiting (grade ≥ 3) | 8 (9.3) | 3 (3.5) | 0.119 |
| Diarrhea (grade ≥ 3) | 7 (8.1) | 0 (0.0) | 0.014 |
| Dehydration (grade ≥ 3) | 2 (2.3) | 3 (3.5) | 0.650 |
| Anorexia (grade ≥ 3) | 1 (1.2) | 0 (0.0) | 1.000 |
| Esophageal perforation (grade ≥ 3) | 0 (0.0) | 1 (1.2) | 1.000 |
| Gastric hemorrhage (grade ≥ 3) | 0 (0.0) | 1 (1.2) | 1.000 |
| Dyspnea (grade ≥ 3) | 0 (0.0) | 1 (1.2) | 1.000 |
| Allergic reaction (grade ≥ 3) | 1 (1.2) | 1 (1.2) | 1.000 |
| Acute coronary syndrome (grade ≥ 3) | 1 (1.2) | 0 (0.0) | 1.000 |
| Any adverse event (grade ≥ 3) | 39 (45.3) | 34 (39.8) | 0.440 |
| Premature discontinuation | 20 (23.3) | 23 (26.7) | 0.597 |
| Postoperative continuation | 34 (39.5) | NA | NA |

Note. Data are numbers of patients with percentages in parentheses.

*: adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0²².

POSTOPERATIVE COURSE

In the chemotherapy group, 84 of 86 (98%) patients underwent esophageal resection, compared to 84 of 86 (98%) in the chemoradiotherapy group. Reasons to refrain from resection were disease progression during therapy (1 patient in the

pCT group) and diagnosis of metastatic disease during surgery (1 patient in the pCT group and 2 patients in the nCRT group). Surgical results and postoperative complications are demonstrated in **Table 3**. In the pCT group, a complicated postoperative course occurred in 58 of 84 patients (69%), whereas in the nCRT group 61 of 84 patients (73%) had a complicated course ($p=0.661$). Severity and incidences of specific postoperative complications were comparable between both groups. Also, duration of hospital stay and postoperative 30-day mortality were comparable. In the pCT group, 5 of 84 (6%) patients died within 90 days after surgery, compared to 6 of 84 (7%), in the nCRT group ($p=0.755$). Of the 5 deaths in

Table 3 Comparative analysis of postoperative course*

| Outcome | pCT (n=84) | nCRT (n=84) | p value |
|---|---------------|----------------|---------|
| Complicated postoperative course | 58 (69.0) | 61 (72.6) | 0.661 |
| Anastomotic leakage [†] | 20 (23.8) | 24 (28.6) | 0.483 |
| Pneumonia [‡] | 29 (34.5) | 29 (34.5) | 1.000 |
| Cardiac arrhythmia [§] | 11 (12.6) | 20 (23.8) | 0.058 |
| Chyle leak | 14 (16.7) | 12 (14.3) | 0.870 |
| Recurrent nerve paresis | 6 (7.1) | 8 (9.5) | 0.577 |
| Wound infection | 3 (3.6) | 5 (6.0) | 0.469 |
| Postoperative bleeding | 2 (1.2) | 2 (2.4) | 1.000 |
| Thromboembolic event | 5 (6.0) | 5 (6.0) | 1.000 |
| Clavien-Dindo grade [¶] | | | 0.334 |
| I | 7 (8.3) | 8 (9.5) | |
| II | 28 (33.3) | 19 (22.6) | |
| III ^a | 0 (0.0) | 3 (3.6) | |
| III ^b | 6 (7.1) | 14 (16.7) | |
| IV | 15 (17.9) | 11 (13.1) | |
| V | 3 (3.6) | 6 (7.1) | |
| Grade IIIb or higher | 23 (27.4) | 31 (36.9) | 0.186 |
| Duration of hospital stay (days) [‡] | 15 [11-23] | 16 [11-27] | 0.465 |
| Duration of ICU stay (days) [‡] | 1 [1-4] | 1 [1-4] | 0.563 |
| 30-day mortality | 1 (1.2) | 2 (2.4) | 1.000 |
| 90-day mortality | 5 (6.0) | 6 (7.1) | 0.755 |

Note. Data are numbers of patients with percentages in parentheses. *: of the 86 and 86 patients treated with neoadjuvant chemotherapy and chemoradiotherapy, 84 and 84 underwent surgery, respectively. †: anastomotic leakage included all clinical and radiologic findings of anastomotic dehiscence or fistula. ‡: pneumonia was defined by the Utrecht pneumonia score⁴². §: cardiac arrhythmia was defined as any change in rhythm on an electrocardiogram requiring treatment. ||: chyle leak was defined as elevated levels of triglycerides in intrathoracic fluid requiring treatment. ¶: Clavien-Dindo classification, a surgical complication grading system^{23,24}. ‡: data presented as median with interquartile range between brackets.

the pCT group 3 died due to postoperative complications and 2 patients died due to rapid tumor progression without severe postoperative complications. In the nCRT group all 6 patients died due to severe postoperative complications. Additional analyses showed that the use of pCT versus nCRT did also not result in different risks of postoperative complications, hospital stay, and mortality when adjusted for type of surgery (open vs. minimally invasive).

PATHOLOGIC ASSESSMENT

Pathologic results are presented in **Table 4**. A pathCR was more frequently observed in patients who underwent nCRT compared to pCT (18% vs. 11%, respectively, $p < 0.001$). Also a good response (Mandard 1 and 2) occurred more

Table 4 Comparative analysis of postoperative histopathology*

| Outcome | pCT (n=84) | nCRT (n=84) | <i>p</i> value |
|---------------------------------------|---------------|----------------|----------------|
| Pathologic T-stage [†] | | | 0.131 |
| ypT0 | 9 (10.7) | 15 (17.9) | |
| ypT1 ^b | 12 (14.3) | 10 (11.9) | |
| ypT2 | 12 (14.3) | 19 (22.6) | |
| ypT3 | 48 (57.1) | 38 (45.2) | |
| ypT4 | 3 (3.6) | 2 (2.4) | |
| Pathologic N-stage [‡] | | | 0.353 |
| ypN0 | 36 (42.9) | 42 (50.0) | |
| ypN1 | 48 (57.1) | 42 (50.0) | |
| Tumor regression grade [§] | | | <0.001 |
| I | 9 (10.7) | 15 (17.9) | |
| II | 5 (6.0) | 16 (19.0) | |
| III | 17 (20.2) | 27 (32.1) | |
| IV | 18 (21.4) | 22 (26.2) | |
| V | 35 (41.7) | 4 (4.8) | |
| Radicality of resection | | | 0.149 |
| R0 | 75 (89.3) | 80 (95.2) | |
| R1 | 9 (10.7) | 4 (4.8) | |

Note. Data are numbers of patients with percentages in parentheses. *: of the 86 and 86 patients treated with neoadjuvant chemotherapy and chemoradiotherapy, 84 and 84 underwent surgery, respectively. †: pathologic tumor stage (pT) classified according to the 7th edition of the International Union Against Cancer (UICC) tumor-node-metastasis (TNM) classification²⁵. ‡: pathologic lymph-node (pN) stage classified according to the 7th edition of the UICC TNM classification²⁵. ||: the (circumferential) resection margin was evaluated using the College of American Pathologist (CAP) criteria. §: histopathologic tumor regression graded according to the system proposed by Mandard²⁷. ||: the (circumferential) resection margin was evaluated using the College of American Pathologist criteria²⁶.

often in the nCRT group compared to the pCT group (37% vs. 17%, $p=0.003$). An R0 resection was achieved in 75 of 84 surgical patients (89%) in the chemotherapy group, compared to 80 of 84 (95%) in the chemoradiotherapy group ($p=0.149$). Additional analyses showed that the use of pCT versus nCRT did also not influence R0 resection rates when adjusted for type of surgery.

SURVIVAL

In the intention-to-treat analysis (including all patients who did and did not undergo surgical resection after propensity score matching), median follow-up was 34 months (range 2-97) in the pCT group and 15 months (range 3-40) in the nCRT group, respectively. At 3 years follow-up, OS (49 vs. 52%; log-rank test $p=0.918$) and PFS (46 vs. 55%; log-rank test $p=0.373$) were comparable between the pCT and nCRT group, respectively (**Figure 1**). Further analysis showed that at 3 years follow-up, locoregional recurrences occurred less frequently in the nCRT group compared to the pCT group (15 vs. 37%, respectively; log-rank test $p=0.018$). No significant difference in the incidence of distant recurrences at 3 years was observed between the pCT and nCRT group (50 vs. 43%; log-rank test $p=0.429$), respectively.

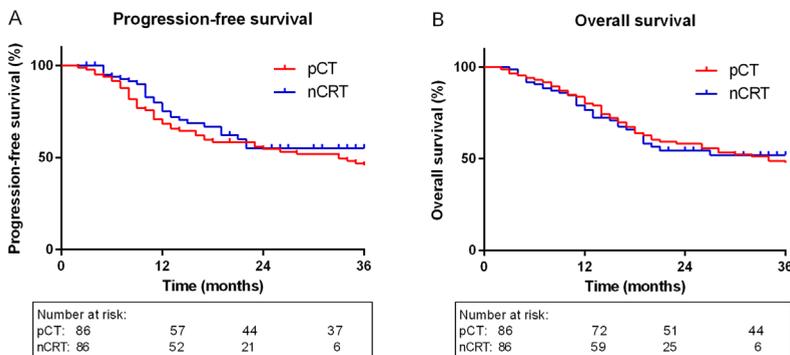


Figure 1 Comparison of progression-free survival (A) and overall survival (B) in propensity score-matched perioperative chemotherapy and neoadjuvant chemoradiotherapy followed by esophagectomy groups.

DISCUSSION

In this propensity score-matched cohort study, outcomes of perioperative chemotherapy were compared to neoadjuvant chemoradiotherapy for patients with resectable esophageal or GEJ adenocarcinoma. No significant improvements were achieved with nCRT as compared to pCT in terms of radical resection rates or progression-free survival and overall survival. However, nCRT was associated with improved tumor downstaging and a higher pathCR rate compared to chemotherapy. This observation likely translated into the observed decrease in locoregional recurrences in the nCRT group.

According to recent literature, pCT and nCRT both improve survival compared to surgery alone in patients treated for esophageal or GEJ adenocarcinoma^{4,6}. In two meta-analyses, indirect treatment comparisons have suggested a greater survival benefit of nCRT over pCT^{5,7}. However, in both meta-analyses the difference between the two groups did not reach statistical significance. This finding corresponds with the direct comparison in our study that showed no significant survival benefit for one of the regimens.

Until now, three studies have made a similar attempt to directly compare nCRT with pCT for patients with esophageal or GEJ adenocarcinoma³⁰⁻³². Stahl et al., randomly allocated 119 patients to either chemotherapy (cisplatin, 5-FU, leucovorin) or chemoradiotherapy (cisplatin, 5-FU, leucovorin, 30 and Gy) both followed by surgery³⁰. The chemoradiotherapy arm showed a higher probability of pathologic complete response (2% after chemotherapy vs. 16% after nCRT, $p=0.03$) and a reduction in locoregional recurrence (41% after chemotherapy vs. 23% after nCRT; $p=0.06$). Although the study was closed early due to slow patient accrual, there was a trend towards a 3-year overall survival advantage (28% vs. 48%, $p=0.07$) for the nCRT group. In a comparable trial by Burmeister et al., 75 patients were randomized to receive either preoperative chemotherapy (cisplatin, 5-FU) or preoperative chemoradiotherapy (cisplatin, 5-FU, and 35 Gy)³¹. This study showed a higher histopathologic complete response (13% vs. 0%) and R0 resection rate (100% vs. 89%) for patients treated with chemoradiotherapy compared to chemotherapy, respectively but no difference in survival was observed³¹. A recent retrospective analysis of 116 patients by Guillaume et al., again showed a higher pathCR rate (20% vs. 3%; $p=0.011$) in patients treated with nCRT (cisplatin, 5-FU, and 45 Gy) compared to perioperative chemotherapy (docetaxel, cisplatin, 5-FU), with comparable survival between the two groups³².

Our finding that nCRT increases the pathCR rate corresponds with the studies discussed above. The nCRT group yielded a 18% pathCR rate compared to 11% in the pCT group ($p < 0.001$), respectively. Additionally, in the current series a significantly lower incidence of locoregional tumor recurrence and a trend towards a higher R0 resection rate was found after nCRT. This supports the theory of effective tumor downstaging in this group. Pathologic response after neoadjuvant treatment is a major determinant of survival in patients with esophageal cancer^{8,27,33-35}. Interestingly, in the current study and in the mentioned comparative studies, this finding did not translate into a significant survival benefit for the nCRT group. However, it is important to address that these studies and the current study are not properly powered to identify potential subtle survival differences between the two treatment arms.

In addition to improving oncologic results, objective evaluation of the risk and benefits must be considered when comparing different types of neoadjuvant therapy. A disadvantage of neoadjuvant therapies is the associated toxicity, which could contribute to an increase in postoperative morbidity and mortality³⁶. In the current study, both treatment strategies caused substantial regimen-specific toxicity that are comparable with earlier reports^{10,15,17}. The majority of patients (61%) were not able to start postoperative chemotherapy in the current study, which corresponds with two previous studies in which only 29% and 42% of the patients completed postoperative chemotherapy, respectively^{4,13}. In the current study no significant difference with regard to severity and incidence of postoperative morbidity or perioperative mortality between the pCT and nCRT groups were observed. The current study is probably underpowered to detect small differences to this regard. However, the results are consistent with two recent meta-analyses that compared postoperative morbidity and mortality between patients treated with pCT or nCRT for esophageal (adeno)carcinoma and found no differences^{38,39}. On the other hand, in a recent randomized controlled trial more severe postoperative complications were observed after nCRT compared to chemotherapy³⁷. This provides a level of uncertainty with regard to the safety of adding radiotherapy to the neoadjuvant chemotherapy.

Postoperative anastomotic leakage occurred quite frequently in the current series (24-29%). Although this appears higher compared to other series, our definition of anastomotic leakage is unrestricted including any sign of clinical, endoscopic

or radiologic proof of anastomotic leakage. As such, the leakage rate in this study appears to be comparable with the leakage rates of 22% to 30% that were recorded in the recent CROSS-trial¹⁰.

Strengths of this study include the use of predominantly prospective collected data. Furthermore, the sample size of this study is relatively large compared to previous comparative studies. Lastly, this is one of the first studies that directly compares two highly recommended multimodality treatment regimens (ECC vs. CROSS) for patients with esophageal or GEJ adenocarcinoma. Potential limitations of this study include its retrospective character and lack of randomization. In order to adjust for the potentially resulting confounding bias, propensity score matching was performed to improve the comparability of the two groups. However, the inability of propensity score matching to adjust for unknown confounders that could explain some of our findings remains a limitation. Another limitation of this study concerns the addition of a diagnostic ¹⁸F-FDG PET/CT later during the study period when patients were more likely to receive nCRT than pCT, which to some extent may have improved the prognosis of nCRT patients included in this study through improved patient selection for treatment with curative intent. Furthermore, the median-follow up in the nCRT group was relatively short. Therefore, subtle effects on progression-free survival and overall survival cannot be excluded. Due to the inclusion of two groups receiving treatment in different time periods it is possible that unknown confounders have changed over time which to some extent might have created differences between the two groups. Currently, several randomized trials comparing chemotherapy and nCRT regimens are underway and should resolve the limitations in the current literature (CROSS versus MAGIC [NCT01726452], Neoscope-trial [NCT01843829]⁴⁰, TOPGEAR-trial [NCT01924819]⁴¹).

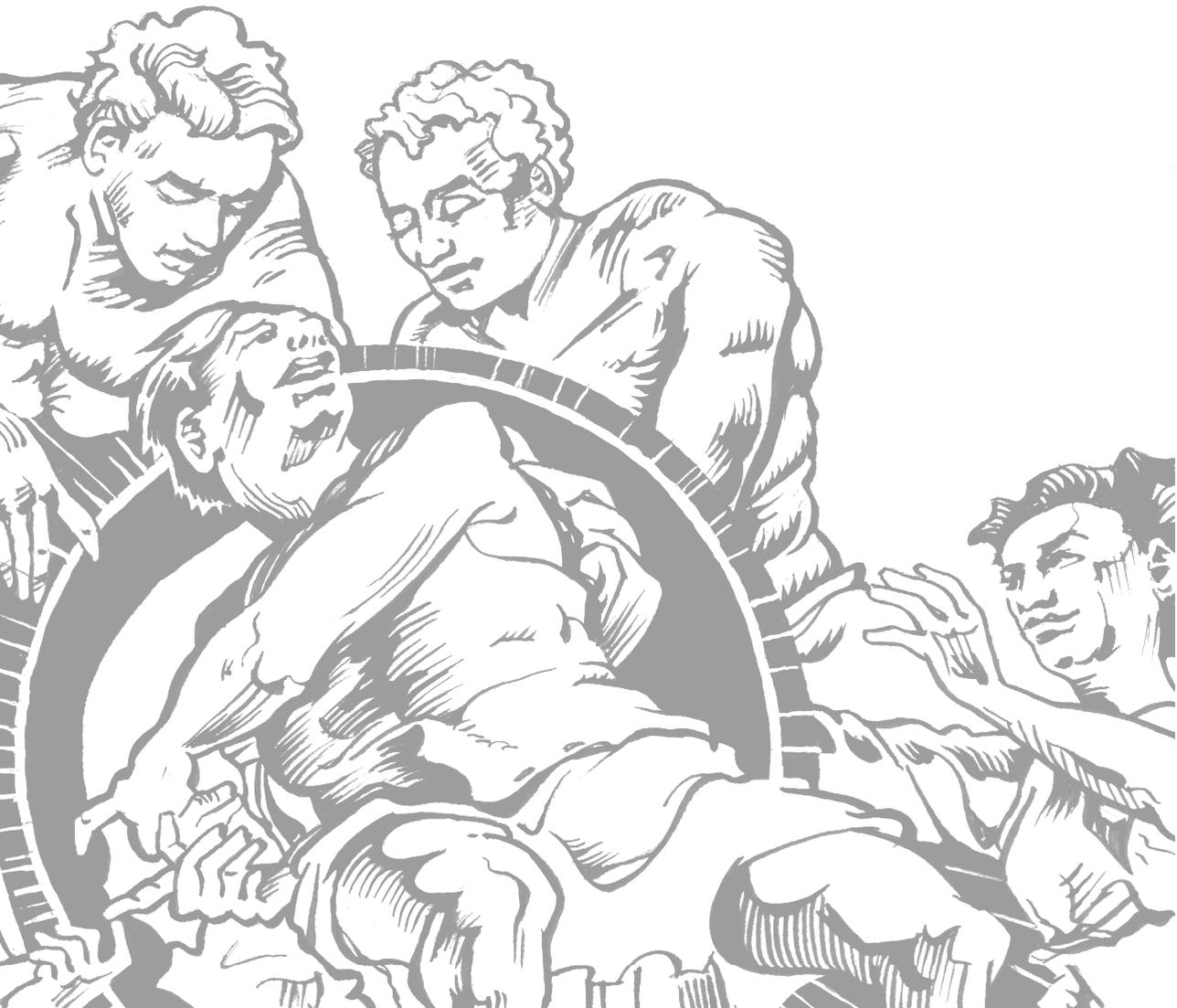
In conclusion, perioperative chemotherapy and neoadjuvant chemoradiotherapy are both associated with substantial regimen-specific adverse events and postoperative morbidity. Neoadjuvant chemoradiotherapy achieves higher pathologic complete response rates and a lower risk of locoregional recurrence, with similar survival compared to perioperative chemotherapy. The acceptable toxicity in combination with improved response rates and locoregional control suggests it is reasonable to consider chemoradiotherapy as standard neoadjuvant treatment strategy for patients with resectable adenocarcinoma of the esophagus or gastroesophageal junction.

REFERENCES

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65:87-108
2. Zhang Y. Epidemiology of esophageal cancer. *World J Gastroenterol* 2013;19:5598-5606
3. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. *Lancet* 2013;381:400-12
4. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20
5. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011;12:681-92
6. Shapiro J, van Lanschot JJ, Hulshof MC, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol* 2015;16:1090-8
7. Ronellenfitsch U, Schwarzbach M, Hofheinz R, et al. Preoperative chemo(radio)therapy versus primary surgery for gastroesophageal adenocarcinoma: systematic review with meta-analysis combining individual patient and aggregate data. *Eur J Cancer* 2013;49:3149-58
8. Meredith KL, Weber JM, Turaga KK, et al. Pathologic response after neoadjuvant therapy is the major determinant of survival in patients with esophageal cancer. *Ann Surg Oncol* 2010;17:1159-67
9. Kidane B, Coughlin S, Vogt K, et al. Preoperative chemotherapy for resectable thoracic esophageal cancer. *Cochrane Database Syst Rev* 2015;5:CD001556
10. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
11. Mariette C, Piessen G, Triboulet JP. Therapeutic strategies in oesophageal carcinoma: role of surgery and other modalities. *Lancet Oncol* 2007;8:545-53
12. Schuhmacher C, Gretschel S, Lordick F, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. *J Clin Oncol* 2010;28:5210-8
13. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCO multicenter phase III trial. *J Clin Oncol* 2011;29:1715-21
14. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med* 1998;339:1979-84
15. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;358:36-46
16. Starling N, Okines A, Cunningham D, et al. A phase II trial of preoperative chemotherapy with epirubicin, cisplatin and capecitabine for patients with localised gastro-oesophageal junctional adenocarcinoma. *Br J Cancer* 2009;100:1725-30

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17. van der Sluis PC, Ubink I, van der Horst S, et al. Safety, efficacy, and long-term follow-up evaluation of perioperative epirubicin, cisplatin, and capecitabine chemotherapy in esophageal resection for adenocarcinoma. *Ann Surg Oncol* 2015;22:1555-63
 18. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)—Esophageal and Esophagogastric Junction Cancers Version 3. 2015. Available at: http://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf
 19. Stahl M, Mariette C, Haustermans K, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24 Suppl 6:vi51-6
 20. Allum WH, Blazeby JM, Griffin SM, et al. Guidelines for the management of oesophageal and gastric cancer. *Gut* 2011;60:1449-72
 21. Haverkamp L, van der Sluis PC, Verhage RJ, et al. End-to-end cervical esophagogastric anastomoses are associated with a higher number of strictures compared with end-to-side anastomoses. *J Gastrointest Surg* 2013;17:872-6
 22. National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0. NCI, NIH, DHHS. May 29, 2009. NIH publication #09-7473
 23. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205-13
 24. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009;250:187-96
 25. Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC Cancer Staging Manual: esophagus and esophagogastric junction. *Ann Surg Oncol* 2010;17:1721-4
 26. Verhage RJ, Zandvoort HJ, ten Kate FJ, et al. How to define a positive circumferential resection margin in T3 adenocarcinoma of the esophagus. *Am J Surg Pathol* 2011;35:919-26
 27. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer* 1994;73:2680-6
 28. Ho D, Imai K, King G, et al. MatchIt: Non-parametric preprocessing for parametric causal inference. *Journal of Statistical Software* 2011;42
 29. van der Sluis PC, Ruurda JP, van der Horst S, et al. Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer, a randomized controlled trial (ROBOT trial). *Trials* 2012;13:230
 30. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009;27:851-6
 31. Burmeister BH, Thomas JM, Burmeister EA, et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. *Eur J Cancer* 2011;47:354-60
 32. Luc G, Vendrely V, Terrebonne E, et al. Neoadjuvant chemoradiotherapy improves histological results compared with perio-

- perative chemotherapy in locally advanced esophageal adenocarcinoma. *Ann Surg Oncol* 2015;22:604-9
33. Chirieac LR, Swisher SG, Ajani JA, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. *Cancer* 2005;103:1347-55
 34. Donahue JM, Nichols FC, Li Z, et al. Complete pathologic response after neoadjuvant chemoradiotherapy for esophageal cancer is associated with enhanced survival. *Ann Thorac Surg* 2009;87:392-8; discussion 398-9
 35. Berger AC, Farma J, Scott WJ, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. *J Clin Oncol* 2005;23:4330-7
 36. Hamilton E, Vohra RS, Griffiths EA. What is the best neoadjuvant regimen prior to oesophagectomy: chemotherapy or chemoradiotherapy? *Int J Surg* 2014;12:196-9
 37. Klevebro F, Johnsen G, Johnson E, et al. Morbidity and mortality after surgery for cancer of the oesophagus and gastro-oesophageal junction: A randomized clinical trial of neoadjuvant chemotherapy vs. neoadjuvant chemoradiation. *Eur J Surg Oncol* 2015;41:920-6
 38. Kumagai K, Rouvelas I, Tsai JA, et al. Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers. *Br J Surg* 2014;101:321-38
 39. Kumagai K, Rouvelas I, Tsai JA, et al. Survival benefit and additional value of preoperative chemoradiotherapy in resectable gastric and gastro-oesophageal junction cancer: a direct and adjusted indirect comparison meta-analysis. *Eur J Surg Oncol* 2015;41:282-94
 40. Mukherjee S, Hurt CN, Gwynne S, et al. NEOSCOPE: a randomised Phase II study of induction chemotherapy followed by either oxaliplatin/capecitabine or paclitaxel/carboplatin based chemoradiation as pre-operative regimen for resectable oesophageal adenocarcinoma. *BMC Cancer* 2015;15:48
 41. Leong T, Smithers BM, Michael M, et al. TOPGEAR: a randomised phase III trial of perioperative ECF chemotherapy versus preoperative chemoradiation plus perioperative ECF chemotherapy for resectable gastric cancer (an international, intergroup trial of the AGITG/TROG/EORTC/NCIC CTG). *BMC Cancer* 2015;15:532
 42. van der Sluis PC, Verhage RJ, van der Horst S, et al. A new clinical scoring system to define pneumonia following esophagectomy for cancer. *Dig Surg* 2014;31:108-16



Chapter 7

Palliative treatment for esophageal cancer

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Submitted

ABSTRACT

The majority of patients diagnosed with esophageal cancer present with unresectable or metastatic disease. Palliative treatment for these patients aims at controlling dysphagia and other cancer-related symptoms, improving quality of life, and prolonging survival. In the past 25 years substantially improved outcomes have been achieved in the treatment of inoperable non-metastatic patients who are medically not fit for surgery or have unresectable locally advanced disease. Concurrent chemoradiotherapy offers the best palliative care in these patients. In distant metastatic esophageal cancer, several doublet or triplet chemotherapy regimens have been established as first-line treatment options. In addition, long-term results of multiple large randomized phase III trials on the addition of targeted therapies have been published in recent years, with substantial impact on contemporary clinical practice and future research directions. For the local treatment of malignant dysphagia, various treatment options have emerged and self-expandable metal stent (SEMS) placement is currently the most widely applied method. Besides the continuous search for improved SEMS designs to minimize the risk of associated complications, substantial efforts have been made to develop and evaluate the efficacy of anti-reflux stents and irradiation stents in recent years. This review outlines the current evidence on the different modern-day, multidisciplinary, palliative interventions for patients with unresectable or metastatic esophageal cancer with an emphasis on key randomized trials. In addition, the ongoing shift towards more treatment with curative intent is discussed, including potentially curative surgery after downstaging by chemoradiotherapy for unresectable disease and local therapies for oligometastatic disease.

INTRODUCTION

Esophageal cancer is diagnosed in approximately 450,000 patients yearly worldwide, while more than 400,000 patients die from this disease every year¹. As a result, esophageal cancer is listed as the eighth most common cancer worldwide and the sixth leading cause of cancer-related mortality^{1,2}. In Europe and the USA, the incidence of esophageal cancer is rising more rapidly than that of any other cancer, because of a similar increase in the frequency of esophageal adenocarcinoma^{3,4}. Esophageal squamous cell carcinoma remains the predominant tumor type in Asia, Africa, and South America, and among African Americans in North America. Despite recent improvements in staging and (multimodality) treatment, esophageal cancer remains a devastating disease with a 5-year overall survival rate of 15-25%².

Although surgery has been the cornerstone of curative treatment for esophageal cancer for the past 50 years, 50-60% of patients are unsuitable for surgery at presentation due to distant metastases (i.e. M1 disease), tumor ingrowth into unresectable adjacent structures (i.e. T4b disease), extensive upper mediastinal or cervical lymph node metastases, or because the patient is medically not fit for surgery due to comorbidities or poor performance status^{5,6}. For this majority of patients with unresectable or metastatic esophageal cancer, the emphasis of treatment is on effective palliative interventions aiming at relief of dysphagia (which is required in 70-90% of patients) and other cancer-related symptoms, improving quality of life (QoL), and prolonging survival³.

In the past 25 years substantially improved outcomes have been achieved in the treatment of inoperable non-metastatic patients who are medically not fit for surgery or have unresectable locally advanced disease. With the introduction and optimization of definitive concurrent chemoradiotherapy (CRT), 5-year survival increased from 0-14% to 20-25% in these patients, indicating a shift from palliative towards more curative intent⁷⁻¹³. In contrast, despite the development of newer and more active chemotherapy agents in the past 30 years, median survival for patients with metastatic disease at presentation remains only around 1 year¹⁴⁻¹⁶. Nonetheless, in the past few years, long-term results of multiple large randomized phase III trials for first-line and second-line chemotherapy and new targeted agents in these patients have been published with substantial impact on contemporary clinical practice and future research directions¹⁷⁻²⁴.

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For the local treatment of malignant dysphagia, various treatment options have emerged including self-expandable stent placement, intraluminal brachytherapy, external beam radiotherapy (EBRT), neodymium-doped yttrium aluminium garnet (Nd:YAG) laser therapy, and photodynamic therapy (PDT)^{2,25}. The most recent Cochrane meta-analysis on interventions for dysphagia in esophageal cancer (updated in 2014) stated that rigid plastic tube insertion, chemotherapy alone, concurrent CRT, and bypass surgery are not recommended for the palliation of dysphagia, because of a high incidence of inefficacy, slow efficacy, complications and recurrent dysphagia²⁶. Besides the continuous search for improved self-expandable stent designs to minimize the risk of associated complications (e.g. tissue in- and overgrowth, stent migration), substantial efforts have been made to develop and evaluate the efficacy of anti-reflux stents as well as irradiation stents in recent years²⁷⁻²⁹. In addition, combinations of different modalities in the treatment of malignant dysphagia are increasingly being studied as these have been suggested to provide improved treatment results compared with single-modality approaches^{26,30,31}.

Optimal knowledge and use of the various palliative treatment approaches for patients with esophageal cancer will contribute to the impact of the rapidly advancing body of evidence in this area, and to achieving best possible outcomes in individual patients. Therefore, this review outlines the current evidence on the different modern-day, multidisciplinary, palliative interventions for patients with unresectable or metastatic esophageal cancer with an emphasis on key randomized trials.

MULTIDISCIPLINARY MANAGEMENT AND SUPPORTIVE CARE

The continuous changes in clinical practice and management of patients with esophageal cancer are best controlled by specialized esophageal/upper gastrointestinal/thoracic cancer multidisciplinary teams (MDTs) with expertise of several disciplines including surgical, medical, and radiation oncology, gastroenterology, radiology, and pathology³². In addition, the presence of palliative care specialists, nutritional services, clinical nurse specialists (or involved nurses), and other supporting disciplines is desirable³³. Palliative treatment recommendations by the MDT should take into account patient's preferences, performance status, comorbidities, nutritional status, and staging information.

The importance of discussing all esophageal cancer patients in (regional) expert MDTs was stressed in a recent population-based study in The Netherlands, in

which large and significant differences between hospitals of diagnosis were found with regard to the proportion of patients they referred for treatment with curative intent, ranging from 33% to 67% ($p=0.002$)³⁴. The authors concluded that these differences were most likely explained by the fact that local non-expert MDTs – where all patients were first discussed before referral – were less proficient in defining the best treatment options for esophageal cancer patients compared to regional expert MDTs³⁴. The finding that several local hospitals had a significantly worse overall survival supported this hypothesis³⁴.

Best supportive care is an integral part of palliative treatment, whether patients are eligible for treatment aiming at tumor reduction or not. Two of the most frequently encountered esophageal cancer-related symptoms include pain and malnutrition, which are major contributors to a detrimental quality of life^{35,36}. In general, pain is treated with combined short-acting and long-acting opiate analgesia, and sometimes with local radiotherapy (e.g. for bone metastases)². Esophageal cancer comes with unique nutritional issues as the disease predisposes patients to dysphagia, cancer-related cachexia, and invasive therapies³⁷. These factors all contribute to malnutrition, which is a strong indicator of poor prognosis, decreased quality of life, and reduced tolerance to treatment for esophageal cancer³⁸⁻⁴⁰. Recent studies and best practice guidelines advocate for early identification of malnutrition and commencement of intensive nutrition intervention to maintain or improve QoL^{36,41,42}. Besides nutritional counseling on oral intake, interventions may include pharmacotherapy (e.g. antiemetics), and enteral feeding through gastrostomy or jejunostomy tubes. However, as enteral feeding is associated with worse QoL compared to having (even little) oral feeding, endoscopic dilation of strictures and placement of esophageal stents are commonly performed (**Figure 1**)³⁷. In fact, one advantage of self-expanding esophageal stents over other interventions is the patient's ability to quickly return to a normal diet, and it has been shown that most patients consequently show improvement of their nutrition parameters^{42,43}.

INOPERABLE LOCALLY ADVANCED DISEASE

EXTERNAL BEAM RADIOTHERAPY

Historically, external beam radiotherapy (EBRT) has played an important role in the palliative management of inoperable locally advanced esophageal cancer². Although this approach alone is associated with minimal toxicity, sustained locoregional remission is rarely achieved. In addition, in the absence of systemic treatment many patients treated by EBRT alone develop distant metastases, and long-term survival is rarely achieved⁴⁴.

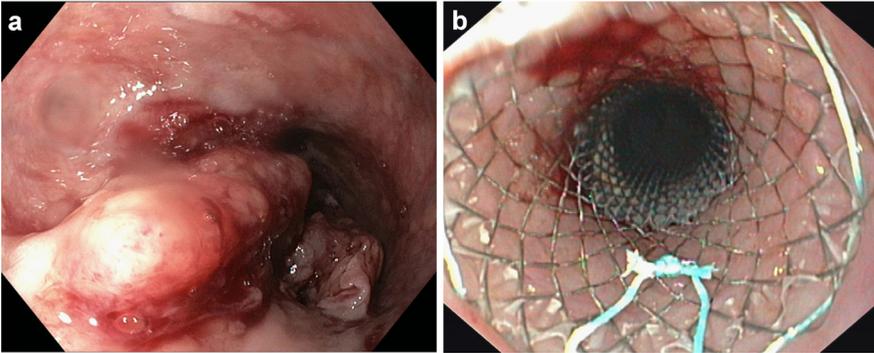


Figure 1 Endoscopic images before (a) and after (b) placement of a partially covered Wallflex (Boston Scientific) self-expandable metal stent for dysphagia caused by an obstructing esophageal tumor.

CONCURRENT CHEMORADIOTHERAPY

Comparison with radiotherapy alone

In view of the limited success of radiotherapy alone, from the early 1990s concurrent CRT for inoperable locally advanced esophageal cancer gained interest because of the synergic effects of radiotherapy and chemotherapy for locoregional control and the systemic effects of chemotherapy on distant (micro)metastases¹³. The landmark RTOG 85-01 study was a US Intergroup randomized controlled phase III trial in 121 inoperable patients that demonstrated significantly reduced locoregional and distant recurrence rates with concurrent CRT (cisplatin/5-fluorouracil [5-FU] + 50 Gy) compared to radiotherapy alone (64 Gy), resulting in a favorable 5-year survival rate of 26% over 0%, respectively^{7,8}.

A meta-analysis (updated in 2006) included 11 randomized trials and confirmed that concurrent CRT significantly improves overall survival compared to radiotherapy alone (pooled hazard ratio [HR] 0.73, 95% confidence interval [CI]: 0.64-0.84), albeit at the expense of additional manageable toxicity¹⁵. More recently, two additional randomized trials supported these findings^{9,46}. One trial in 125 squamous cell carcinoma patients reported superior 5-year overall survival rates with concurrent CRT over radiotherapy alone (25% vs 14%, HR 0.65, 95% CI: 0.44-0.98, $p=0.04$), at the cost of an increased risk of manageable late ulcers (15% vs 5%, $p=0.08$), and strictures (28% vs 13%, $p=0.05$)⁹. Likewise, in 130 patients with locoregional lymph node metastases 3-year overall survival rates with concurrent CRT versus radiotherapy alone were 40% versus 19%, respectively ($p=0.007$)⁴⁶. As such, concurrent CRT is the preferred approach in inoperable locally advanced esophageal cancer.

Alternatives to cisplatin/5-FU

Although the combination of cisplatin and 5-FU (CF) has been most frequently used in combination with radiotherapy, results from three retrospective studies and a prospective phase II study suggested that concurrent carboplatin/paclitaxel with radiotherapy may provide superior overall survival and a favorable toxicity profile⁴⁷⁻⁵⁰. However, these two chemotherapy regimens have not been directly compared in a randomized fashion. Definitive concurrent CRT with docetaxel and cisplatin for esophageal squamous cell carcinoma has also yielded promising results in a single-center prospective cohort study, although comparative information is lacking⁵¹. In the recent phase II/III randomized PRODIGE5/ACCORD17 trial (n=267), oxaliplatin/5-FU/leucovorin (FOLFOX) plus 50 Gy had comparable performance with CF plus 50 Gy in terms of toxicity, progression-free survival (9.7 vs 9.4 months, p=0.64), and overall survival (median 20.2 vs 17.5, p=0.70)⁵².

Addition of the targeted agent cetuximab (a monoclonal epidermal growth factor receptor [EGFR] antagonist) to CF and 50 Gy radiotherapy cannot be recommended, since in the randomized placebo-controlled phase II SCOPE1 trial (n=258) the addition of cetuximab to cisplatin/capecitabine resulted in decreased overall survival (median 22.1 vs 25.4 months, p=0.035)⁵. Also, the addition of cetuximab significantly increased non-hematological toxicity in that trial, which precluded continuation to a phase III trial⁵. In the multicenter phase II PACT study (n=90), the addition of panitumumab (an EGFR inhibitor) to concurrent CRT with carboplatin/paclitaxel did not increase the (pathologic) response rate in the neoadjuvant treatment setting⁵³.

Radiation dose escalation

Although concurrent CRT improved locoregional control compared to radiotherapy alone, locoregional recurrence after CRT still occurs in about 50% of patients, of which 50% manifests without concurrent distant metastases¹¹. The majority of locoregional recurrences occur at the site of the primary tumor, suggesting a potential benefit of radiation dose escalation of the primary tumor, but not at the site of the lymph nodes¹¹. The key RTOG 94-05 phase III trial (which followed the RTOG 85-01 trial) evaluated the possibility of radiation dose escalation in 218 patients by comparing a radiation dose of 64.8 Gy to 50.4 Gy, both with concurrently administered chemotherapy (CF)⁵⁴. The trial was closed after an interim analysis because of a lack of improved locoregional control and increased mortality in the high-dose radiotherapy group⁵⁴. On the basis of these results, 50.4 Gy is the standard dose across the USA and Europe.

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Although dose escalation up to 64.8 Gy did not increase survival or locoregional control in RTOG 94-05⁵⁴, these results may have been partly biased by the higher toxicity-related drop-out rate and lower administered dose of chemotherapy in the high radiation dose group. In addition, outdated radiation treatment modalities were used in the RTOG 94-05 study. With the sophisticated advances in modern radiotherapy including improved image guidance and intensity-modulated radiotherapy (IMRT), the dose distribution and coverage over the target volume is largely improved which allows for safer dose escalation, without increasing toxicities to normal tissue⁵⁵. Therefore, dose escalation studies with modern radiotherapy techniques aiming to improve locoregional control are warranted, such as the ongoing Dutch multicenter phase III Art-Deco (NTR3532) or the French phase II/III CONCORDE (NCT01348217) trials, testing dose escalation to 61.6 or 66 Gy versus a standard 50.4 or 50 Gy dose with carboplatin/paclitaxel or FOLFOX, respectively.

SYSTEMIC TREATMENT FOR METASTATIC DISEASE

FIRST-LINE SYSTEMIC TREATMENT

Systemic therapy can offer palliation, improve quality of life, and prolong survival in patients with metastatic esophageal cancer⁵⁶. The decision to offer best supportive care alone or in combination with systemic therapy involves balancing clinical risk factors such as the patient's performance status and comorbidities, potential benefits and harms of the proposed treatment, and the patient's preferences^{2,32}.

Best supportive care, single agent and combination chemotherapy

A Cochrane meta-analysis (last updated in 2010) concluded from 3 randomized controlled trials conducted in the early 1990s that chemotherapy provides a clear survival benefit over best supportive care alone (pooled HR 0.37, 95% CI: 0.24-0.55)⁵⁶. Single chemotherapy agents only have modest activity in esophageal cancer, with single-agent response rates ranging from 10% to 25% for older agents (e.g. 5-FU, cisplatin, mitomycin) and from 15% to 45% for newer agents (e.g. the oral 5-FU pro-drugs capecitabine and S-1, the taxanes paclitaxel and docetaxel, and irinotecan)¹⁶. The Cochrane meta-analysis of 13 trials (which mostly evaluated older chemotherapy regimens) concluded that combination chemotherapy of 2 or 3 agents is superior to single-agent chemotherapy with respect to response rates (35% vs 18%, pooled odds ratio [OR] 2.91, 95% CI: 2.15-3.93), median time-to-progression (5.6 vs 3.6 months, HR 0.67, 95% CI: 0.49-0.93), and median overall survival (8.3 vs 6.8 months, HR 0.82, 95% CI: 0.74-0.90)⁵⁶.

Fluoropyrimidine/platinum

The combination of a fluoropyrimidine with a platinum agent remains an important backbone chemotherapy regimen in contemporary trials and clinical practice¹⁶. CF is the most frequently investigated regimen with response rates of 20% to 50%, and remains a viable option as first-line systemic therapy in esophageal cancer³². However, because of substantial toxicity and burdensome administration of CF, from the 2000s multiple large randomized trials have assessed the safety and efficacy of substituting cisplatin with oxaliplatin, and infusional 5-FU with oral 5-FU prodrugs (capecitabine or S-1)^{17,57-61}. These trials indicated that regimens such as oxaplatin/infusional 5-FU, oxaliplatin/capecitabine, capecitabine/cisplatin, and S-1/cisplatin have at least similar efficacy and mostly less toxicity and easier administration compared with CF⁶².

Anthracyclines

From the late 1990s, in the United Kingdom lower-dose CF combined with the anthracycline epirubicin (ECF) was established as the reference regimen, because in a key randomized phase III trial (n=274) ECF achieved superior response rates (46% vs 21%, p=0.00003), median overall survival (8.7 vs 6.1 months, p=0.0005), and QoL compared with a previous standard regimen (5-FU/doxorubicin/methotrexate [FAMTX])^{63,64}. In a subsequent randomized phase III trial (n=580), ECF had similar response rates and survival compared with mitomycin/cisplatin/5-FU (MCF), but was superior in terms of QoL⁶⁵. Then, the next landmark study from the UK was the randomized phase III REAL-2 trial (n=1,002) comparing ECF with ECX (substituting 5-FU with capecitabine), EOF (substituting cisplatin with oxaliplatin), and EOX (substituting CF with oxaliplatin/capecitabine)⁵⁷. The primary outcome of non-inferiority in overall survival was reached for all the combinations, with similar response rates (40-48%) and toxicity⁵⁷. EOX was associated with improved median overall survival compared to ECF (11.2 vs 9.9 months, p=0.02), which suggests that oxaliplatin and capecitabine have at least comparable efficacy to CF and can be used as replacements⁵⁷.

Of note, despite the routine use of ECF or one of its derivatives in the United Kingdom, the anticipated superiority of this triplet over the fluoropyrimidine/platinum doublet has not been studied in properly powered phase III randomized trials¹⁶. Indirect evidence comes from a Cochrane meta-analysis (last updated in 2010) of 3 randomized trials⁶⁵⁻⁶⁷, that suggested that triplets containing anthracyclines, cisplatin and 5-FU provide superior overall survival compared to doublets or triplets containing CF without an anthracycline (pooled HR 0.77, 95% CI: 0.62-

0.95)⁵⁶. However, the pooled estimate was predominantly based on the results of the largest among the 3 trials (82% weight), which was the previously described ECF versus MCF trial⁶⁵ that - only after exclusion of 246 esophageal cancer patients by the authors of the meta-analysis leaving 334 GOJ and gastric cancer patients - showed superior overall survival of the anthracycline-based ECF triplet over the non-anthracycline-based MCF triplet⁵⁶. This implies that the Cochrane meta-analysis did not truly question the relevance of the addition of an anthracycline to a CF doublet. A recent meta-analysis of the 2 other studies^{66,67} revealed that the potential overall survival benefit of the addition of an anthracycline to CF doublet therapy did not meet statistical significance (HR 0.70, 95% CI: 0.42-1.15)⁶⁸. The benefit of adding epirubicin to CF in esophageal cancer is further questioned by the finding that in the predominant trial⁶⁵ of the Cochrane meta-analysis⁵⁶ anthracycline-based ECF appeared superior to non-anthracycline-based (M)CF only after exclusion of esophageal cancer patients.

Taxanes

In contrast to the unclear benefit of adding an anthracycline to CF, the key randomized phase III V325 trial in 445 untreated patients with GOJ or gastric cancer showed that adding a taxane (docetaxel) to CF improved response rates (37% vs 25%, $p=0.01$), median time-to-progression (5.6 vs 3.7 months, $p<0.001$), and overall survival (median 9.2 vs 8.6 months, 2-year 18% vs 9%, $p=0.02$)⁶⁹. However, DCF was associated with significantly increased toxicity including grade ≥ 3 neutropenia (82% vs 57%) and febrile neutropenia (29% vs 12%), which has hindered widespread acceptance of this regimen⁶⁹. The authors did report that patients in the DCF experienced a slower decrement in QoL measurements⁷⁰. The increased toxicity with docetaxel was confirmed in the recent randomized phase II FLOT65+ trial in which docetaxel was added to oxaliplatin/5-FU/leucovorin⁷¹. To achieve the same efficacy but increased tolerability, a multitude of studies have tested various modified DCF (mDCF) regimens⁷²⁻⁷⁴. Recently, in a large phase III randomized trial from China ($n=243$) a mDCF regimen (with 20% decreased dosage for all 3 compounds compared to the V325 trial⁶⁹) retained its beneficial efficacy over CF in terms of response rates, progression-free and overall survival, but with fewer toxicity than described for DCF⁷⁵. The potential generalizability of these findings to Western populations deserves further investigation.

Targeted agents

Combining cytotoxic chemotherapy with targeted therapies is a promising approach to improving the treatment of esophageal cancer. The ToGA trial was the

first randomized phase III trial (n=594) to evaluate the efficacy and safety of adding trastuzumab in HER2-positive gastric and GOJ adenocarcinoma to cisplatin/capecitabine or CF⁷⁶. HER2-positivity rates were 33% and 21%, respectively, for patients with GOJ and gastric cancers⁷⁶. A statistically and clinically significant improvement in overall survival was observed with the addition of trastuzumab to chemotherapy (median 13.8 vs 11.1 months, p=0.0046), without increasing toxicity⁷⁶. This study established a standard role for HER2-testing in patients with advanced GOJ and gastric cancer, and treatment with trastuzumab in combination with chemotherapy in HER2-positive tumors³². Adding lapatinib (an EGFR and HER2 tyrosine kinase inhibitor) to oxaliplatin/capecitabine in patients with HER2-positive advanced esophagogastric adenocarcinoma in the recent phase III randomized TRIO-013/LOGiC trial (n=487) did not significantly improve survival²⁴.

Agents targeting the vascular endothelial growth factor (VEGF) angiogenesis pathway, the hepatocyte growth factor (HGF)/MET pathway, the phosphoinositide 3 kinase inhibitor/mammalian target of rapamycin (PI3K/mTOR) pathway and other agents targeting the epidermal growth factor receptor family (EGFR) have also been investigated in clinical trials. The recently published randomized phase III trials that evaluated the addition of anti-EGFR therapy were negative in terms of progression-free and overall survival, including the REAL-3 (EOX +/- panitumumab, n=553) and EXPAND (capecitabine/cisplatin +/- cetuximab, n=904) trials^{18,77}. Adding rilotumumab (a monoclonal HGF antibody) to ECX resulted in improved progression-free survival compared to adding placebo in a recent randomized phase II trial, and a phase III trial is currently in progress⁷⁸. The addition of bevacizumab (a VEGFR antibody) to cisplatin/capecitabine (or CF) demonstrated no superior efficacy in the multinational randomized phase III AVAGAST trial (n=774) nor in the similarly designed Chinese AVATAR trial (n=202)^{79,80}. Of note, in subgroup analyses of the AVAGAST trial, benefit of survival was seen in patients from Latin and North America, while patients from Asia did not benefit. There is a geographic heterogeneity in incidence, mortality and response to treatment, but the exact mechanism is unclear^{81,82}. The search for selective biomarkers is essential to improve current treatment strategies.

SECOND-LINE SYSTEMIC PALLIATIVE TREATMENT

Randomized studies have demonstrated a modest but relevant median survival benefit of about 1.5 months with paclitaxel, docetaxel or irinotecan single-agent chemotherapy compared to best supportive care in patients who progressed

after first-line chemotherapy and have good performance status^{20,83,84}. In the key randomized phase III REGARD trial (n=355), ramucirumab (a VEGFR-2 antibody) showed a significant median survival benefit of 1.4 months as single-agent compared to best supportive care in the second-line (median 5.2 vs 3.8 months, p=0.047)²¹. Similarly, in the second-line phase III randomized RAINBOW trial combination paclitaxel and ramucirumab resulted in significantly increased overall survival compared to paclitaxel alone (median 9.6 vs 7.4, p<0.0001)²³.

In contrast, the Asian randomized phase III TyTAN trial (n=261) failed to demonstrate a survival benefit with the combination of lapatinib and paclitaxel compared to paclitaxel alone in patients with HER2-positive gastric cancer in the second-line⁸⁵. A randomized phase II trial (n=37) from Germany that explored the activity of lapatinib in combination with capecitabine versus lapatinib alone in the second-line treatment of HER2-positive esophagogastric cancer was closed prematurely for futility⁸⁶. In view of the currently available evidence, several investigators suggested that lapatinib is probably not an effective agent for treating advanced esophagogastric cancer^{24,85-87}. Likewise, gefitinib (an EGFR tyrosine kinase inhibitor) was tested in the recent randomized COG study against placebo in the second-line (n=449) and did not show an overall survival benefit (median 3.7 vs 2.7 months, p=0.29)¹⁹. With the growing body of evidence, one may conclude that there is a lack of benefit from anti-EGFR therapy in esophagogastric cancer, when used without a predictive biomarker for patient selection^{5,18,19,77}.

LOCAL TREATMENT FOR METASTATIC DISEASE

An overview of key randomized trials comparing different types of stents (e.g. covered versus uncovered stents) for local palliative treatment in patients with metastatic esophageal cancer is provided in **Table 1**. An overview of key randomized trials comparing different local treatment options (e.g. stents versus brachytherapy) in patients with metastatic esophageal cancer is provided in **Table 2**.

STENT PLACEMENT

Plastic tube versus expandable stent

In the 1970s an endoscopically inserted plastic prosthesis for the palliation of malignant dysphagia was introduced for the first time⁸⁸, after which multiple rigid plastic tube designs were marketed. However, from the 1990s these plastic tubes have been superseded by self-expanding metal stents (SEMSs) which appeared safer in multiple randomized studies⁸⁹⁻⁹⁵, and also more effective in palliating dysphagia

in some of these studies^{91,93,95}. In addition, SEMSs are preferred over plastic tubes because placement can be performed under fluoroscopic and/or endoscopic guidance, and generally do not require dilation prior to placement which relates to the reduced risk of hemorrhage and perforation. Because of the ease of placement, manageable associated morbidity, and swift relief of dysphagia, SEMS placement is the most widely applied method for the management of dysphagia^{2,96}.

Types of expandable stents

Since their introduction most expandable stents have undergone multiple modifications. For example, most expandable stents have evolved from an uncovered to a (partially) covered form to minimize tissue ingrowth, and diameters of the stents have often been increased to reduce the risk of stent migration and food bolus obstruction³. These and other advances in stent designs have resulted in the fact that currently a broad array of expandable stents is available for the palliation of malignant dysphagia. The types of expandable stents can be categorized as follows: uncovered SEMSs, partially covered SEMSs, fully covered SEMSs, and self-expandable plastic stents (SEPSs). All of these expandable stent types provide very similar rapid relief of dysphagia, with on average a decrease of the dysphagia score from 3 (able to swallow liquids) to 1 (occasional dysphagia for some solid food)²⁷. However, each stent type carries specific advantages and disadvantages regarding the risk of recurrent dysphagia and adverse events, with not one type being significantly superior to the other types in all aspects.

Tissue ingrowth and stent migration

Two key randomized trials (n=42 and n=62) demonstrated a substantially higher risk of tumoral or non-tumoral tissue ingrowth (causing recurrent dysphagia) with uncovered SEMS compared to covered SEMS (20-30% vs 3-4%)^{97,98}. Consequently, uncovered SEMSs, such as the Strecker (Boston Scientific, Natick, MA, USA) stent, have been abandoned for palliating malignant dysphagia³. However, the two randomized studies also demonstrated that the risk of stent migration was higher with covered SEMSs compared to uncovered SEMSs (12-32% vs 0-7%)^{97,98}. Indeed, stent migration is a commonly encountered problem particularly with fully covered SEMS, such as the Alimaxx-E (Alveolus, Charlotte, NC, USA) and FerX-Ella (Ella-CS, Hradec Kralove, Czech Republic) stents, which have been reported to migrate in up to 36% of cases⁹⁹⁻¹⁰¹.

Table 1 Key randomized trials in local palliative treatment for metastatic esophageal cancer involving comparisons

| Comparison | Study | n | Interventions | Safety |
|--------------------------------------|--------------------------|-----------|--|----------------------------------|
| | | | | Major complications [†] |
| SEMS vs plastic tube | Knyrim 1993 | 42 | Uncov Wall vs Wilson Cook | 10 vs 48%* |
| | De Palma 1996 | 39 | Uncov UF vs Wilson Cook | 0 vs 22%* |
| | Roseveare 1998 | 31 | Cov Z vs Atkinson | 13 vs 19% |
| | Siersema 1998 | 75 | Cov Z vs Celestin Pulsion | 11 vs 26% |
| | Sanyika 1999 | 40 | Cov Wall vs Proctor Livingstone | 0 vs 20% |
| | O'Donnell 2002 | 50 | Cov Wall/UF vs Wilson Cook | 24 vs 8% |
| | Shenfine 2009 | 159 | Z vs Wilson Cook | 27 vs 27% |
| Cov vs uncov SEMS | Adam 1997 | 42 | Cov Wall vs. Uncov Strecker | 9 vs 5% |
| | Vakil 2001 | 62 | Cov vs uncov SEMS (NS) | 13 vs 7% |
| Cov SEMS vs other cov SEMS (or SEPS) | Siersema 2001 | 100 | Cov UF vs cov Wall vs. cov Z | 21 vs 15 vs 28% |
| | Sabharwal 2003 | 53 | Cov UF vs cov Wall | 3 vs 9% |
| | Conio 2007 | 101 | Cov UF vs cov Polyflex [‡] | 6 vs 9% |
| | Verschuur 2008 | 125 | Cov UF vs Niti-S vs. Polyflex [‡] | 17 vs 20 vs 7% |
| | Kim 2009 | 37 | Cov vs double-layered Niti-S | 16 vs 6% |
| | van Heel 2012 | 80 | Cov UF vs cov Evolution | 25 vs 5%* |
| | SEMS vs anti-reflux SEMS | Homs 2004 | 30 | Open vs a-r FerX-Ella |
| Shim 2005 | | 36 | Open vs a-r Do vs. a-r S-type | = |
| Wenger 2006 | | 41 | Open Z/UF/Wall vs Dua a-r Z | 14 vs 5% |
| Power 2007 | | 49 | Cov UF vs a-r Hanaro | NR |
| Sabharwal 2008 | | 49 | Cov UF+PPI vs a-r FerX-Ella | 12 vs 5% |
| Blomberg 2010 | | 65 | Open Z/UF/Wall vs Dua a-r Z | 8 vs 7% |
| SEMS vs irradiation SEMS | Guo 2008 | 53 | MTN vs ¹²⁵ I-loaded stent | 35 vs 41% |
| | Dai 2013 | 67 | Cov nitinol vs ¹²⁵ I-eluted stent | 19 vs 10% |
| | Zhu 2014 | 148 | Cov nitinol vs ¹²⁵ I-loaded stent | 33 vs 30% |

Note. If not provided by the authors, differences in proportions were computed using the Chi-square test or Fisher's exact test. a-r: anti-reflux. Cov: covered. KPS: Karnofsky performance scale. NR: not reported. NS: not specified. PPI: proton pump inhibitor. Uncov: uncovered. WHO: World Health Organization performance status. *: statistically significant difference between necrosis. †: self-expanding plastic stent. =: no significant difference (numbers not specified). ‡: enjoyment of swallowing SEMS attributed to increased pain.

between different stents

| Efficacy | | | |
|--------------------------|------------------|--|---------------------------|
| Tissue in- or overgrowth | Migration | QoL after treatment | Overall survival (months) |
| 24 vs 0%* | 0 vs 24%* | Similar KPS | Mean 5.5 vs 4.8 |
| 13 vs 8% | 0 vs 15% | NR | Median 6.6 vs 6.2 |
| 13 vs 0% | 7 vs 13% | Favoring SEMS ^a | Median 3.2 vs 1.3* |
| 22 vs 11% | 0 vs 8% | NR | Median 2.3 vs 2.7 |
| 5 vs 10% | 5 vs 30% | NR | NR |
| 36 vs 24% | 8 vs 12% | Trend favoring SEMS ^b | Median 3.5 vs 2.0 |
| 5 vs 13% | 12 vs 31%* | Trend disfavoring SEMS ^c | Median 3.0 vs 3.9 |
| 4 vs 20% | 32 vs 0%* | NR | Median 1.6 vs 2.0 |
| 3 vs 30%* | 12 vs 7% | Similar KPS | = |
| 3 vs 15 vs 12% | 18 vs 9 vs 12% | Similar WHO | Mean 3.4 vs 3.7 vs 3.6 |
| 3 vs 5% | 6 vs 5% | NR | NR |
| 19 vs 20% | 4 vs 13% | NR | Median 4.0 vs 4.4 |
| 31 vs 24 vs 10%* | 17 vs 12 vs 29%* | Similar WHO | Median 4.3 vs 5.2 vs 3.4 |
| 26 vs 0%* | 5 vs 0% | NR | Median 2.0 vs 2.4 |
| 20 vs 3%* | 8 vs 3% | NR | Median 2.5 vs 2.5 |
| NR | 13 vs 33% | No improved reflux relief | Median 2.9 vs 3.5 |
| NR | NR | S-type superior reflux relief [†] | Median 3.7 vs 3.5 vs 3.6 |
| NR | 14 vs 11% | No improved reflux relief | Median 2.2 vs 1.9 |
| NR | 0% vs 0% | Hanaro superior reflux relief [†] | NR |
| NR | 23 vs 32% | No improved reflux relief | = |
| NR | 11 vs 18% | No improved reflux relief | Median 2.3 vs 2.1 |
| 23 vs 30% | 12 vs 7% | NR | Median 4.0 vs 7.0* |
| NR | NR | NR | Median 3.0 vs 4.8* |
| NR | 0% vs 0% | NR | Median 4.8 vs 5.8* |

test in case of small cell counts.

pump inhibitor. QoL: quality of life. SEMS: self-expandable metal stent. SEPS: self-expanding plastic stent. UF: Ultraflex the groups. †: defined as procedure-related perforation, hemorrhage, aspiration pneumonia, fistula formation or pressure 89% vs 33%. ‡: SEMS superior in 21 of 26 EORTC QLQ-30 components (not significant). †: lower mean QoL index with

Table 2 Key randomized trials in local palliative treatment for metastatic esophageal cancer involving comparisons between

| Comparison | Study | n | Interventions | Safety |
|-----------------------|-----------------|-----|--|-----------------------------------|
| | | | | Major adverse events [†] |
| Brachy vs brachy | Sur 1998 | 172 | 2x6 vs 2x8 vs 3x6 Gy brachy | 14 vs 25 vs 42%* |
| | Sur 2002 | 232 | 3x6 vs 2x8 Gy brachy | 19 vs 24% |
| Brachy vs brachy+EBRT | Sur 2004 | 60 | 2x8 Gy brachy vs 2x8 Gy brachy + 10x3 Gy EBRT | 33 vs 17% |
| | Rosenblatt 2010 | 219 | 2x8 Gy brachy vs 2x8 Gy brachy + 10x3 Gy EBRT | 8 vs 18% |
| SEMS vs laser | Adam 1997 | 60 | Cov Wall vs Nd YAG (or APC) | 9 vs 11% |
| | Dallal 2001 | 65 | Uncov Strecker/UF or cov Wall vs Nd-YAG (or APC) | 23 vs 18% |
| SEMS vs brachy | Homs 2004 | 209 | Cov UF vs 1x12 Gy brachy | 25 vs 13%* |
| | Bergquist 2005 | 65 | Cov UF vs 3x7 Gy brachy | Unclear |
| SEMS vs SEMS+EBRT | Javed 2012 | 79 | Cov UF vs cov UF + 10x3 Gy EBRT | = |
| SEMS+brachy vs brachy | Amdal 2013 | 41 | Cov SEMS (NS) + 3x8 Gy brachy vs 3x8 Gy brachy | 19 vs 0% |

Note. Only randomized trials that included at least one brachytherapy, EBRT or SEMS arm are listed, as these modalities APC: argon plasma coagulation. Brachy: brachytherapy. Cov: covered. EBRT: external beam radiotherapy. NS: not groups. [†]: such as procedure-related perforation, hemorrhage, aspiration pneumonia, fistula formation, pressure necrosis, difference (numbers not specified). ^a: significantly favoring brachytherapy + EBRT with regard to dysphagia, odynophagia, favoring brachy + EBRT on EORTC QLQ-C30 and QLQ-OES18 global health and functioning scales. ^d: laser group fatigue, cognitive, emotional, and social function scales. ^f: but significantly longer dysphagia-free period in brachytherapy/EORTC QLQ-30 role/emotional/cognitive/social functioning scales. ^b: significantly favoring SEMS on EORTC OES-23 EORTC QLQ-OG25 health-related QoL scores.

different (combinations of) modalities

| Efficacy | | | |
|------------------------------------|-----------------------------------|--------------------------------------|---------------------------|
| Dysphagia score after treatment | Persistent or recurrent dysphagia | QoL after treatment | Overall survival (months) |
| = | 31 vs 10 vs 18%* | NR | = |
| = | 12 vs 14% | NR | Median 9.1 vs 6.9 |
| = | = | NR | Median 7.2 vs 7.5 |
| Mean 1.2 vs 0.8 | 15 vs 21% | Favoring brachy + EBRT* ^a | = |
| Median 1.0 vs 2.0* | 33 vs 22% ^d | NR | Median 1.6 vs 1.8 |
| Median 2.0 vs 2.0 | 13 vs 21% ^d | Favoring laser* ^c | Median 2.2 vs 4.1* |
| ≥1 grade [‡] : 76 vs 73% | 40 vs 43% ^f | Favoring brachytherapy* ^g | Median 4.8 vs 5.1 |
| Median 2 vs 2 | NR | Favoring SEMS* ^h | Mean 4.9 vs 5.2 |
| 5 months: 2.6 vs 1.5* | 21 vs 17% | Similar QoL ⁱ | Median 3.9 vs 5.9* |
| ≥1 grade [‡] : 71 vs 39%* | NR | Similar QoL ^j | Median 2.5 vs 4.1 |

form the mainstay of contemporary treatment.

specified. NR: not reported. SEMS: self-expandable metal stent. UF: Ultraflex. *: statistically significant difference between stricture, migration of the device or (food bolus) obstruction. ‡: improvement by at least 1 grade. =: no significant regurgitation, chest pain, and performance status. ^b: percentage improvement on QLQ OES-18 dysphagia scale. ^c: trend was re-treated routinely. ^e: significantly favoring laser on EORTC QLQ-30 and OES-24 physical function/health, pain, radiotherapy group. ^g: significantly favoring brachytherapy on EORTC OES-23 dysphagia and eating scales, and on dysphagia scale at 1 month, but not at ≥3 months. ⁱ: similar EORTC QLQ-C30 functioning and health scores. ^j: similar

Partially covered SEMS, such as the Ultraflex (Boston Scientific), Wallflex (Boston Scientific), and Evolution (Cook Ireland Ltd, Limerick, Ireland) stents, have been developed with the aim to reduce the migration risk by allowing embedding of the uncovered stent ends. Randomized studies involving the partially covered Ultraflex, Wallflex, or Evolution stents, have reported migration rates of 0-23%^{28,101-108}, 5-14%^{28,105,107,109}, or 3%¹⁰⁶, respectively. However, partially covered stents are at increased risk of tumor in- and overgrowth at the stent ends, which has been reported to occur in 3-31%^{102,103,105,106,109}, 5-15%^{105,109}, and 3%¹⁰⁶, respectively, for partially covered Ultraflex, Wallflex, and Evolution stents.

SEMS versus SEMS or SEPS

The partially covered Ultraflex (Boston Scientific) SEMS has been the most frequently used stent worldwide in both research and clinical practice¹⁰⁶. The first three published randomized trials (n=100, n=53, and n=101) comparing the Ultraflex SEMS to other SEMSs or SEPSs did not show any significant differences in treatment efficacy^{102,105,109}. However, in one of these trials the Ultraflex stent was compared to the self-expandable plastic Polyflex stent in 100 patients, and the authors reported a significantly higher complication rate in the plastic stent group¹⁰². Subsequently, a three-arm randomized trial (n=125) confirmed that the fully covered Polyflex stent was associated with a significantly increased risk of stent migration (29%) compared with the Ultraflex stent (17%) and Niti-S stent (12%)¹⁰³. One could argue that these findings leave (partially) covered SEMS as the stent of choice for patients with malignant dysphagia.

In a recent randomized trial (n=80) comparing the recently introduced Evolution (Cook Medical, Limerick, Ireland) stent with the Ultraflex stent, both partially covered SEMS were equally effective in improving dysphagia, but the Evolution stent was associated with significantly lower reintervention rates (10% vs 38%, p=0.004) and fewer major complications (8% vs 25%, p=0.04)¹⁰⁶. These observed benefits of the Evolution stent have been ascribed to the stent design including a higher radial force than the Ultraflex stent, internal and external (double-layered) silicone coating to prevent tumor ingrowth, proximal and distal flares to prevent migration, and a larger stent diameter to prevent food bolus obstruction¹⁰⁶. Although the results achieved with the Evolution stent in the randomized trial were consistent with previous findings of a single-arm prospective multicenter study¹¹⁰, further research is indicated to validate the potential superiority over other stent designs.

Anti-reflux stents

Patients can suffer from acid reflux after stent placement, particularly when the stent is placed across the GOJ²⁷. Various anti-reflux stent designs have been developed to overcome this and evaluated in several small randomized controlled trials (n=30 to n=65)^{28,100,101,107,108,111}. Reported results on the efficacy of the anti-reflux stents are conflicting, with some trials suggesting improved control of reflux symptoms^{108,111} while other trials found no such effect^{28,100,101,107}. Since some anti-reflux stent designs were seemingly functional and provided new perspectives for palliative treatment, further research in larger trials is indicated for optimization of patient selection for this intervention. Nonetheless, the routine use of antireflux stents can currently not be recommended. The use of antireflux stents may be reserved for patients with refractory reflux esophagitis despite high-dose proton pump inhibitor (PPI) treatment^{27,33}.

Irradiation stents

To combine the advantages of rapid dysphagia relief by using SEMS with the longer-term benefits of brachytherapy, a novel stent loaded with ¹²⁵I seeds has been developed^{29,112}. An initial single-center randomized trial in China, placing the irradiation stents in 27 patients and conventional stents in 26 controls, found that dysphagia scores after 2 months were better with the irradiation stent, and that survival was significantly improved (median 7.0 vs 4.0 months, $p < 0.001$)¹¹². A subsequent larger multicenter randomized controlled trial from China showed that the novel stent coated with ¹²⁵I seeds (n=73) was equally well tolerated and provided similar rapid relief of dysphagia, but significantly prolonged survival (median 5.8 versus 4.8 months, $p = 0.0046$) compared with a conventional covered SEMS (n=75)²⁹. Also, an iodine-eluting esophageal stent was developed and tested in a randomized trial in China in which 31 patients received an iodine-eluting stent and 36 patients received a conventional stent¹¹³. Again in this trial survival was significantly improved with the irradiation stent (median 4.8 vs 3.0 months, $p = 0.0022$), without causing more complications¹¹³. The consistently reported improvement in efficacy of irradiation stents warrants further evaluation and validation in populations outside of China before potential widespread application might be justified.

Esophagorespiratory fistula

Malignant esophagorespiratory fistula is a feared complication of primary or recurrent tumor growth of esophageal cancer, or of tumor necrosis caused by chemotherapy and/or radiotherapy. Since aspiration pneumonia and poor

nutritional intake are frequent consequences of such fistula resulting in a poor survival of 1-6 weeks with supportive care alone, prompt intervention is crucial¹¹⁴. Surgical options include closure or resection of the fistula or bypass surgery, but these methods are associated with high morbidity and mortality rates²⁷. As such, placement of a (partially) covered SEMS is the treatment of choice for an esophagorespiratory fistula (**Figure 2**)². Several studies have shown that this approach results in successful fistula closure in about 80-90% of patients, with minimal procedural morbidity and almost zero mortality¹¹⁵⁻¹¹⁷. In addition, a small number of patients with high esophageal tumors involving the trachea may benefit from simultaneous tracheal stenting³³.

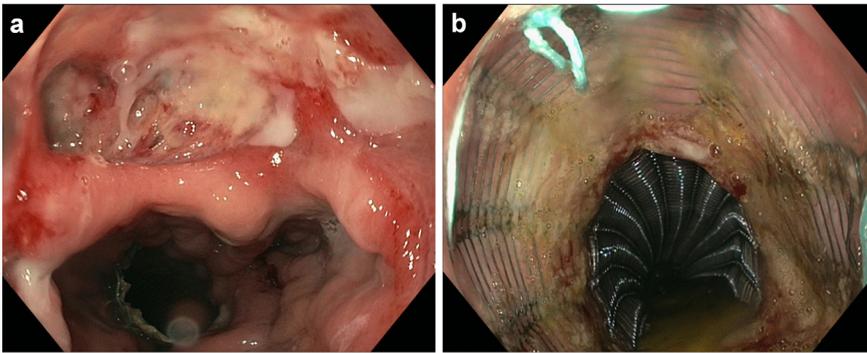


Figure 2 Endoscopic images of a malignant esophagorespiratory fistula (a) which was successfully sealed using a wide body Ultraflex (Boston Scientific) self-expandable metal stent (b).

INTRALUMINAL BRACHYTHERAPY

After stent placement, intraluminal brachytherapy is the second most studied approach for the palliative management of malignant dysphagia. Brachytherapy offers an elegant way to deliver relatively high radiation doses to esophageal tumors with minimal exposure to adjacent healthy organs-at-risk¹¹⁸. The landmark SIREC study was the first and largest randomized trial comparing stent placement (with a partially covered Ultraflex) with brachytherapy (1x12 Gy) for the palliation of dysphagia from esophageal cancer (n=209)¹⁰⁴. Dysphagia improved more rapidly after stent placement than after brachytherapy, but this difference in efficacy diminished gradually over time with brachytherapy providing superior relief of dysphagia after approximately 3 months of follow-up¹⁰⁴.

A similar trend of improved short-term outcomes with SEMS, but beneficial long-term outcomes with brachytherapy, was observed in a subsequent smaller

randomized trial (n=65)¹¹⁹. Since in the SIREC-trial brachytherapy was also associated with a slight benefit in QoL and fewer major complications (13% vs 25%, p=0.02) compared to SEMS placement, brachytherapy should be considered in all patients with a life expectancy exceeding 3 months^{104,118}. Stent placement as sole treatment may be reserved for patients with a short life-expectancy, where the immediacy of symptomatic relief offered by this procedure clearly dominates^{104,118}. It should be noted that the long-term beneficial effect of brachytherapy in the SIREC-trial was partly explained by additional SEMS placement during follow-up in 45% of the patients allocated to brachytherapy, because of a lack of brachytherapy effect, indicating the frequent need - and efficacy - of combination treatment^{27,104}.

Besides the favorable evidence for brachytherapy in the palliation of malignant dysphagia, multiple factors have limited widespread use. First, since this treatment modality holds the potential for devastating complications, safe use requires input from an experienced multidisciplinary team consisting of a dedicated radiation oncologist, as well as medical physicists, and radiographers¹¹⁸. Second, multiple countries have limited availability of this type of radiotherapy for esophageal cancer. For example, the College of Radiologists (London, UK) showed that brachytherapy treatment for all tumor sites accounts for only 2.5% of all radiotherapy patients, related to little access to, and expertise in, this type of radiotherapy in the United Kingdom¹²⁰. Of 59 US hospitals described in another report, only 6% had access to brachytherapy¹²¹. In other countries, such as China, stent placement is the major or even the sole therapy for unresectable esophageal cancer patients because of poor economic conditions, poor adherence to guidelines and fear of complications of brachytherapy²⁹. Finally, high quality clinical data that define the optimal dose schedules (with or without combined EBRT) are limited and outdated^{118,122,123}.

ENDOSCOPIC ABLATIVE THERAPIES

The Cochrane meta-analysis of interventions for dysphagia in esophageal cancer (updated in 2014) concluded that endoscopic ablative therapies including laser therapy and PDT had greater requirements for re-intervention and expertise compared to SEMS²⁶. Laser therapy has been compared with SEMS in two randomized studies showing that the two interventions have similar efficacy, but that SEMS placement has a better technical success rate and requires less re-interventions^{97,124}. Indeed, a well-known disadvantage of laser therapy is that repeated sessions are required to achieve and maintain adequate palliation³¹. The current role of PDT in the palliative treatment of malignant dysphagia is limited because of the complexity of the technique, along with the high costs of

the photosensitizers and the laser itself³⁰. In addition, over the past two decades PDT has only sporadically been studied in randomized studies and these suggest inferiority of PDT compared to brachytherapy or SEMS, particularly in terms of complication and re-intervention rates³⁰.

COMBINATION THERAPY

7

Although there is no absolute superiority of any particular local intervention (i.e. SEMS placement, different types of SEMS, brachytherapy or endoscopic ablative therapies) for the palliation of malignant dysphagia, it is increasingly being recognized that combinations of different modalities may prolong the dysphagia-free period, decrease the need for re-interventions, or even increase overall survival^{26,30,31}. This hypothesis first gained ground in early randomized studies showing that the addition of brachytherapy or EBRT to laser therapy approximately doubled the dysphagia-free interval and reduced the need for re-interventions^{31,125,126}. Among 2 randomized trials comparing a combination of brachytherapy plus EBRT with brachytherapy alone, one large trial (n=219) found that QoL outcomes were significantly favoring combination treatment¹²⁷, whereas in the other trial (n=60) outcomes between both arms were similar¹²⁸.

In contemporary trials, emphasis has been on combining the short-term benefits of SEMS placement with the long-term benefits of EBRT or brachytherapy, but the evidence remains scarce^{120,129,130}. In a recent single-center randomized study (n=84) the combination of SEMS placement followed by EBRT appeared superior to SEMS placement alone in terms of dysphagia-free survival (mean 119 vs 97 days, p=0.054) and overall survival (median 180 vs 120 days, p=0.009), without inducing additional toxicity¹³⁰. Likewise, investigators from the UK have recently initiated the randomized multicenter phase III ROCS (Radiotherapy after Oesophageal Cancer Stenting) trial comparing stent alone versus stent plus palliative EBRT in 496 patients with dysphagia from incurable esophageal cancer¹²⁰. EBRT was chosen over brachytherapy for this trial, because EBRT is readily accessible by patients at regional cancers across the UK, and there is little access to - or expertise in - brachytherapy for esophageal cancer patients in the UK¹²⁰. Recently, in a small single-center randomized study (n=41) patients receiving SEMS followed by brachytherapy had significantly improved dysphagia at 3 weeks (but similar scores at 7 weeks) after randomization compared to patients receiving brachytherapy alone, indicating superiority for the combined treatment in patients who need rapid relief of dysphagia while maintaining the longer-term benefits from brachytherapy¹²⁹.

SHIFT TOWARDS CURATIVE INTENT

The established treatment options for inoperable or metastatic esophageal cancer described above are largely based on moderate to high quality (randomized) trials. In addition, there is growing evidence for non-established treatment options from preliminary non-randomized studies that shift the field towards more curative intent. These promising non-established treatment approaches include potentially curative surgery after downstaging by chemoradiotherapy for unresectable disease and local therapies for oligometastatic disease.

Surgery after tumor downstaging

Locoregional control and survival rates after concurrent CRT for patients with unresectable disease caused by tumor ingrowth into unresectable adjacent structures (clinical T4bNxM0) remain particularly poor^{11,131,132}. However, there is increasing evidence that chemoradiotherapy may result in sufficiently strong tumor downstaging in selected patients to allow for potentially curative surgical resection^{133,134}. Such multimodality treatment involving neoadjuvant CRT followed by esophagectomy has convincingly been shown to result in superior locoregional control and survival rates in initially resectable (T1b-4aNxM0) esophageal cancer^{135,136}. Indeed, a recent systematic review performing an indirect comparison of available studies on CRT followed by surgery versus CRT alone, concluded that CRT plus surgery appeared superior to CRT alone for T4bNxM0 esophageal cancer with respect to local control and short-term prognosis (median 1-year survival among available studies, 57% vs 39.5%)¹³⁷. However, the authors also stated that differences in long-term survival may be marginal (median 5-year survival among available studies, 20% vs 10%) due to operative morbidity and inadequate control of distant metastasis¹³⁷. Furthermore, data from randomized trials are lacking.

Investigators from Japan have demonstrated that the survival rate of clinical T4bNxM0 patients after chemo(radio)therapy and subsequent esophagectomy was comparable to patients with initially resectable (T1b-4aNxM0) esophageal cancer, but only in those clinical T4bNxM0 patients (61%) in whom a microscopic radical (R0) resection could be performed¹³³. In this setting, it is the authors' opinion that the steady and up till ten times magnified three-dimensional view achieved with robotic assistance is helpful to visualize the correct dissection plane and enable a fine dissection between the esophagus and adjacent tissue, closer to the structures that need to be preserved (**Figure 3**)¹³⁸. The observation that patients may only benefit when a R0 resection is achieved - along with the high postoperative mortality rates of 18-21%^{133,139,140} reported in these patients - strongly

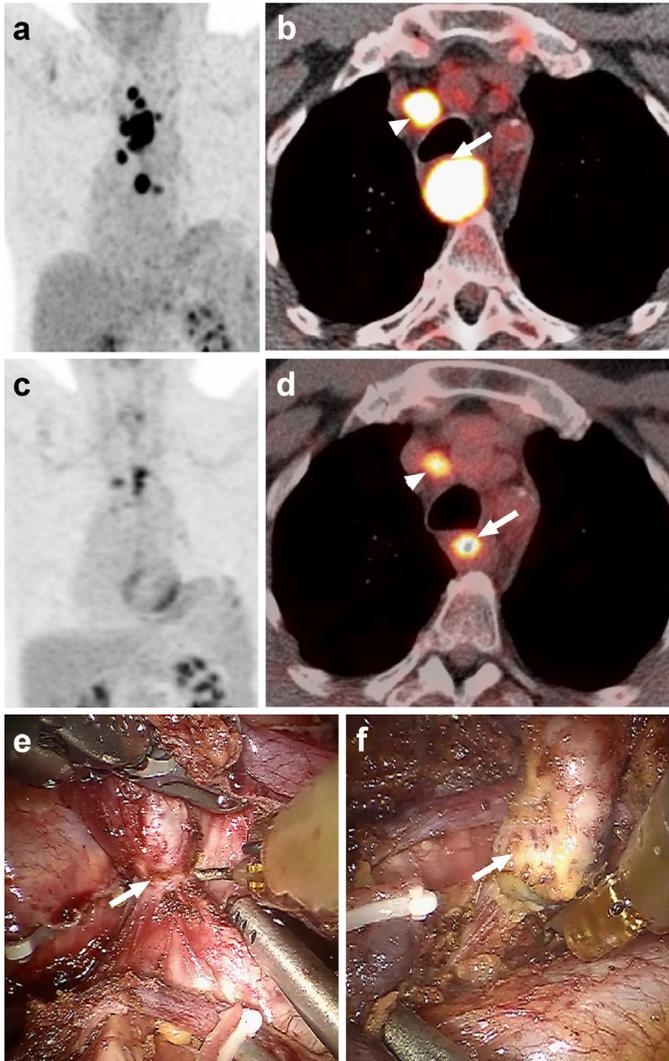


Figure 3 ^{18}F -FDG PET/CT images before concurrent CRT in a patient with a clinical T4bN3M0 esophageal squamous cell carcinoma, considered unresectable due to tumoral ingrowth into the trachea (*arrow*) and upper mediastinal lymph node metastases (*arrowhead*) (**a,b**). Corresponding ^{18}F -FDG PET/CT images after CRT demonstrate a major response to treatment, although residual ^{18}F -FDG uptake in the esophagus (*arrow*) and one paratracheal lymph node (*arrowhead*) was present (**c,d**). The malignancy was deemed resectable after downstaging by CRT, and the patient underwent a robot-assisted minimally invasive transthoracic esophagectomy (**e**) with lymphadenectomy; an enlarged paratracheal lymph was separately removed (**f**). Histopathology revealed residual cancer in both the primary tumor and a paratracheal lymph node (ypT2N1), which was radically resected (R0).

underscores the necessity of selecting proper candidates for potentially curative, but highly invasive, esophagectomy. One study revealed that a major clinical tumor response (based on CT and endoscopy) was the single most important predictor of a R0 resection¹³⁹. However, CT- and endoscopy-based response measurements are known to correlate poorly with true pathologic response, and response assessment may be improved by using ¹⁸F-FDG PET or functional MRI¹⁴¹⁻¹⁴⁵. As such, accurate treatment response assessment could aid in an improved selection of patients with clinical T4bNxM0 disease for esophagectomy after chemo(radio)therapy. In addition, a decrease in postoperative mortality rates with increasing experience has been observed, suggesting that surgery for T4bNxM0 esophageal cancer after downstaging should be centralized in high-volume centers with highly experienced teams¹³³.

Oligometastases

Although systemic therapy remains the standard of care for patients with newly diagnosed metastatic disease, patients in which the radiographically apparent metastases are limited in number and extent (i.e. oligometastases) are increasingly considered amenable to potentially curative localized therapy directed at their metastases^{146,147}. Such localized therapy may include surgery (e.g. for liver metastases¹⁴⁸ or lung metastases¹⁴⁹), radiofrequency ablation, cryoablation or (stereotactic body) radiotherapy¹⁵⁰. Although the trend is less pronounced than observed in colorectal, lung and breast cancer metastases, oligometastases from esophageal cancer are also increasingly being treated locally with curative intent^{14,147,151-153}. However, high quality studies to determine the efficacy of such approaches in esophageal cancer patients are lacking and therefore strongly desired, with particular emphasis on which patients are likely to derive a benefit.

CONCLUSIONS

Palliative treatment of esophageal carcinoma is best approached by a multidisciplinary team. Concurrent CRT is the preferred treatment option for patients with inoperable locally advanced esophageal cancer. Contemporary trials regarding concurrent CRT focus on radiation dose escalation and on substituting conventional CF regimens for less toxic and more effective compounds. In patients with distant metastatic disease and an adequate performance status, palliative combination chemotherapy is recommended as this improves survival compared to best supportive care or single-agent chemotherapy. Combination therapy containing a fluoropyrimidine and a platinum compound is recommended.

Triplet combination therapy (with the addition of a taxane), can be administered to increase the response rate. Triplets only moderately improve survival rates compared to doublet therapy at the expense of increased toxicity. In recent years, targeted therapies with trastuzumab (in patients with HER2 overexpression) and ramucirumab have established a role in the first-line and second-line treatment, respectively.

No absolute superiority of any particular local intervention for the palliation of malignant dysphagia exists. Self-expanding metal stent placement relieves dysphagia more rapidly than other modalities, which is particularly preferred in patients with severe dysphagia or short life expectancy. Covered stents are superior at resisting tissue in- and overgrowth compared to partially covered or uncovered stents but at the price of increased rates of migration. Despite slower improvement of dysphagia, high-dose rate brachytherapy provides a suitable alternative with fewer complications and additional benefits in terms of quality of life and survival. Due to the equivocal evidence, routine use of anti-reflux stents cannot be recommended. Novel irradiation stents appear to share the advantages of immediate dysphagia relief of stents and the longer-term benefits of brachytherapy. As combining different local interventions appears to provide improved outcomes, future well-designed multicenter randomized trials are required to evaluate and optimize the safety and efficacy of such approaches.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359-86
2. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. *Lancet* 2013;381:400-12
3. Diamantis G, Scarpa M, Bocus P, et al. Quality of life in patients with esophageal stenting for the palliation of malignant dysphagia. *World J Gastroenterol* 2011;17:144-50
4. Edgren G, Adami HO, Weiderpass E, et al. A global assessment of the oesophageal adenocarcinoma epidemic. *Gut* 2013;62:1406-14
5. Crosby T, Hurt CN, Falk S, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. *Lancet Oncol* 2013;14:627-37
6. Polednak AP. Trends in survival for both histologic types of esophageal cancer in US surveillance, epidemiology and end results areas. *Int J Cancer* 2003;105:98-100
7. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992;326:1593-8
8. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 1999;281:1623-7
9. Kumar S, Dimri K, Khurana R, et al. A randomised trial of radiotherapy compared with cisplatin chemo-radiotherapy in patients with unresectable squamous cell cancer of the esophagus. *Radiother Oncol* 2007;83:139-47
10. Gwynne S, Hurt C, Evans M, et al. Definitive chemoradiation for oesophageal cancer--a standard of care in patients with non-metastatic oesophageal cancer. *Clin Oncol (R Coll Radiol)* 2011;23:182-8
11. Versteijne E, van Laarhoven HW, van Hooft JE, et al. Definitive chemoradiation for patients with inoperable and/or unresectable esophageal cancer: locoregional recurrence pattern. *Dis Esophagus* 2015;28:453-9
12. Araujo CM, Souhami L, Gil RA, et al. A randomized trial comparing radiation therapy versus concomitant radiation therapy and chemotherapy in carcinoma of the thoracic esophagus. *Cancer* 1991;67:2258-61
13. Kleinberg L, Gibson MK, Forastiere AA. Chemoradiotherapy for localized esophageal cancer: regimen selection and molecular mechanisms of radiosensitization. *Nat Clin Pract Oncol* 2007;4:282-94
14. Parry K, Visser E, van Rossum PS, et al. Prognosis and treatment after diagnosis of recurrent esophageal carcinoma following esophagectomy with curative intent. *Ann Surg Oncol* 2015;22 Suppl 3:S1292-300
15. Blom RL, Lagarde SM, van Oudenaarde K, et al. Survival after recurrent esophageal carcinoma has not improved over the past 18 years. *Ann Surg Oncol* 2013;20:2693-8

16. Ku GY, Ilson DH. Chemotherapeutic options for gastroesophageal junction tumors. *Semin Radiat Oncol* 2013;23:24-30
17. Ajani JA, Buyse M, Lichinitser M, et al. Combination of cisplatin/S-1 in the treatment of patients with advanced gastric or gastroesophageal adenocarcinoma: Results of noninferiority and safety analyses compared with cisplatin/5-fluorouracil in the First-Line Advanced Gastric Cancer Study. *Eur J Cancer* 2013;49:3616-24
18. Waddell T, Chau I, Cunningham D, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013;14:481-9
19. Dutton SJ, Ferry DR, Blazeby JM, et al. Gefitinib for oesophageal cancer progressing after chemotherapy (COG): a phase 3, multicentre, double-blind, placebo-controlled randomised trial. *Lancet Oncol* 2014;15:894-904
20. Ford HE, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol* 2014;15:78-86
21. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014;383:31-9
22. Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French intergroup (Federation Francophone de Cancerologie Digestive, Federation Nationale des Centres de Lutte Contre le Cancer, and Groupe Cooperateur Multidisciplinaire en Oncologie) study. *J Clin Oncol* 2014;32:3520-6
23. Wilke H, Muro K, van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014;15:1224-35
24. Hecht JR, Bang YJ, Qin SK, et al. Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC-a randomized phase III trial. *J Clin Oncol* 2016;34:443-51
25. Christie NA, Patel AN, Landreneau RJ. Esophageal palliation--photodynamic therapy/stents/brachytherapy. *Surg Clin North Am* 2005;85:569-82
26. Dai Y, Li C, Xie Y, et al. Interventions for dysphagia in oesophageal cancer. *Cochrane Database Syst Rev* 2014;10:CD005048
27. Vleggaar FP, Siersema PD. Expandable stents for malignant esophageal disease. *Gastrointest Endosc Clin N Am* 2011;21:377-88
28. Blomberg J, Wenger U, Lagergren J, et al. Antireflux stent versus conventional stent in the palliation of distal esophageal cancer. A randomized, multicenter clinical trial. *Scand J Gastroenterol* 2010;45:208-16

29. Zhu HD, Guo JH, Mao AW, et al. Conventional stents versus stents loaded with (125)iodine seeds for the treatment of unresectable oesophageal cancer: a multicentre, randomised phase 3 trial. *Lancet Oncol* 2014;15:612-9
30. Rupinski M, Zagorowicz E, Regula J, et al. Randomized comparison of three palliative regimens including brachytherapy, photodynamic therapy, and APC in patients with malignant dysphagia (CONSORT 1a) (Revised II). *Am J Gastroenterol* 2011;106:1612-20
31. Spencer GM, Thorpe SM, Blackman GM, et al. Laser augmented by brachytherapy versus laser alone in the palliation of adenocarcinoma of the oesophagus and cardia: a randomised study. *Gut* 2002;50:224-7
32. Ajani JA, D'Amico TA, Almhanna K, et al. Esophageal and esophagogastric junction cancers, version 1.2015. *J Natl Compr Canc Netw* 2015;13:194-227
33. Allum WH, Blazeby JM, Griffin SM, et al. Guidelines for the management of oesophageal and gastric cancer. *Gut* 2011;60:1449-72
34. Koeter M, van Steenberghe LN, Lemmens VE, et al. Hospital of diagnosis and probability to receive a curative treatment for oesophageal cancer. *Eur J Surg Oncol* 2014;40:1338-45
35. Cheng KK, Lee DT. Effects of pain, fatigue, insomnia, and mood disturbance on functional status and quality of life of elderly patients with cancer. *Crit Rev Oncol Hematol* 2011;78:127-37
36. Silvers MA, Savva J, Huggins CE, et al. Potential benefits of early nutritional intervention in adults with upper gastrointestinal cancer: a pilot randomised trial. *Support Care Cancer* 2014;22:3035-44
37. Miller KR, Bozeman MC. Nutrition therapy issues in esophageal cancer. *Curr Gastroenterol Rep* 2012;14:356-66
38. Bozzetti F. Nutritional support in patients with oesophageal cancer. *Support Care Cancer* 2010;18 Suppl 2:S41-50
39. Di Fiore F, Leclaire S, Pop D, et al. Baseline nutritional status is predictive of response to treatment and survival in patients treated by definitive chemoradiotherapy for a locally advanced esophageal cancer. *Am J Gastroenterol* 2007;102:2557-63
40. Odelli C, Burgess D, Bateman L, et al. Nutrition support improves patient outcomes, treatment tolerance and admission characteristics in oesophageal cancer. *Clin Oncol (R Coll Radiol)* 2005;17:639-45
41. Baldwin C, McGough C, Norman AR, et al. Failure of dietetic referral in patients with gastrointestinal cancer and weight loss. *Eur J Cancer* 2006;42:2504-9
42. Bower M, Jones W, Vessels B, et al. Role of esophageal stents in the nutrition support of patients with esophageal malignancy. *Nutr Clin Pract* 2010;25:244-9
43. Siddiqui AA, Glynn C, Loren D, et al. Self-expanding plastic esophageal stents versus jejunostomy tubes for the maintenance of nutrition during neoadjuvant chemoradiation therapy in patients with esophageal cancer: a retrospective study. *Dis Esophagus* 2009;22:216-22
44. Zhu LL, Yuan L, Wang H, et al. A meta-analysis of concurrent chemoradiotherapy for advanced esophageal cancer. *PLoS One* 2015;10:e0128616
45. Wong R, Malthaner R. Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus. *Cochrane Database Syst Rev* 2006;(1):CD002092

46. Han J, Zhu W, Yu C, et al. Clinical study of concurrent chemoradiotherapy or radiotherapy alone for esophageal cancer patients with positive lymph node metastasis. *Tumori* 2012;98:60-5
47. Courrech Staal EF, Aleman BM, van Velthuisen ML, et al. Chemoradiation for esophageal cancer: institutional experience with three different regimens. *Am J Clin Oncol* 2011;34:343-9
48. Ruppert BN, Watkins JM, Shirai K, et al. Cisplatin/irinotecan versus carboplatin/paclitaxel as definitive chemoradiotherapy for locoregionally advanced esophageal cancer. *Am J Clin Oncol* 2010;33:346-52
49. Wang H, Ryu J, Gandara D, et al. A phase II study of paclitaxel, carboplatin, and radiation with or without surgery for esophageal cancer. *J Thorac Oncol* 2007;2:153-7
50. Honing J, Smit JK, Muijs CT, et al. A comparison of carboplatin and paclitaxel with cisplatin and 5-fluorouracil in definitive chemoradiation in esophageal cancer patients. *Ann Oncol* 2014;25:638-43
51. Li QQ, Liu MZ, Hu YH, et al. Definitive concomitant chemoradiotherapy with docetaxel and cisplatin in squamous esophageal carcinoma. *Dis Esophagus* 2010;23:253-9
52. Conroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. *Lancet Oncol* 2014;15:305-14
53. Kordes S, Cats A, Meijer SL, et al. Targeted therapy for advanced esophagogastric adenocarcinoma. *Crit Rev Oncol Hematol* 2014;90:68-76
54. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002;20:1167-74
55. Lin SH, Wang L, Myles B, et al. Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs intensity-modulated radiotherapy for esophageal cancer. *Int J Radiat Oncol Biol Phys* 2012;84:1078-85
56. Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2010;(3):CD004064
57. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;358:36-46
58. Al-Batran SE, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2008;26:1435-42
59. Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol* 2009;20:666-73
60. Okines AF, Norman AR, McCloud P, et al. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. *Ann Oncol* 2009;20:1529-34

61. Ajani JA, Rodriguez W, Bodoky G, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. *J Clin Oncol* 2010;28:1547-53
62. Ter Veer E, Mohammad NH, Lodder P, et al. The efficacy and safety of S-1-based regimens in the first-line treatment of advanced gastric cancer: a systematic review and meta-analysis. *Gastric Cancer* 2016;19:696-712
63. Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997;15:261-7
64. Waters JS, Norman A, Cunningham D, et al. Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. *Br J Cancer* 1999;80:269-72
65. Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. *J Clin Oncol* 2002;20:1996-2004
66. A randomized, comparative study of combination chemotherapies in advanced gastric cancer: 5-fluorouracil and cisplatin (FP) versus 5-fluorouracil, cisplatin, and 4'-epirubicin (FPEPIR). Kyoto Research Group for Chemotherapy of Gastric Cancer (KRGCGC). *Anticancer Res* 1992;12:1983-8
67. Kim TW, Choi SJ, Ahn JH, et al. A prospective randomized phase III trial of 5-fluorouracil and cisplatin (FP) versus epirubicin, cisplatin, and 5-fu (ECF) in the treatment of patients with previously untreated advanced gastric cancer (AGC). *Eur J Cancer* 2001;37:S314
68. Mohammad NH, ter Veer E, Ngai L, et al. Optimal first-line chemotherapeutic treatment in patients with locally advanced or metastatic esophagogastric carcinoma: triplet versus doublet chemotherapy: a systematic literature review and meta-analysis. *Cancer Metastasis Rev* 2015;34:429-41
69. van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006;24:4991-7
70. Ajani JA, Moiseyenko VM, Tjulandin S, et al. Quality of life with docetaxel plus cisplatin and fluorouracil compared with cisplatin and fluorouracil from a phase III trial for advanced gastric or gastroesophageal adenocarcinoma: the V-325 Study Group. *J Clin Oncol* 2007;25:3210-6
71. Al-Batran SE, Pauligk C, Homann N, et al. The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65+). *Eur J Cancer* 2013;49:835-42
72. Lorenzen S, Hentrich M, Haberl C, et al. Split-dose docetaxel, cisplatin and leucovorin/fluorouracil as first-line therapy in advanced gastric cancer and adenocarcinoma of the gastroesophageal junction: results of a phase II trial. *Ann Oncol* 2007;18:1673-9
73. Overman MJ, Kazmi SM, Jhamb J, et al. Weekly docetaxel, cisplatin, and 5-fluorouracil as initial therapy for patients with advanced gastric and esophageal cancer. *Cancer* 2010;116:1446-53

74. Tebbutt NC, Cummins MM, Sourjina T, et al. Randomised, non-comparative phase II study of weekly docetaxel with cisplatin and 5-fluorouracil or with capecitabine in oesophagogastric cancer: the AGITG ATTAX trial. *Br J Cancer* 2010;102:475-81
75. Wang J, Xu R, Li J, et al. Randomized multicenter phase III study of a modified docetaxel and cisplatin plus fluorouracil regimen compared with cisplatin and fluorouracil as first-line therapy for advanced or locally recurrent gastric cancer. *Gastric Cancer* 2016;19:234-44
76. Bang YJ, van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010;376:687-97
77. Lordick F, Kang YK, Chung HC, et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013;14:490-9
78. Iveson T, Donehower RC, Davidenko I, et al. Rilotumumab in combination with epirubicin, cisplatin, and capecitabine as first-line treatment for gastric or oesophagogastric junction adenocarcinoma: an open-label, dose de-escalation phase 1b study and a double-blind, randomised phase 2 study. *Lancet Oncol* 2014;15:1007-18
79. Ohtsu A, Shah MA, van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2011;29:3968-76
80. Shen L, Li J, Xu J, et al. Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: randomized, double-blind, phase III study (AVATAR study). *Gastric Cancer* 2015;18:168-76
81. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006;24:2137-50
82. Bollschweiler E, Boettcher K, Hoelscher AH, et al. Is the prognosis for Japanese and German patients with gastric cancer really different? *Cancer* 1993;71:2918-25
83. Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer* 2011;47:2306-14
84. Kang JH, Lee SI, Lim do H, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 2012;30:1513-8
85. Satoh T, Xu RH, Chung HC, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN--a randomized, phase III study. *J Clin Oncol* 2014;32:2039-49

86. Lorenzen S, Riera Knorrenschild J, Haag GM, et al. Lapatinib versus lapatinib plus capecitabine as second-line treatment in human epidermal growth factor receptor 2-amplified metastatic gastro-oesophageal cancer: a randomised phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. *Eur J Cancer* 2015;51:569-76
87. Iqbal S, Goldman B, Fenoglio-Preiser CM, et al. Southwest Oncology Group study S0413: a phase II trial of lapatinib (GW572016) as first-line therapy in patients with advanced or metastatic gastric cancer. *Ann Oncol* 2011;22:2610-5
88. Atkinson M, Ferguson R. Fiberoptic endoscopic palliative intubation of inoperable oesophagogastric neoplasms. *Br Med J* 1977;1:266-7
89. Knyrim K, Wagner HJ, Bethge N, et al. A controlled trial of an expansile metal stent for palliation of esophageal obstruction due to inoperable cancer. *N Engl J Med* 1993;329:1302-7
90. De Palma GD, di Matteo E, Romano G, et al. Plastic prosthesis versus expandable metal stents for palliation of inoperable esophageal thoracic carcinoma: a controlled prospective study. *Gastrointest Endosc* 1996;43:478-82
91. Roseveare CD, Patel P, Simmonds N, et al. Metal stents improve dysphagia, nutrition and survival in malignant oesophageal stenosis: a randomized controlled trial comparing modified Gianturco Z-stents with plastic Atkinson tubes. *Eur J Gastroenterol Hepatol* 1998;10:653-7
92. Siersema PD, Hop WC, Dees J, et al. Coated self-expanding metal stents versus latex prostheses for esophagogastric cancer with special reference to prior radiation and chemotherapy: a controlled, prospective study. *Gastrointest Endosc* 1998;47:113-20
93. Sanyika C, Corr P, Haffejee A. Palliative treatment of oesophageal carcinoma--efficacy of plastic versus self-expandable stents. *S Afr Med J* 1999;89:640-3
94. O'Donnell CA, Fullarton GM, Watt E, et al. Randomized clinical trial comparing self-expanding metallic stents with plastic endoprosthesis in the palliation of oesophageal cancer. *Br J Surg* 2002;89:985-92
95. Shenfine J, McNamee P, Steen N, et al. A randomized controlled clinical trial of palliative therapies for patients with inoperable esophageal cancer. *Am J Gastroenterol* 2009;104:1674-85
96. Sgourakis G, Gockel I, Radtke A, et al. The use of self-expanding stents in esophageal and gastroesophageal junction cancer palliation: a meta-analysis and meta-regression analysis of outcomes. *Dig Dis Sci* 2010;55:3018-30
97. Adam A, Ellul J, Watkinson AF, et al. Palliation of inoperable esophageal carcinoma: a prospective randomized trial of laser therapy and stent placement. *Radiology* 1997;202:344-8
98. Vakil N, Morris AI, Marcon N, et al. A prospective, randomized, controlled trial of covered expandable metal stents in the palliation of malignant esophageal obstruction at the gastroesophageal junction. *Am J Gastroenterol* 2001;96:1791-6
99. Uitdehaag MJ, van Hooft JE, Verschuor EM, et al. A fully-covered stent (Alimaxx-E) for the palliation of malignant dysphagia: a prospective follow-up study. *Gastrointest Endosc* 2009;70:1082-9
100. Homs MY, Wahab PJ, Kuipers EJ, et al. Esophageal stents with antireflux valve for tumors of the distal esophagus and gastric cardia: a randomized trial. *Gastrointest Endosc* 2004;60:695-702

- 7
101. Sabharwal T, Gulati MS, Fotiadis N, et al. Randomised comparison of the FerX Ella antireflux stent and the ultraflex stent: proton pump inhibitor combination for prevention of post-stent reflux in patients with esophageal carcinoma involving the esophago-gastric junction. *J Gastroenterol Hepatol* 2008;23:723-8
 102. Conio M, Repici A, Battaglia G, et al. A randomized prospective comparison of self-expandable plastic stents and partially covered self-expandable metal stents in the palliation of malignant esophageal dysphagia. *Am J Gastroenterol* 2007;102:2667-77
 103. Verschuur EM, Repici A, Kuipers EJ, et al. New design esophageal stents for the palliation of dysphagia from esophageal or gastric cardia cancer: a randomized trial. *Am J Gastroenterol* 2008;103:304-12
 104. Homs MY, Steyerberg EW, Eijkenboom WM, et al. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. *Lancet* 2004;364:1497-1504
 105. Siersema PD, Hop WC, van Blankenstein M, et al. A comparison of 3 types of covered metal stents for the palliation of patients with dysphagia caused by esophagogastric carcinoma: a prospective, randomized study. *Gastrointest Endosc* 2001;54:145-53
 106. van Heel NC, Haringsma J, Boot H, et al. Comparison of 2 expandable stents for malignant esophageal disease: a randomized controlled trial. *Gastrointest Endosc* 2012;76:52-8
 107. Wenger U, Johnsson E, Arnelo U, et al. An antireflux stent versus conventional stents for palliation of distal esophageal or cardia cancer: a randomized clinical study. *Surg Endosc* 2006;20:1675-80
 108. Power C, Byrne PJ, Lim K, et al. Superiority of anti-reflux stent compared with conventional stents in the palliative management of patients with cancer of the lower esophagus and esophago-gastric junction: results of a randomized clinical trial. *Dis Esophagus* 2007;20:466-70
 109. Sabharwal T, Hamady MS, Chui S, et al. A randomised prospective comparison of the Flamingo Wallstent and Ultraflex stent for palliation of dysphagia associated with lower third oesophageal carcinoma. *Gut* 2003;52:922-6
 110. van Boeckel PG, Repici A, Vleggaar FP, et al. A new metal stent with a controlled-release system for palliation of malignant dysphagia: a prospective, multicenter study. *Gastrointest Endosc* 2010;71:455-60
 111. Shim CS, Jung IS, Cheon YK, et al. Management of malignant stricture of the esophagogastric junction with a newly designed self-expanding metal stent with an antireflux mechanism. *Endoscopy* 2005;37:335-9
 112. Guo JH, Teng GJ, Zhu GY, et al. Self-expandable esophageal stent loaded with ¹²⁵I seeds: initial experience in patients with advanced esophageal cancer. *Radiology* 2008;247:574-81
 113. Dai Z, Zhou D, Hu J, et al. Clinical application of iodine-eluting stent in patients with advanced esophageal cancer. *Oncol Lett* 2013;6:713-8
 114. Reed MF, Mathisen DJ. Tracheoesophageal fistula. *Chest Surg Clin N Am* 2003;13:271-89
 115. Ross WA, Alkassab F, Lynch PM, et al. Evolving role of self-expanding metal stents in the treatment of malignant dysphagia and fistulas. *Gastrointest Endosc* 2007;65:70-6

116. May A, Ell C. Palliative treatment of malignant esophagorespiratory fistulas with Gianturco-Z stents. A prospective clinical trial and review of the literature on covered metal stents. *Am J Gastroenterol* 1998;93:532-5
117. Shin JH, Song HY, Ko GY, et al. Esophagorespiratory fistula: long-term results of palliative treatment with covered expandable metallic stents in 61 patients. *Radiology* 2004;232:252-9
118. Lettmaier S, Strnad V. Intraluminal brachytherapy in oesophageal cancer: defining its role and introducing the technique. *J Contemp Brachytherapy* 2014;6:236-41
119. Bergquist H, Wenger U, Johnsson E, et al. Stent insertion or endoluminal brachytherapy as palliation of patients with advanced cancer of the esophagus and gastroesophageal junction. Results of a randomized, controlled clinical trial. *Dis Esophagus* 2005;18:131-9
120. Adamson D, Blazeby J, Nelson A, et al. Palliative radiotherapy in addition to self-expanding metal stent for improving dysphagia and survival in advanced oesophageal cancer (ROCS: Radiotherapy after Oesophageal Cancer Stenting): study protocol for a randomized controlled trial. *Trials* 2014;15:402
121. Suntharalingam M, Moughan J, Coia LR, et al. The national practice for patients receiving radiation therapy for carcinoma of the esophagus: results of the 1996-1999 Patterns of Care Study. *Int J Radiat Oncol Biol Phys* 2003;56:981-7
122. Sur RK, Donde B, Levin VC, et al. Fractionated high dose rate intraluminal brachytherapy in palliation of advanced esophageal cancer. *Int J Radiat Oncol Biol Phys* 1998;40:447-53
123. Sur RK, Levin CV, Donde B, et al. Prospective randomized trial of HDR brachytherapy as a sole modality in palliation of advanced esophageal carcinoma--an International Atomic Energy Agency study. *Int J Radiat Oncol Biol Phys* 2002;53:127-33
124. Dallal HJ, Smith GD, Grieve DC, et al. A randomized trial of thermal ablative therapy versus expandable metal stents in the palliative treatment of patients with esophageal carcinoma. *Gastrointest Endosc* 2001;54:549-57
125. Sander R, Hagenmueller F, Sander C, et al. Laser versus laser plus afterloading with iridium-192 in the palliative treatment of malignant stenosis of the esophagus: a prospective, randomized, and controlled study. *Gastrointest Endosc* 1991;37:433-40
126. Sargeant IR, Tobias JS, Blackman G, et al. Radiotherapy enhances laser palliation of malignant dysphagia: a randomised study. *Gut* 1997;40:362-9
127. Rosenblatt E, Jones G, Sur RK, et al. Adding external beam to intra-luminal brachytherapy improves palliation in obstructive squamous cell oesophageal cancer: a prospective multi-centre randomized trial of the International Atomic Energy Agency. *Radiother Oncol* 2010;97:488-94
128. Sur R, Donde B, Falkson C, et al. Randomized prospective study comparing high-dose-rate intraluminal brachytherapy (HDRILBT) alone with HDRILBT and external beam radiotherapy in the palliation of advanced esophageal cancer. *Brachytherapy* 2004;3:191-5
129. Amdal CD, Jacobsen AB, Sandstad B, et al. Palliative brachytherapy with or without primary stent placement in patients with oesophageal cancer, a randomised phase III trial. *Radiother Oncol* 2013;107:428-33

- 7
130. Javed A, Pal S, Dash NR, et al. Palliative stenting with or without radiotherapy for inoperable esophageal carcinoma: a randomized trial. *J Gastrointest Cancer* 2012;43:63-9
 131. Nishimura Y, Suzuki M, Nakamatsu K, et al. Prospective trial of concurrent chemoradiotherapy with protracted infusion of 5-fluorouracil and cisplatin for T4 esophageal cancer with or without fistula. *Int J Radiat Oncol Biol Phys* 2002;53:134-9
 132. Nishimura Y, Koike R, Ogawa K, et al. Clinical practice and outcome of radiotherapy for esophageal cancer between 1999 and 2003: the Japanese Radiation Oncology Study Group (JROSG) Survey. *Int J Clin Oncol* 2012;17:48-54
 133. Shimoji H, Karimata H, Nagahama M, et al. Induction chemotherapy or chemoradiotherapy followed by radical esophagectomy for T4 esophageal cancer: results of a prospective cohort study. *World J Surg* 2013;37:2180-8
 134. Pimiento JM, Weber J, Hoffe SE, et al. Outcomes associated with surgery for T4 esophageal cancer. *Ann Surg Oncol* 2013;20:2706-12
 135. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
 136. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011;12:681-92
 137. Makino T, Doki Y. Treatment of T4 esophageal cancer. Definitive chemo-radiotherapy vs chemo-radiotherapy followed by surgery. *Ann Thorac Cardiovasc Surg* 2011;17:221-8
 138. Ruurda JP, van der Sluis PC, van der Horst S, et al. Robot-assisted minimally invasive esophagectomy for esophageal cancer: A systematic review. *J Surg Oncol* 2015;112:257-65
 139. Karimata H, Shimoji H, Nishimaki T. Clinicopathological factors predicting R0 resection and long-term survival after esophagectomy in patients with T4 esophageal cancer undergoing induction chemotherapy or chemoradiotherapy. *Surg Today* 2015;45:479-86
 140. Noguchi T, Moriyama H, Wada S, et al. Resection surgery with neoadjuvant chemoradiotherapy improves outcomes of patients with T4 esophageal carcinoma. *Dis Esophagus* 2003;16:94-8
 141. van Rossum PS, Fried DV, Zhang L, et al. The incremental value of subjective and quantitative assessment of ¹⁸F-FDG PET for the prediction of pathologic complete response to preoperative chemoradiotherapy in esophageal cancer. *J Nucl Med* 2016;57:691-700
 142. van Rossum PS, Goense L, Meziani J, et al. Endoscopic biopsy and EUS for the detection of pathologic complete response after neoadjuvant chemoradiotherapy in esophageal cancer: a systematic review and meta-analysis. *Gastrointest Endosc* 2016;83:866-79
 143. van Rossum PS, van Lier AL, Lips IM, et al. Imaging of oesophageal cancer with FDG-PET/CT and MRI. *Clin Radiol* 2015;70:81-95
 144. van Rossum PS, van Lier AL, van Vulpen M, et al. Diffusion-weighted magnetic resonance imaging for the prediction of pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer. *Radiother Oncol* 2015;115:163-70

145. van Rossum PS, van Hillegersberg R, Lever FM, et al. Imaging strategies in the management of oesophageal cancer: what's the role of MRI? *Eur Radiol* 2013;23:1753-65
146. Weichselbaum RR, Hellman S. Oligo-metastases revisited. *Nat Rev Clin Oncol* 2011;8:378-82
147. Milano MT, Katz AW, Zhang H, et al. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. *Int J Radiat Oncol Biol Phys* 2012;83:878-86
148. Al-Asfoor A, Fedorowicz Z, Lodge M. Resection versus no intervention or other surgical interventions for colorectal cancer liver metastases. *Cochrane Database Syst Rev* 2008;(2):CD006039
149. Sternberg DI, Sonett JR. Surgical therapy of lung metastases. *Semin Oncol* 2007;34:186-96
150. Timmerman RD, Bizakis CS, Pass HI, et al. Local surgical, ablative, and radiation treatment of metastases. *CA Cancer J Clin* 2009;59:145-70
151. Martel G, Hawel J, Rekman J, et al. Liver resection for non-colorectal, non-carcinoid, non-sarcoma metastases: a multicenter study. *PLoS One* 2015;10:e0120569
152. Huddy JR, Ni MZ, Markar SR, et al. Point-of-care testing in the diagnosis of gastrointestinal cancers: current technology and future directions. *World J Gastroenterol* 2015;21:4111-20
153. Bartlett EK, Simmons KD, Wachtel H, et al. The rise in metastasectomy across cancer types over the past decade. *Cancer* 2015;121:747-57



Chapter 8

Prognosis and treatment after diagnosis of recurrent esophageal carcinoma following esophagectomy with curative intent

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Annals of Surgical Oncology 2015;22:1292-300

ABSTRACT

BACKGROUND

Strategies for the treatment of recurrence after initial curative esophagectomy are increasingly being recognized. The aim of this study was to identify prognostic factors that affect survival in patients with recurrence and to evaluate treatment strategies.

METHODS

A prospective database (2003-2013) was used to collect consecutive patients with esophageal carcinoma treated with initial curative esophagectomy. Locations, symptoms, and treatment of recurrence were registered. Post-recurrence survival was defined as the time between the first recurrence and death or last follow-up.

RESULTS

Of the 335 selected patients, 171 (51%) developed recurrence. Multivariable analysis identified distant recurrence as opposed to locoregional recurrence [hazard ratio (HR) 2.15, 95% confidence interval (CI) 1.27-3.65; $p=0.005$], more than three recurrent locations (HR 2.42, 95% CI 1.34-4.34; $p=0.003$), and treatment (HR 0.29, 95% CI 0.20-0.44; $p<0.001$) as independent prognostic factors associated with post-recurrence survival. Primary tumor characteristics, including neoadjuvant therapy, histologic type, pTN stage, and radicality, did not independently influence post-recurrence survival. Treatment was initiated in 62 patients (37%) and included chemotherapy, radiotherapy, and/or surgery. Median post-recurrence survival of all patients was 3.0 months (range 0-112). In total, six patients (4%) were still disease-free following treatment, indicating cure.

CONCLUSIONS

In patients treated for esophageal cancer at curative intent, distant recurrence and more than three recurrent locations were independent prognostic factors associated with worse post-recurrence survival, irrespective of primary tumor characteristics. Although survival after recurrence was poor, treatment can prolong survival and can even lead to cure in selected patients.

INTRODUCTION

Esophageal carcinoma is the sixth leading cause of cancer-related mortality worldwide and the incidence is rapidly increasing^{1,2}. Multimodality treatment combining neoadjuvant chemo(radio)therapy and surgical resection has improved the prognosis for resectable non-metastatic disease³. However, more than half of the patients develop recurrence within 3 years after treatment with curative intent⁴⁻⁷. The prognosis of recurrent esophageal cancer is poor with a median survival after developing a recurrence of 3 to 10 months^{4,8-10}. Therefore, detecting prognostic factors affecting post-recurrence survival and determining effectiveness of treatment strategies for recurrence are of high importance. Treatment can be attempted in a fair number of patients with recurrent disease and may include chemotherapy, radiotherapy, surgery, or a combination^{9,11,12}. However, the optimal treatment strategy for esophageal cancer patients with recurrent disease is not yet established and patients respond differently to treatment with a wide range in long-term survival¹².

The aim of this study was to investigate prognostic factors that affect survival in patients diagnosed with recurrent disease after prior esophagectomy with curative intent for esophageal carcinoma. A second aim was to evaluate the different treatment strategies applied.

METHODS

PATIENTS

In this single-center cohort study patients were selected from a prospectively assembled database at the University Medical Center Utrecht, The Netherlands. Between October 2003 and December 2013, 379 consecutive patients were planned for esophagectomy with curative intent for esophageal carcinoma. Patients with an unresectable tumor (cT4b) or metastatic disease (M1) detected intraoperatively were excluded (n=22). Patients deceased within 90 days after surgery or during hospitalization, were also excluded (n=22). Of the remaining 335 patients, 171 were diagnosed with recurrent disease and were included in this study. Histopathologic staging was performed according to the TNM-7 staging system of the American Joint Committee on Cancer (AJCC)¹³. All patients were discussed at a multidisciplinary tumor board meeting preoperatively, postoperatively and after developing recurrent disease. Institutional Review Board approval was obtained and the informed consent requirement was waived for this study.

TREATMENT

Eligible patients with locally advanced disease (cT \geq 2 or cN+) and without clinical evidence of metastatic disease (cM0) received either perioperative chemotherapy or neoadjuvant chemoradiation according to the Dutch guidelines. Eligible patients were >18 years of age, had a WHO performance status \leq 2, and did not lose >10% of their body weight. Before 1 June 2012, the standard treatment for patients with esophageal carcinoma consisted of perioperative chemotherapy (epirubicin, cisplatin and 5-fluorouracil)¹⁴ and, after that, patients underwent neoadjuvant chemoradiation (carboplatin AUC2 and paclitaxel 50 mg/m² weekly during 5 weeks concomitant with 41.4 Gy (23x 1.8 Gy)³. Before 2008 neoadjuvant therapy was not a part of the standard protocol and most patients were operated on without neoadjuvant therapy. Patients not eligible for neoadjuvant treatment were treated with surgical esophageal resection alone. After esophagectomy with en bloc lymphadenectomy, all patients underwent gastric tube reconstruction with a cervical anastomosis.

HISTOPATHOLOGIC ANALYSIS

The resected specimens were reviewed by experienced pathologists in accordance with the TNM-7 staging system of the AJCC¹³. The resection margins were evaluated using the definitions of the College of American Pathologists^{15,16}.

FOLLOW-UP AND DEFINITION OF RECURRENCE

After esophagectomy, patients were followed at the outpatient clinic with an interval of 3 months in the first year, 6 months in the second year and 12 months thereafter until discharge after 5 years of follow-up. Follow-up consisted of medical history and physical examination. In case of clinical suspicion of tumor recurrence, diagnostic imaging was performed. Recurrence was confirmed by histopathologic biopsy or clinical follow-up. Only the initial number and sites of recurrences were evaluated. The pattern of recurrence was classified as locoregional, distant or a combination of both. Recurrences at the anastomotic site or within the area of previous resection and nodal clearance in the mediastinum or upper abdomen were classified as locoregional recurrence. Distant recurrence was defined as recurrence in distant organs, pleura or peritoneal cavity, or distant lymph nodes. Disease-free survival was defined as time between day of surgery and day of recurrent disease. Post-recurrence survival was defined as the time between the first recurrence and death or last follow-up.

TREATMENT OF RECURRENCE

Treatment for recurrent disease was discussed at a multidisciplinary tumor board meeting and recommended if the patient was eligible. General considerations regarding eligibility included patient condition, location of recurrences, prior toxicity from chemo- or radiotherapy, and patient's wish. Treatment consisted of chemotherapy, radiotherapy and/or surgery focused on tumor reduction. Radiotherapy focused on tumor reduction was defined as radiotherapy with a radiation dose >30 Gy, excluding palliative radiotherapy for bone metastases. In all other cases, patients were treated with best supportive care.

STATISTICAL ANALYSIS

To assess prognostic factors for post-recurrence survival univariable and multivariable analyses by means of Cox proportional hazard models were used, providing hazard ratios (HRs) with 95% confidence intervals (CIs). All variables with $p < 0.20$ in univariable analysis were entered in a multivariable analysis. Kaplan-Meier survival curves were constructed for the prognostic factors that remained significantly associated with post-recurrence survival in multivariable analysis. A p -value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS version 21 for Windows.

RESULTS

PATIENT CHARACTERISTICS

The median follow-up of the 335 consecutive patients treated with esophagectomy in the study period was 22.0 months (range 2-135). Of all patients, 171 (51%) developed recurrent disease and those patients were included in this study. The clinical and histopathologic characteristics of these 171 patients are shown in **Table 1**. Mean age was 63 years (SD 8.8) and most patients were male ($n=131$, 77%). Perioperative chemotherapy was administered in 63 patients (37%) and neoadjuvant chemoradiation in 35 (21%). The surgical procedure consisted of a transthoracic approach in 132 patients (77%) and a transhiatal approach in the remaining 39 patients (23%). Tumor histology was adenocarcinoma in 136 patients (80%). Histopathology revealed $\geq pT3$ ($n=129$, 75%) and $pN+$ disease ($n=123$, 72%) in the majority of patients. Of all patients that developed a recurrence, 139 (81%) underwent a microscopically radical (R0) resection.

Table 1 Clinical and histopathologic characteristics of 171 patients with recurrent disease after esophagectomy with curative intent

| | n | (%) |
|---|-----|-----------|
| Gender | | |
| Male | 131 | (77) |
| Female | 40 | (23) |
| Age, years [mean \pmSD] | 63 | \pm 8.8 |
| ASA score | | |
| 1 | 49 | (29) |
| 2 | 95 | (56) |
| \geq 3 | 27 | (16) |
| Neoadjuvant therapy | | |
| No neoadjuvant therapy | 72 | (42) |
| Chemotherapy | 63 | (37) |
| Radiotherapy | 1 | (1) |
| Chemoradiation | 35 | (21) |
| Surgical approach | | |
| Transthoracic | 132 | (77) |
| Transhiatal | 39 | (23) |
| Adjuvant therapy | | |
| No adjuvant therapy | 137 | (80) |
| Chemotherapy | 34 | (20) |
| Histologic type | | |
| Adenocarcinoma | 136 | (80) |
| Squamous cell carcinoma | 34 | (20) |
| Other | 1 | (<1) |
| pT stage | | |
| T0 | 9 | (5) |
| T1 | 16 | (9) |
| T2 | 17 | (10) |
| T3 | 121 | (71) |
| T4 | 8 | (5) |
| pN stage | | |
| N0 | 48 | (28) |
| N1 | 49 | (29) |
| N2 | 47 | (28) |
| N3 | 27 | (16) |
| Number of harvested lymph nodes (median [range]) | 20 | [2-80] |
| Radicality | | |
| R0 | 139 | (81) |
| R1 | 32 | (19) |

PATTERN OF RECURRENCE

Median time to recurrence was 9.0 months (range 1-86), and 164 patients (96%) developed recurrence within 3 years after surgery. The most common presenting symptoms were pain (n=38, 22%), malaise (n=23, 14%), dysphagia (n=21, 12%) and anorexia (n=21, 12%). The diagnosis of recurrent disease was based on computed tomography (CT) findings in 118 patients (69%), whereas in other patients the diagnosis was made with either endoscopic ultrasound upper (EUS), upper endoscopy, positron emission tomography (¹⁸F-FDG PET) or magnetic resonance imaging (MRI). The type of recurrence and the number of locations are presented in **Table 2**. Distant recurrence was the most common type of recurrent disease (n=76, 44%) and the liver was the most commonly affected site (n=50, 15%).

FACTORS AFFECTING POST-RECURRENCE SURVIVAL

Median post-recurrence survival was 3.0 months (range 0-112). The overall 1- and 2-year post-recurrence survival rates were 17% and 7%. Nodal status, type of recurrence, number of locations, time to recurrence and treatment of recurrence were significantly associated with post-recurrence survival in univariable analysis (**Table 3, Figure 1**). In multivariable analysis, distant recurrence (HR 2.15, 95% CI 1.27-3.65; $p=0.005$), >3 recurrent tumor locations (HR 2.42, 95% CI 1.34-4.34; $p=0.003$) and treatment (HR 0.29, 95% CI 0.20-0.44; $p<0.001$) were identified as independent prognostic factors associated with post-recurrence survival (**Table 3**). The median post-recurrence survival of patients with distant and locoregional recurrence was 2.0 months and 12.0 months respectively, and for patients with >3 recurrent tumor locations and a solitary recurrence 2.0 months and 6.0 months respectively. Patients who received treatment had a median post-recurrence survival of 9.0 months as compared to 2.0 months in patients treated with best supportive care. Primary tumor characteristics including neoadjuvant therapy, histologic type, pTN-stage, and radicality of resection did not independently influence post-recurrence survival in multivariable analysis.

TREATMENT OF RECURRENCE

Best supportive care was given to 109 patients (63%). Patients receiving best supportive care were mainly either not eligible for treatment due to a poor performance status (n=63, 37%) or refused treatment (n=29, 17%). Some patients were not eligible due to prior toxicity of the neoadjuvant treatment regimen (n=4, 4%) or due to tumor location (n=4, 4%). Treatment focused on tumor reduction was applied in 62 patients (37%) (**Table 2**). Patients with locoregional recurrence (n=19, 70%) and solitary recurrence (n=24, 49%) more often received treatment

Table 2 Location and treatment recurrence of 171 patients with recurrent disease after esophagectomy with curative intent

| | n | (%) |
|---|-----|------|
| Type of recurrence | | |
| Locoregional | 27 | (16) |
| Distant | 76 | (44) |
| Combined | 68 | (40) |
| Location distant recurrence | | |
| Liver | 50 | (15) |
| Lung | 41 | (13) |
| Abdominal lymph nodes | 40 | (12) |
| Retroperitoneal | 40 | (12) |
| Bone | 30 | (9) |
| Other | 123 | (38) |
| Number of locations with recurrence | | |
| 1 | 49 | (29) |
| 2-3 | 62 | (36) |
| >3 | 60 | (35) |
| Type of management | | |
| <i>Treatment focused on tumor reduction</i> | | |
| Chemotherapy | 62 | (37) |
| Radiotherapy | 24 | (14) |
| Chemoradiation | 11 | (6) |
| Surgery | 13 | (8) |
| Surgery + chemotherapy | 5 | (3) |
| Surgery + radiotherapy | 4 | (2) |
| Other | 4 | (2) |
| <i>Best supportive care</i> | | |
| Condition | 109 | (63) |
| Patient wish | 63 | (37) |
| Toxicity | 29 | (17) |
| Location | 4 | (2) |
| Other | 4 | (2) |
| Unknown | 6 | (4) |
| | 3 | (2) |

focused on reduction compared with those with distant recurrence (26, 34%) and >3 recurrent tumor locations (n=14, 23%). Different chemotherapy regimens were administered in 41 patients; most patients received a combination of epirubicin, cisplatin and capecitabine (n=20, 48%). After treatment with chemotherapy only, 2 patients (5%) clinically showed a complete tumor regression. One patient had a solitary metastasis in the liver and the other patient had a solitary locoregional recurrence in the gastric conduit and truncal node. Both patients were alive at last follow-up (35 and 112 months after diagnosis of recurrence).

Table 3 Univariable and multivariable Cox regression analysis of potential prognostic factors for survival after diagnosis of recurrent esophageal carcinoma

| | Univariable analysis | | | Multivariable analysis | | |
|--------------------------------------|----------------------|------------|------------------|------------------------|------------|------------------|
| | HR | 95% CI | p-value | HR | 95% CI | p-value |
| Age (years) | 1.02 | 1.00-1.04 | 0.055 | 1.00 | 0.99-1.02 | 0.670 |
| Neoadjuvant therapy | | | | | | |
| None | Reference | - | - | Reference | - | - |
| Chemotherapy | 1.39 | 0.98-1.99 | 0.067 | 1.02 | 0.70-1.49 | 0.936 |
| Radiotherapy | 3.45 | 0.47-25.23 | 0.222 | 7.85 | 0.99-62.54 | 0.052 |
| Chemoradiation | 1.26 | 0.82-1.94 | 0.297 | 0.84 | 0.50-1.41 | 0.512 |
| Histologic type | | | | | | |
| Adenocarcinoma | Reference | - | - | | | |
| Squamous cell carcinoma | 1.24 | 0.84-1.84 | 0.272 | | | |
| Other | 1.10 | 0.15-7.93 | 0.922 | | | |
| pT stage | | | | | | |
| T0 | Reference | - | - | Reference | - | - |
| T1-2 | 0.47 | 0.21-1.06 | 0.067 | 0.60 | 0.25-1.41 | 0.243 |
| T3-4 | 0.70 | 0.34-1.45 | 0.341 | 0.78 | 0.34-1.76 | 0.545 |
| pN stage | | | | | | |
| N0 | Reference | - | - | Reference | - | - |
| N1 | 1.80 | 1.18-2.75 | 0.007 | 1.50 | 0.95-2.37 | 0.080 |
| N2-3 | 1.35 | 0.91-1.99 | 0.131 | 1.10 | 0.70-1.73 | 0.689 |
| Radicality | | | | | | |
| R0 | Reference | - | - | | | |
| R1 | 1.20 | 0.81-1.77 | 0.363 | | | |
| Type of recurrence | | | | | | |
| Locoregional | Reference | - | - | Reference | - | - |
| Distant | 2.10 | 1.30-3.41 | 0.003 | 2.15 | 1.27-3.65 | 0.005 |
| Combined | 2.54 | 1.55-4.16 | <0.001 | 1.58 | 0.89-2.81 | 0.120 |
| Number of locations | | | | | | |
| 1 | Reference | - | - | Reference | - | - |
| 2-3 | 1.21 | 0.81-1.79 | 0.357 | 1.30 | 0.83-2.00 | 0.250 |
| >3 | 2.20 | 1.46-3.32 | <0.001 | 2.42 | 1.34-4.34 | 0.003 |
| Time to recurrence (months) | 0.98 | 0.96-1.00 | 0.013 | 0.99 | 0.98-1.01 | 0.263 |
| Treatment of recurrence | | | | | | |
| Best supportive care | Reference | - | - | Reference | - | - |
| Treatment focused on tumor reduction | 0.27 | 0.19-0.38 | <0.001 | 0.29 | 0.20-0.44 | <0.001 |

Note: Bold values indicate statistical significance (i.e. $p < 0.05$). All variables with $p < 0.2$ from univariable analysis were used for multivariate analysis.

HR: hazard ratio, CI: confidence interval.

Table 4 Characteristics, treatment, and survival of 13 patients treated with surgical resection for recurrent esophageal

| Case | Age (y) | Sex | pTNM stage | Time to recurrence (months) | Type of recurrence | Location recurrence |
|------|---------|--------|------------|-----------------------------|--------------------|---|
| 1 | 56 | Male | T3N2M0 | 11 | Distant | Abdominal LN |
| 2 | 44 | Male | T3N2M0 | 3 | Distant | Abdominal wall Inguinal cutane |
| 3 | 74 | Female | T4aN2M0 | 2 | Distant | Upper leg Inguinal LN Abdominal wall Abdominal LN |
| 4 | 67 | Male | T3N2M0 | 8 | Distant | Brain, lung, liver |
| 5 | 53 | Male | T0N0M0 | 21 | Distant | Brain |
| 6 | 77 | Female | T3N0M0 | 14 | Distant | Brain |
| 7 | 75 | Male | T1bN0M0 | 31 | Distant | Lung |
| 8 | 62 | Female | T3N0M0 | 12 | Distant | Brain |
| 9 | 50 | Male | T3N0M0 | 32 | Distant | Vesiculae seminales |
| 10 | 65 | Male | T3N3M0 | 8 | Combined | Quadriceps muscles Paraesophageal LN |
| 11 | 56 | Male | T2N0M0 | 13 | Locoregional | Gastric conduit |
| 12 | 65 | Male | T1aN0M0 | 10 | Distant | Liver |
| 13 | 62 | Male | T3N0M0 | 20 | Distant | Brain |

CT: chemotherapy. LN: lymph node. RT: radiotherapy.

DISCUSSION

In this single-center cohort study, 171 patients with recurrent disease after treatment with curative intent for esophageal carcinoma were analyzed and factors affecting post-recurrence survival were evaluated. Distant recurrence and more than 3 recurrent locations were identified as independent prognostic factors associated with a worse post-recurrence survival, irrespective of primary tumor characteristics. Furthermore, treatment focused on tumor reduction as opposed to best supportive care prolonged survival in eligible patients and a selected group of patients were treated curatively.

This study confirms the poor prognosis of recurrent esophageal cancer reported in other series^{4,8-10} with a median post-recurrence survival of 3.0 months and a 2-year survival rate of only 7%. Hence, understanding of the prognostic factors influencing survival is important to identify patients who could have an improved

carcinoma

| Surgical intervention | Other treatments | | Curative intent | Status | Survival after recurrence (months) |
|--|------------------|-----|-----------------|--------|------------------------------------|
| | CT | RT | | | |
| LN resection | No | No | Yes | Dead | 53 |
| Tumor resection | Yes | No | Yes | Dead | 9 |
| Tumor resection LN resection | No | Yes | No | Dead | 4 |
| Metastasectomy brain lesion | No | Yes | No | Dead | 5 |
| Metastasectomy brain lesion | No | Yes | Yes | Dead | 7 |
| Metastasectomy brain lesion | No | No | Yes | Dead | 1 |
| Partial pulmonary resection | No | No | Yes | Dead | 18 |
| Metastasectomy brain lesion | No | No | Yes | Dead | 4 |
| Excision vesiculae seminales | No | No | Yes | Dead | 11 |
| Metastasectomy quadriceps muscles | Yes | No | Yes | Alive | 87 |
| Resection gastric conduit with jejunal reconstruction | No | No | Yes | Alive | 46 |
| Hemihepatectomy | Yes | No | Yes | Alive | 53 |
| Metastasectomy brain lesion | No | Yes | Yes | Alive | 5 |

post-recurrence survival by selecting them for the appropriate treatment. In accordance with the literature, distant recurrence was associated with a worse survival in this study reflecting aggressive tumor biology^{6,12,17}. Furthermore, this study showed that patients with > 3 recurrent tumor locations have a worse post-recurrence survival compared to those with less involved locations, which could also be explained by the more aggressive behavior of multiple recurrences. The survival of patients with > 3 recurrent locations was extremely poor, with a median survival of 2.0 months after the diagnosis of recurrence as compared to 6.0 months in patients with a solitary recurrence. The majority of patients had a poor clinical condition at the time of diagnosis of recurrence and were therefore considered ineligible for treatment focused on tumor reduction. The patients that did undergo treatment had a significantly prolonged survival, which is likely explained by a combination of appropriate patient selection and treatment effectiveness.

In 13 of 171 patients (8%) surgical resection of the recurrence was performed (**Table 4**). Most of these patients had a solitary recurrence ($n=9$, 69%) at a distant location ($n=11$, 85%). The surgical resections are outlined in **Table 4**; 5 patients (38%) underwent metastasectomy of a brain lesion. Median post-recurrence survival in patients who underwent resection was 11 months (95% CI 4.5-17.5). In 11 of 13 patients (85%) the resection was performed with curative intent. Of these patients, 4 of 11 (36%) were still alive at last follow-up with a follow-up of 5, 46, 53, and 87 months after the diagnosis of their recurrence, whereas the remaining 7 patients (64%) deceased due to disease progression.

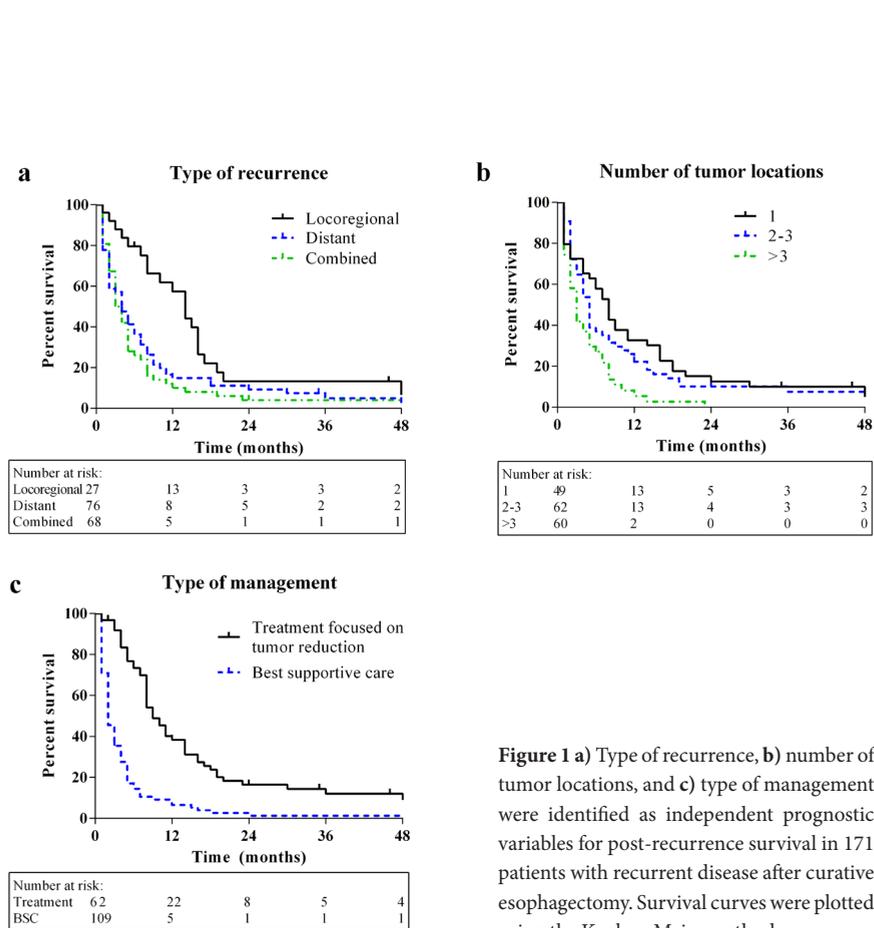


Figure 1 a) Type of recurrence, b) number of tumor locations, and c) type of management were identified as independent prognostic variables for post-recurrence survival in 171 patients with recurrent disease after curative esophagectomy. Survival curves were plotted using the Kaplan–Meier method.

As has been reported in previous studies^{4,9,18}, all different treatment strategies resulted in a prolonged survival in the current study. This finding suggests that all patients with recurrent disease should be stimulated to undergo treatment if the condition of the patients allows it. The median post-recurrence survival in the treated group was 8.5 months compared to 2.0 months for those who were treated with best supportive care. It needs to be acknowledged that the majority of patients who received best supportive care were not eligible for therapy, causing bias through selection-by-indication in this comparison. Nonetheless, most patients that were not eligible had advanced disease (i.e. distant recurrence or > 3 recurrent locations), which reflects high dependency of the patient's condition on the site and number of recurrent tumors.

Patients were treated with various therapies of which chemotherapy was the most commonly applied. The benefit of a surgical resection of recurrent esophageal carcinoma is not yet completely elucidated. A few reports showed improved survival after surgical resection^{11,19,20}. However, in most studies the resection was combined with either chemo- or radiotherapy and performed only in a small number of patients. Also in this study a small group of patients (n=13) underwent resection of their recurrence. The majority (n=9) had oligometastasis. Patients with oligometastases represent a special tumor behavior that is likely to gain from local control. In other types of cancer, the current literature shows also a survival benefit with long disease free survival from local control with surgery for patients with oligometastases^{21,22}. Importantly, 4 patients had complete tumor remission after the resection and were still alive at last follow up. Other studies also reported long-term survival after treatment of recurrent disease for esophageal carcinoma^{11,23-25}. These findings suggest that a favorable outcome can be expected after surgical resection in a selected patient group, especially for those with solitary or localized recurrence of esophageal cancer.

Although treatment of recurrence resulted in prolonged survival, the majority of patients (63%) received best supportive care. This is in contrast with some other studies where the proportion of patients receiving best supportive care ranged from 12 to 44%^{9,11,17,26,27}. An explanation for the high percentage of best supportive care in this cohort could lie in the follow-up strategy. The current follow-up strategy is based on the existing literature showing that routine diagnostic imaging is of no benefit with regard to survival and costs²⁸. Furthermore, the consensus-based guidelines from the National Comprehensive Cancer Network also suggest to only perform diagnostic imaging when clinically indicated²⁹. Hence, this follow up strategy is widely performed in the Netherlands. However, this strategy could have

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resulted in more advanced recurrent tumor stages at the moment of diagnosis. Since the patient's condition is largely determined by the number and site of recurrences, patients with multiple metastases are often not eligible for therapy. Therefore, the follow-up strategy may need revision according to the findings of the current study. In light of the new insights in the concept of oligometastases and the new combined treatment options we suggest to routinely perform a follow-up of patients with ¹⁸F-FDG PET/CT in the first 6-12 months following primary treatment³⁰. Another explanation for the high 'best supportive care' rate could be the large proportion of patients (27%) who refused any form of treatment. In most other studies, only a fraction of patients did not receive treatment based on patient's choice^{17,26,27}. According to the results of the current study, eligible patients might be encouraged for treatment focused on tumor reduction to improve their survival. Unfortunately no information on quality of life was obtained from patients that were treated for recurrence. Quality of life is of paramount importance in patients being treated with palliative intent.

In conclusion, survival after developing a recurrence after esophagectomy with curative intent is poor. Distant recurrence and >3 recurrent locations were identified as independent factors associated with a worse survival, irrespective of primary tumor characteristics. Treatment focused on tumor reduction using various strategies contributed to a prolonged survival in all patients. Hence, focus is needed to improve patient selection for treatment in recurrent esophageal carcinoma. Additionally, in a small group of patients (4%) curative treatment of recurrent esophageal carcinoma appears possible.

REFERENCES

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65:87-108
2. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. *Lancet* 2013;381:400-12
3. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
4. Dresner SM, Griffin SM. Pattern of recurrence following radical oesophagectomy with two-field lymphadenectomy. *Br J Surg* 2000;87:1426-33
5. Nakagawa S, Kanda T, Kosugi S, et al. Recurrence pattern of squamous cell carcinoma of the thoracic esophagus after extended radical esophagectomy with three-field lymphadenectomy. *J Am Coll Surg* 2004;198:205-11
6. Mariette C, Balon JM, Piessen G, et al. Pattern of recurrence following complete resection of esophageal carcinoma and factors predictive of recurrent disease. *Cancer* 2003;97:1616-23
7. Hulscher JB, van Sandick JW, Tijssen JG, et al. The recurrence pattern of esophageal carcinoma after transhiatal resection. *J Am Coll Surg* 2000;191:143-8
8. Kunisaki C, Makino H, Takagawa R, et al. Surgical outcomes in esophageal cancer patients with tumor recurrence after curative esophagectomy. *J Gastrointest Surg* 2008;12:802-10
9. Blom RL, Lagarde SM, van Oudenaarde K, et al. Survival after recurrent esophageal carcinoma has not improved over the past 18 years. *Ann Surg Oncol* 2013;20:2693-8
10. Abate E, DeMeester SR, Zehetner J, et al. Recurrence after esophagectomy for adenocarcinoma: defining optimal follow-up intervals and testing. *J Am Coll Surg* 2010;210:428-35
11. Hiyoshi Y, Morita M, Kawano H, et al. Clinical significance of surgical resection for the recurrence of esophageal cancer after radical esophagectomy. *Ann Surg Oncol* 2015;22:240-6
12. Su XD, Zhang DK, Zhang X, et al. Prognostic factors in patients with recurrence after complete resection of esophageal squamous cell carcinoma. *J Thorac Dis* 2014;6:949-57
13. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010;17:1471-4
14. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20
15. Deeter M, Dorer R, Kuppusamy MK, et al. Assessment of criteria and clinical significance of circumferential resection margins in esophageal cancer. *Arch Surg* 2009;144:618-24
16. Verhage RJ, Zandvoort HJ, ten Kate FJ, et al. How to define a positive circumferential resection margin in T3 adenocarcinoma of the esophagus. *Am J Surg Pathol* 2011;35:919-26
17. Kato H, Fukuchi M, Miyazaki T, et al. Classification of recurrent esophageal cancer after radical esophagectomy with two- or three-field lymphadenectomy. *Anticancer Res* 2005;25:3461-7

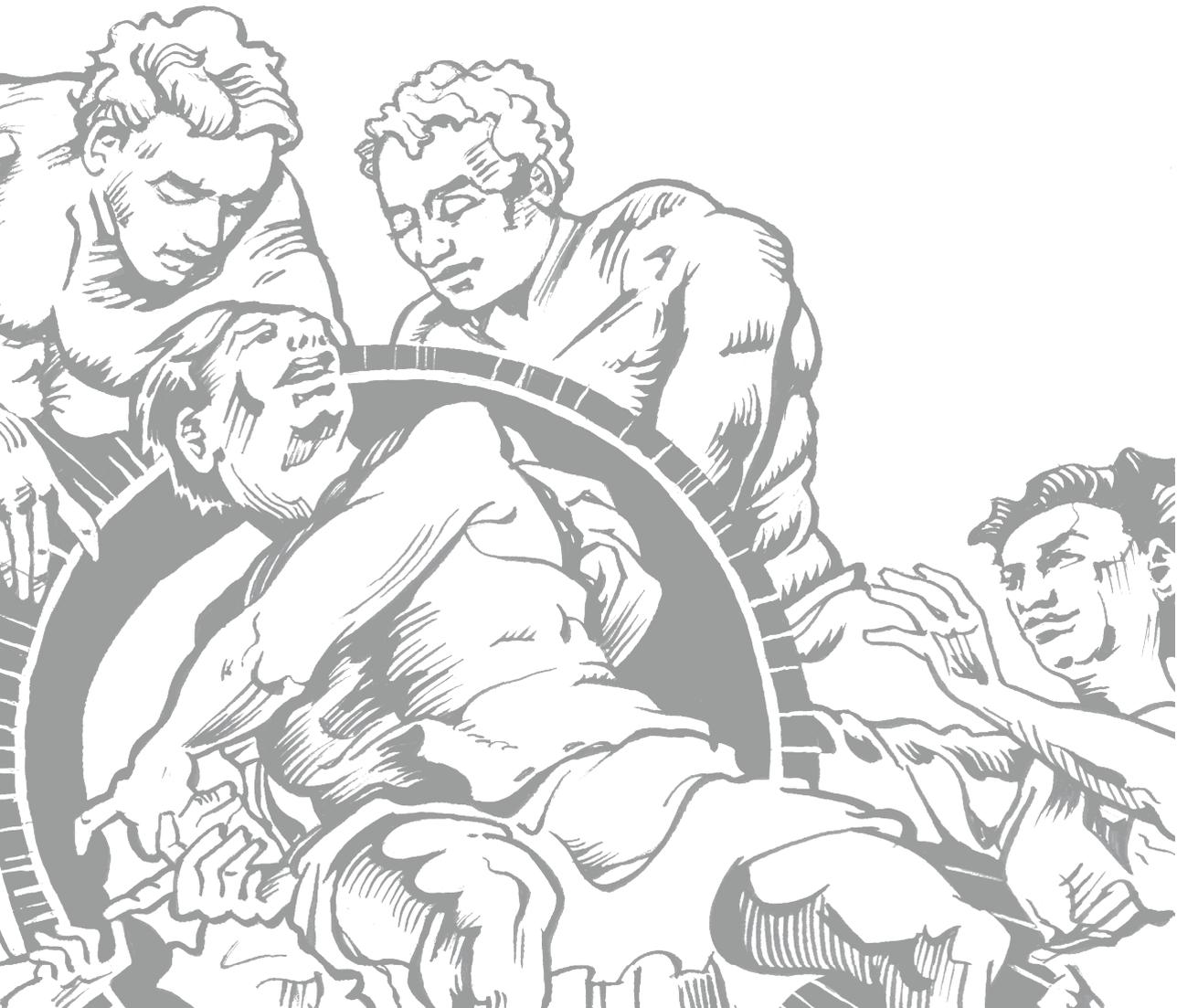
18. Miyata H, Yamasaki M, Kurokawa Y, et al. Survival factors in patients with recurrence after curative resection of esophageal squamous cell carcinomas. *Ann Surg Oncol* 2011;18:3353-61
19. Motoyama S, Saito R, Okuyama M, et al. Long-term survival after salvage resection of recurrent esophageal cancer with anterior mediastinal lymph node involvement: report of a case. *Surg Today* 2006;36:827-30
20. Yano M, Takachi K, Doki Y, et al. Prognosis of patients who develop cervical lymph node recurrence following curative resection for thoracic esophageal cancer. *Dis Esophagus* 2006;19:73-7
21. Salama JK, Chmura SJ. Surgery or ablative radiotherapy for breast cancer oligometastases. *Am Soc Clin Oncol Educ Book* 2015;35:e8-15
22. Niibe Y, Hayakawa K. Oligometastases and oligo-recurrence: the new era of cancer therapy. *Jpn J Clin Oncol* 2010;40:107-11
23. Iitaka D, Shiozaki A, Fujiwara H, et al. Case involving long-term survival after esophageal cancer with liver and lung metastases treated by multidisciplinary therapy: report of a case. *Surg Today* 2013;43:556-61
24. Yamamoto T, Tachibana M, Kinugasa S, et al. Esophagectomy and hepatic arterial chemotherapy following hepatic resection for esophageal cancer with liver metastasis. *J Gastroenterol* 2001;36:560-3
25. Chen F, Sato K, Sakai H, et al. Pulmonary resection for metastasis from esophageal carcinoma. *Interact Cardiovasc Thorac Surg* 2008;7:809-12
26. Hsu PK, Wang BY, Huang CS, et al. Prognostic factors for post-recurrence survival in esophageal squamous cell carcinoma patients with recurrence after resection. *J Gastrointest Surg* 2011;15:558-65
27. Sugiyama M, Morita M, Yoshida R, et al. Patterns and time of recurrence after complete resection of esophageal cancer. *Surg Today* 2012;42:752-8
28. Sudo K, Taketa T, Correa AM, et al. Locoregional failure rate after preoperative chemoradiation of esophageal adenocarcinoma and the outcomes of salvage strategies. *J Clin Oncol* 2013;31:4306-10
29. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology. Available via: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
30. Goense L, van Rossum PS, Reitsma JB, et al. Diagnostic performance of ¹⁸F-FDG PET and PET/CT for the detection of recurrent esophageal cancer after treatment with curative intent: a systematic review and meta-analysis. *J Nucl Med* 2015;56:995-1002



PART III

TREATMENT RESPONSE PREDICTION





Chapter 9

Endoscopic biopsy and EUS for the detection of pathologic complete response after neoadjuvant chemoradiotherapy in esophageal cancer: a systematic review and meta-analysis

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ABSTRACT

BACKGROUND AND AIMS

Accurate determination of residual cancer status after neoadjuvant chemoradiotherapy (nCRT) for esophageal cancer could assist in selecting the optimal treatment strategy. The aim of this study was to review the evidence on the diagnostic accuracy of endoscopic biopsy and endoscopic ultrasound (EUS) after nCRT for detecting residual cancer at the primary tumor site (ypT+) and regional lymph nodes (ypN+) as opposed to a pathologic complete response (ypT0 and ypN0).

METHODS

PubMed/MEDLINE, Embase, and the Cochrane library were systematically searched. The analysis included diagnostic studies reporting on the accuracy of endoscopic biopsy or EUS in detecting residual cancer versus complete response after nCRT for esophageal cancer with histopathology as reference standard. Bivariate random-effects models were used to estimate pooled sensitivities and specificities and examine sources of heterogeneity.

RESULTS

Twenty-three studies, comprising 12 endoscopic biopsy studies (1,281 patients), 11 EUS studies reporting on ypT-status (593 patients), and 10 EUS studies reporting on ypN-status (602 patients), were included. Pooled estimates for sensitivity of endoscopic biopsy after nCRT for predicting ypT+ was 34.5% (95% confidence interval [CI]: 26.0%-44.1%) and for specificity 91.0% (95% CI: 85.6%-94.5%). Pooled estimates for sensitivity of EUS after nCRT was 96.4% (95% CI: 91.7%-98.5%) and for specificity 10.9% (95% CI: 3.5%-29.0%) for detecting ypT+, and 62.0% (95% CI: 46.0%-75.7%) and 56.7% (95% CI: 41.8%-70.5%) for detecting ypN+, respectively.

CONCLUSIONS

Endoscopic biopsy after nCRT is a specific but not sensitive method for detecting residual esophageal cancer. Although EUS after nCRT yields a high sensitivity, only a limited number of patients will have negative findings at EUS with still a substantial false-negative rate. Furthermore, EUS provides only moderate accuracy for detecting residual lymph node involvement. Based on these findings, these endoscopic modalities cannot be used to withhold surgical treatment in test-negative patients after nCRT.

INTRODUCTION

Esophageal cancer continues to affect more than 450,000 people worldwide and its incidence is rapidly increasing¹. In patients with resectable non-metastatic esophageal cancer, neoadjuvant chemoradiotherapy (nCRT) followed by surgery is increasingly applied as standard treatment with curative intent^{2,3}. A pathologic complete response (pathCR) to nCRT is observed in approximately 25% to 30% of patients³⁻⁶. Many studies have reported that this absence of viable tumor cells at both the primary tumor site and regional lymph nodes (i.e. ypT0N0) is associated with favorable overall survival rates of approximately 60% to 70%⁴⁻⁶. Several investigators have speculated that surgery (with accompanying morbidity and mortality) may be safely omitted in patients who achieve ypT0N0, but accurately identifying these patients is challenging⁷. A reliable diagnosis of residual cancer before surgery would enable investigators to study the feasibility and outcome of a tailored treatment algorithm in which complete responders after nCRT could be offered close clinical follow-up instead of esophagectomy⁸.

Endoscopy with biopsy is widely accepted as the standard initial procedure to provide a histologic diagnosis for esophageal cancer with high accuracy⁹. The role of endoscopic ultrasound (EUS) before treatment is well-established for assessing depth of tumor invasion (T-stage) and regional lymph node involvement (N-stage) of esophageal tumors^{10,11}. By its unique visualization of the esophageal wall and surrounding tissues, EUS provides an accuracy of >80% for initial T-staging and >70% for initial N-staging in patients who underwent surgical resection without neoadjuvant treatment¹¹⁻¹³. However, the accuracy of the endoscopic modalities after nCRT is thought to be impeded by difficulties of endoscopic biopsy to obtain tissue samples in the irradiated luminal surface, and of EUS to differentiate between residual tumor and inflammation or fibrosis.

The clinical value and accuracy of endoscopic biopsy and EUS for predicting residual cancer after nCRT remains controversial due to varying study designs and methodological quality, heterogeneous patient populations and conflicting results among individual studies in the current literature. Some investigators have found post-treatment endoscopic biopsy useful in this setting^{7,14}, whereas others abandoned its routine application due to poor predictive ability¹⁵⁻¹⁷. Similarly, although at present time many experts in the field do not recommend to perform EUS for treatment response assessment in esophageal cancer¹⁷⁻²¹, others do support its use in this setting²²⁻²⁴. Despite the controversies, endoscopic biopsy and/or EUS after neoadjuvant treatment have arguably been considered standard of care in

many centers around the world for the past decade^{7,14,15,19,21-23,25}. Also, up to the present day sequential endoscopic biopsies and EUS measurements are of interest as important part of ongoing multi-center clinical trials aiming to assess response to nCRT in esophageal cancer²⁶.

In order to critically appraise and potentially overcome shortcomings of individual studies the aim of this study was to systematically review and meta-analyze the diagnostic performance of endoscopic biopsy and EUS after nCRT in esophageal cancer for detecting residual cancer at the primary tumor site (ypT+) and regional lymph nodes (ypN+) as opposed to a pathologic complete response (ypT0 and ypN0). We were specifically interested in determining how accurate the endoscopic absence of malignant abnormalities rules out the presence of residual cancer (i.e. the negative predictive value [NPV]).

METHODS

The study protocol has been registered in the PROSPERO international database of prospectively registered systematic reviews, which is accessible at <http://www.crd.york.ac.uk/prospere>, with registration number CRD42015016527.

SEARCH STRATEGY

A systematic search was performed and last updated on the 14th of July 2015 to identify all diagnostic studies that reported on the diagnostic accuracy of endoscopic biopsy or EUS after nCRT in esophageal cancer to predict histopathologic residual cancer versus complete response. Databases of Medline (via PubMed), Embase and the Cochrane library were searched according to the search strategy presented in **Table 1**.

STUDY SELECTION

After removal of duplicates among the retrieved articles, titles and abstracts were screened for eligibility by two authors independently (P.S.N.v.R. and J.M.). Subsequently, full texts of potentially relevant articles were accessed and evaluated for inclusion by the same two authors independently. Any disagreements were resolved by consensus.

Diagnostic studies that reported on the accuracy of endoscopic biopsy or EUS after nCRT for esophageal cancer and discriminating between ypT+ and ypT0 or between ypN+ and ypN0 were considered eligible. Only studies using histopathologic examination after surgical resection as the reference standard

Table 1 Search strategy and results as on 14 July 2015

| No. | Search query | Pubmed | Embase | Cochrane |
|-----|---|--------------|--------------|-----------|
| #1 | eus OR endoscopic ultrasound OR endoscopic ultrasonography OR endoscopic biopsy OR endoscopic biopsies OR gastroscopy OR endosonography OR endoscopic sonography OR endoscopic OR endoscopy | 146,403 | 212,825 | 13,058 |
| #2 | esophageal OR esophagus OR oesophageal OR oesophagus OR gastro- esophageal OR gastro- oesophageal OR gastroesophageal OR oesophagogastric OR esophagogastric | 131,842 | 172,871 | 8,868 |
| #3 | cancer OR cancers OR tumor OR tumour OR tumors OR tumours OR neoplasm OR neoplasms OR malignancy OR malignancies OR adenocarcinoma OR adenocarcinomas OR carcinoma OR carcinomas | 2,289,820 | 2,934,415 | 99,870 |
| #4 | response OR neoadjuvant OR chemotherapy OR chemoradiotherapy OR chemoradiation OR preoperative | 1,927,724 | 2,406,894 | 177,055 |
| #5 | #1 AND #2 AND #3 AND #4 | 1,730 | 2,949 | 83 |

were included. Neoadjuvant treatment consisted of concurrent chemotherapy and radiotherapy in at least 90% of the study population; studies reporting on neoadjuvant chemotherapy only (without radiotherapy) were excluded. If a subgroup of >10 patients (but less than 90% of the study population) underwent nCRT, authors were contacted to provide specific data on the subgroup of patients undergoing nCRT. Sufficient reported data were required to allow construction of 2x2 tables consisting of true-positive (TP), false-positive (FP), true-negative (TN), and false-negative (FN) results.

Reviews, editorials, letters to the editor, studies with ≤ 10 included patients, case reports and congress abstracts were excluded. In addition, publications written in other languages than Dutch, English or German were excluded from this review. If

multiple articles were published on one study population or significant overlap of study populations was found between multiple articles, only the article describing the largest series was included. Finally, reference lists of selected articles and related reviews were screened for other potentially suitable articles.

DATA EXTRACTION AND QUALITY ASSESSMENT

Study and patient characteristics along with treatment- and timing-related factors were extracted from each study and 2x2 tables were constructed including TP, FP, TN, and FN numbers. The methodological quality of the selected studies was critically appraised by two authors independently (P.S.N.v.R. and L.G.) using the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) instrument²⁷, and disagreements were resolved by consensus. For each study the provided signaling questions of the QUADAS-2 instrument were used to determine the risk of bias and applicability concerns ('low', 'high', or 'unclear') on four key domains including patient selection, index test, reference standard, and flow and timing. Evaluating applicability concerns regarding the index test, e.g. description of used endoscopic instruments and experience of the endoscopists, for each study required specific expertise and was performed by two experienced gastroenterologists (P.D.S. and F.P.V.).

The signaling questions provided by QUADAS-2 raised some specific considerations in view of the current topic. First, the authors considered exclusion of patients with a non-traversable tumor by the endoscope an implicit limitation of endoscopic examinations and not a limitation of methodological quality. Second, blinding of the index test for the reference standard and vice versa were not considered in the risk of bias assessment in our review since the index tests were not retrospectively scored and histopathology is an objective procedure. Third, because nCRT-induced tissue reactions are known to propagate for some weeks after completion of nCRT, a time interval between completion of nCRT and endoscopic examination of <2 weeks was considered a high risk of bias^{24,28,29}. In addition, delayed verification bias was deemed to be a concern in studies with a time delay between endoscopic examination and surgical resection of >2 weeks.

STATISTICAL ANALYSIS

The presence of residual cancer after nCRT was considered the target condition of interest. The classification of the index test was as follows: endoscopic biopsy that was positive versus negative for cancer, and presence versus absence of a residual mass on EUS. For the lymph nodes, the usual four features including size (i.e. either

5 mm or 10 mm as criterion), shape, echogenicity, and margins were considered by the studies. The final classification of target condition present (i.e. ypT+ or ypN+) or absent (i.e. ypT0 or ypN0) was based on histopathology of the resected specimen. On the basis of the number of TP, FP, TN, and FN results, sensitivity and specificity along with 95% confidence intervals (CIs) were calculated and presented in Forest plots. A bivariate random-effects model for diagnostic meta-analysis was used to obtain pooled estimates of sensitivity and specificity³⁰. The bivariate approach models pairs of logit-transformed sensitivity and specificity from individual studies simultaneously, thereby incorporating any potential correlation between sensitivity and specificity. The random-effects approach for both sensitivity and specificity incorporates heterogeneity beyond chance due to clinical and methodological differences between studies. The within-study variances (i.e. the precision by which sensitivities and specificities are measured) were modeled using the binomial distribution.

Subgroup analyses were performed by extending the basic bivariate model with study-level covariates to study the effects of specific study characteristics on sensitivity, specificity, or both. Four study characteristics were examined: predominant tumor type (studies including $\geq 85\%$ adenocarcinoma [AC] patients versus studies including $\geq 85\%$ squamous cell carcinoma [SCC] patients), publication year (<2005 vs. ≥ 2005), sample size (<70 patients vs. ≥ 70 patients), and used size criterion for a positive lymph node (≥ 5 mm vs. ≥ 10 mm). In addition, sensitivity analyses were conducted excluding studies with a high exclusion rate (i.e. $\geq 20\%$) to determine the impact of potential partial verification bias caused by the exclusions on the pooled estimates for sensitivity and specificity.

Implications of the pooled findings in a virtual cohort of 1,000 patients were presented in a table using modern-day prevalences of ypT+, ypT0, ypN+, and ypN0 that were found in the original CROSS-trial³, which were kindly provided by the CROSS-study group for the overall population, and for AC and SCC separately. Statistical analyses were performed using R 3.1.2 open-source software (<http://www.R-project.org>; 'lme4' package for fitting nonlinear mixed-effects models). A p-value of <0.05 was considered statistically significant.

RESULTS

IDENTIFICATION OF STUDIES

The systematic search yielded 4,636 citations of which 79 were retrieved for full text screening. Of these, 58 articles were excluded for various reasons as

presented in **Figure 1**. In 9 excluded articles all or a significant proportion ($\geq 10\%$) of patients were not treated with nCRT^{18,29,31-37}. Data on subgroups of nCRT patients (excluding chemotherapy-alone patients) were requested from 4 study authors^{18,28,29,37}, with results obtained from one study²⁸. Among other excluded articles, 5 studies demonstrated significant overlap with other (larger) studies that were included³⁸⁻⁴², one study performed post-nCRT endoscopy without biopsy⁴³, one article interpreted EUS by the post-nCRT maximum tumor thickness (MTT) rather than T-stage²⁴, and two studies reported numbers on good versus poor pathologic response instead of complete response versus presence of residual cancer^{44,45}. Two studies performing post-nCRT EUS were suitable for analysis of endoscopic biopsy²² or EUS for N-restaging⁴⁶ only, since no distinction between microscopic residual cancer or ypT1 and pathologic complete response (i.e. ypT0) was made in the T-restaging results of EUS. One study on T- and N-restaging using post-nCRT EUS was selected for T-restaging only⁴⁷, since significant overlap of the N-restaging results was found with a larger and more recently published study²³.

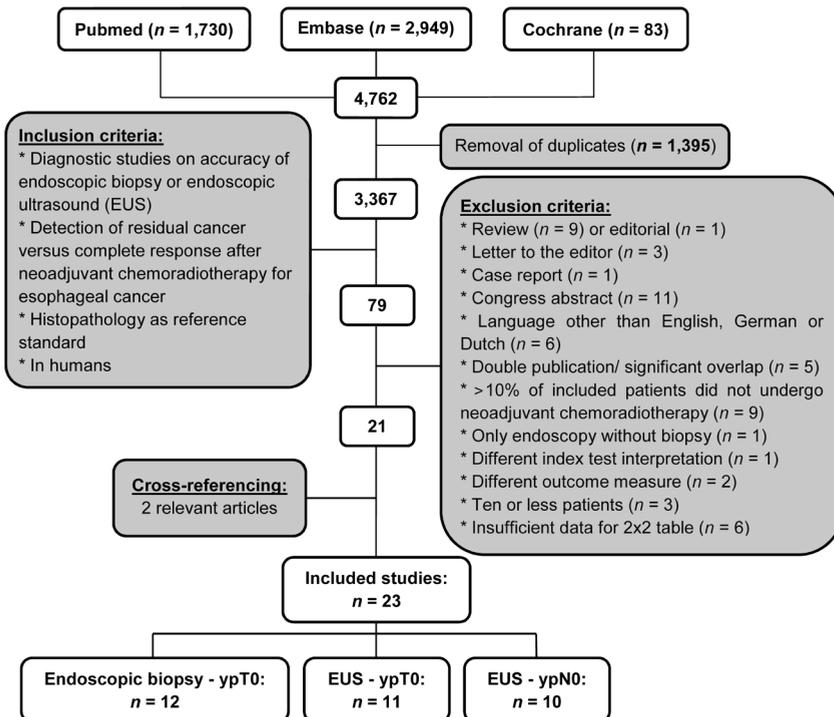


Figure 1 Flowchart summarizing search results and study selection.

Two relevant articles were found through cross-referencing and subsequently included in our review^{9,48}. These articles were not part of the initial search result, because the titles and abstracts did not include the ‘endoscopy’ search term (or synonyms). The final analysis included 23 studies; 12 studies (1,281 patients) evaluating post-nCRT endoscopic biopsy^{7,9,14-17,20,22,25,48-50}, 11 studies (593 patients) examining post-nCRT EUS for detecting residual primary cancer^{17,19-21,28,47,51-55}, and 10 studies (602 patients) assessing post-nCRT EUS for detecting residual lymph node metastasis^{19-21,23,28,46,51,53-55}.

STUDY CHARACTERISTICS

In total, 1,281 patients that underwent post-nCRT endoscopic biopsy and 593 patients that were examined by post-nCRT EUS for T-restaging were included, of which 74.2% (950 of 1,281) and 71.3% (423 of 593) had residual primary cancer (i.e. ypT+), respectively. From a total of 602 included patients that underwent post-nCRT EUS for N-restaging, 34.6% (208 of 602) had residual lymph node metastasis (i.e. ypN+). General characteristics of the included studies are outlined in **Table 2**. Only 4 studies were prospectively designed to answer our research question^{17,47,48,53}. Typically, studies included either mainly AC patients^{7,9,19,20,23,46,47,49,50} or mainly SCC patients^{14,15,21,22,25,48,51,53}. Neoadjuvant treatment regimens were based on cisplatin and 5-fluorouracil in the majority of studies, with concurrent total radiation doses ranging from 30 to 50.4 Gy. The time interval between completion of nCRT and surgery varied across studies from 10 days to >10 weeks, and the timing of the endoscopic procedure ranged from <1 week to 6 weeks after nCRT (and 0 to 11.1 weeks before surgery).

QUALITY ASSESSMENT

The results of the quality assessment are presented in **Table 3**. Most studies included a consecutive series of patients with appropriate exclusions only. In general, the endoscopic procedure and pathologic assessment were sufficiently described and considered valid. Partial verification bias was of particular concern in most studies, since often not all patients that underwent post-nCRT endoscopic examination underwent subsequent surgical resection which could lead to underestimation of both sensitivity and specificity estimates (e.g. by omitting surgery in patients with progressive disease or reversely omitting surgery in patients with an anticipated complete response, respectively). The index test was performed >2 weeks after nCRT and ≤2 weeks before surgery in four studies only^{17,22,48,54}. Applicability was of concern in several studies that selected patients with tumor stages other than

Table 2 Characteristics of the included studies

| Modality - outcome | Study, year | Country | Data acquisition | No. included | No. excluded | Sex (M/F) | Age (years) mean±SD [range] |
|---|------------------|---------|------------------|--------------|-----------------|-----------|-----------------------------|
| Endoscopic biopsy - ypT+ only | Kim, 2001 | Korea | Prosp | 94 | 44 | 87/7 | NR ± NR [NR] |
| | Shaukat, 2004 | USA | Retro | 30 | 0 | 25/5 | 50 ± NR [36-79] |
| | Yang, 2004 | USA | Retro | 183 | 118 | 61/4 | 60 ± 9.4 [32-78] |
| | Peng, 2009 | USA | Retro | 67 | 0 | 57/10 | 63 ± 11 [28-90] |
| | Sarkaria, 2009 | USA | Retro | 443 | 287 | 126/30 | 61 ± NR [NR] |
| | Miyata, 2011 | Japan | Retro | 123 | 0 | 107/16 | 61 ± NR [NR] |
| | Ajani, 2012 | USA | Retro | 322 | 0 | 282/40 | NR ± NR [23-81] |
| | Owaki, 2012 | Japan | Retro | 38 | 5 | 33/0 | 61 ± 8.2 [NR] |
| | Molena, 2014 | USA | Retro | 116 | 0 | 71/45 | 60 ± 9.6 [NR] |
| | Chao, 2015 | Japan | Retro | 227 | 0 | 222/5 | 56 ± 9.1 [NR] |
| EUS - ypT+ only | Giovannini, 1997 | France | NR | 32 | 0 | 28/4 | 54 ± NR [38-70] |
| | Cerfolio, 2005 | USA | Prosp | 67 | 19 | 41/7 | 68 ± NR [48-76] |
| EUS - ypN+ only | Agarwal, 2004 | USA | Retro | 97 | 0 | 88/9 | 58 ± NR [32-74] |
| | Eloubeidi, 2011 | USA | Retro | 207 | 35 | 148/24 | 61 ± NR [30-88] |
| Endoscopic biopsy and EUS - ypT+ | Schneider, 2008 | Germany | Prosp | 91 | 11+14 and 11+10 | 74/17 | 59 ± NR [21-74] |

| Tumor type (AC/SCC/other) | Tumor stage | Type of CRT | Criteria negative index test | Time interval between CRT and surgery | Timing of index test |
|---------------------------|-------------|---|--------------------------------------|---------------------------------------|---|
| 92/1/1 | I-III | 5-FU + Cis, and 48 Gy | Biopsy: no carcinoma | 4-5 wks | 3-4 wks after CRT, 1-2 wks before surgery |
| 27/3/0 | 0-IV | NS | Biopsy: no carcinoma | NR | 3-6 wks after CRT, 3-6 wks before surgery |
| 57/6/2 | II-III | 5-FU + Cis + Pac, and 40-45 Gy | Biopsy: no carcinoma | 4-6 wks | <4.3 wks before surgery |
| 67/0/0 | II-III | 5-FU + Cis + Pac, and 50.4 Gy | Biopsy: no carcinoma | NR | 4-6 wks after CRT |
| 117/39/0 | II-III | Cis-based, and 50.4 Gy | Biopsy: no carcinoma | Median 9.4 wks | NR |
| 0/123/0 | II-III | Cis + 5-FU, and 40 Gy | Biopsy: no carcinoma | 4-6 wks | <1 wk after CRT |
| 302/20/0 | I-III | Fluor + Plat/Tax, and 45-50.4 Gy | Biopsy: no carcinoma | 5-6 wks | NR |
| 0/33/0 | I-III | Cis + 5-FU, and 40 Gy | Biopsy: no carcinoma | 5-7 wks | ≤1.4 wks before surgery |
| 0/116/0 | II-III | Cis and 50.4 Gy | Biopsy: no carcinoma | Mean 9.0 wks, SD 4.2 | NR |
| 0/227/0 | II-IV | 5-FU + Cis, and 30 Gy | Biopsy: no carcinoma | NR | 4-6 wks after CRT |
| 7/25/0 | I-III | Cis + 5-FU, and 30 Gy | yuT0 | Mean 3 wks [1.7-5] | 2 wks after CRT |
| 43/5/0 | II-IV | Cis, and RT (NS) | yuT0 | NR | Median 3.9 wks after CRT |
| 84/13/0 | I-III | Cis and/or Tax + 5-FU (+ CPT-11), and 45 Gy | ypN0 (size <5mm) | 4-6 wks | NR |
| 131/15/5 | I-III | Chemotherapy (NS), and 50.4 Gy | yuN0 (size<1cm) | NR | NR |
| 31/49/0 | I-III | Cis + 5-FU, and 36 Gy | Biopsy: no carcinoma <i>and</i> yuT0 | 2.3-4.4 wks | 2-3 wks after CRT, 0.3-1.4 wks before surgery |

Table 2 (continued)

| Modality - outcome | Study, year | Country | Data acquisition | No. included | No. excluded | Sex (M/F) | Age (years) mean±SD [range] |
|--|---------------|---------|---------------------|-----------------|-----------------|--------------|-----------------------------------|
| EUS - ypT+ and EUS - ypN+ | Dittler, 1994 | Germany | NR | 18 | 0 | NR | NR |
| | Bowrey, 1999 | USA | NR | 17 | 3 | 10/7 | 60 ± NR [47-72] |
| | Laterza, 1999 | Italy | Prosp | 111 | 38 | NR | NR |
| | Zuccaro, 1999 | USA | Retro | 72 | 13 | NR | 60 ± NR [30-77] |
| | Willis, 2002 | USA | Retro | 41 | 0 | 32/9 | 61 ± NR [29-76] |
| | Griffin, 2012 | USA | Retro | 104 | 31 | 64/9 | 62 ± NR [40-79] |
| | Yen, 2012 | Taiwan | Retro | 566 | 476+7 | 86/4 | 56 ± NR [34-88] |
| Endoscopic biopsy and EUS - ypT+ and EUS - ypN+ | Kalha, 2004 | USA | Retro | 83 | 0 | 77/6 | 59 ± NR [NR] |

AC: adenocarcinoma. BLM: bleomycin. Car: carboplatin, Cet: cetuximab. Cis: cisplatin. CPT-11: irinotecan. ultrasonography. Fluor: fluoropyrimidine. FNA-: fine-needle aspiration negative. FUDR: 5'-deoxy-5-leucovorin. MCSA: maximum cross-sectional area. Mit: mitomycin. NR: not reported. NS: not specified. carcinoma. SD: standard deviation. Tax: taxol. VP-16: etoposide. u: 'based on (endoscopic) ultrasound'. wk(s): 5-fluorouracil.

| Tumor type (AC/SCC/other) | Tumor stage | Type of CRT | Criteria negative index test | Time interval between CRT and surgery | Timing of index test |
|---------------------------|-------------|---|---|---------------------------------------|---|
| 0/18/0 | II-III | 5-FU (+ Cis + Leuc + Eto), and 30 or 40 Gy | yuT0 <i>and</i> yuN0 (size NR) | NR | NR |
| 10/7/0 | II-III | Cis + 5-FU, and 40 Gy | yuT0 <i>and</i> yuN0 (size <6mm) | NR | <2 wks after CRT |
| 0/73/0 | I-III | Cis + 5-FU, and 30 Gy | yuT0 <i>and</i> yuN0 (size NR) | Mean 3.6 wks | 2 wks after CRT |
| 41/18/0 | I-III | Cis + 5-FU, and 45 Gy | yuT0 <i>and</i> yuN0 (size<1cm) | 4-6 wks | 4 wks after CRT |
| 28/12/1 | I-III | Cis (or Car) + 5-FU, and ≥30 Gy | yuT0 <i>and</i> ypN0 (size NR) | Median 3.7 wks [0-10.4] | Median 1.9 wks [0-5.9] after CRT, median 1.9 wks [0-4.6] before surgery |
| 66/7/0 | II-III | Plat, and 45-50 Gy | yuT0 <i>and</i> ypN0 (size NR) | NR | 4-6 wks after CRT, 3.1 wks [0.3-11.1] before surgery |
| 0/83/0 | II-IV | Cis + 5-FU or Pac (+ Cet or Leuc + 5-FU), and 40 Gy | yuT0 <i>and</i> yuN0 (size <5mm) | NR | Mean 2.7 wks before surgery |
| 83/0/0 | Ia-III | Cis + 5-FU + Pac + CPT-11, and 45 Gy | Biopsy: no carcinoma <i>and</i> yuT0 <i>and</i> yuN0 (size<1cm) | >1.4 wks | >1.4 wks after CRT, <2 wks before surgery |

CRT: chemoradiotherapy. Doc: docetaxel. Dox: doxorubicin. Epi: epirubicin. Eto: etoposid. EUS: endoscopic fluorodeoxyuridine. Gem: gemcitabine. GM-CSF: granulocyte-macrophage colony-stimulating factor. Leuc: paclitaxel. Plat: platinum. Prosp: prospective. Retro: retrospective. RT: radiotherapy. SCC: squamous cell week(s). y: 'after neoadjuvant treatment'. yMTT: maximum tumor thickness after chemoradiotherapy. 5-FU:

Table 3 Quality assessment of the included studies according to the QUADAS-2 tool²⁷

| Modality - outcome | Study, year | Risk of bias | | | | | Applicability concerns | | |
|--|------------------|-------------------|------------|--------------------|-----------------|--------------------|------------------------|------------|--------------------|
| | | Patient selection | Index test | Reference standard | Flow and timing | PVB* Time interval | Patient selection | Index test | Reference standard |
| Endoscopic biopsy - ypT+ only | Kim, 2001 | L | L | U | H | L | L | L | U |
| | Shaukat, 2004 | L | L | L | U | H | H | L | L |
| | Yang, 2004 | H | L | L | H | H | H | U | L |
| | Peng, 2009 | L | L | L | U | H | L | L | L |
| | Sarkaria, 2009 | L | L | U | U | U | L | U | U |
| | Miyata, 2011 | L | L | L | H | H | L | U | L |
| | Ajani, 2012 | L | L | L | U | U | L | U | L |
| | Owaki, 2012 | L | L | L | L | L | L | L | L |
| | Molena, 2014 | L | L | L | U | U | L | U | L |
| Chao, 2015 | L | L | L | U | U | H | L | L | |
| EUS - ypT+ only | Giovannini, 1997 | L | L | U | U | U | H | H | U |
| | Cerfolio, 2005 | L | L | U | H | U | H | H | U |
| EUS - ypN+ only | Agarwal, 2004 | L | L | L | U | U | L | U | L |
| | Eloubeidi, 2011 | L | L | U | U | U | U | L | U |
| Endoscopic biopsy and EUS - ypT+ | Schneider, 2008 | L | L | L | H | L | H | H | L |
| EUS - ypT+ and EUS - ypN+ | Dittler, 1994 | U | U | U | U | U | H | U | U |
| | Bowrey, 1999 | L | L | L | U | U | L | H | L |
| | Laterza, 1999 | L | U | U | U | U | H | H | U |
| | Zuccaro, 1999 | L | L | U | H | L | L | H | U |
| | Willis, 2002 | L | U | L | U | H | H | H | L |
| | Griffin, 2012 | L | U | L | H | H | L | U | L |
| | Yen, 2012 | L | L | L | H | H | H | L | L |
| Endoscopic biopsy and EUS - ypT+ and EUS - ypN+ | Kalha, 2004 | L | L | L | L | H | L | H | L |

*PVB: partial verification bias.

I to III^{21,25,47,49}, used an outdated total radiation dose of <40 Gy^{25,51-53,55}, did not satisfactorily specify the applied nCRT regimen^{23,47,49}, or included some patients (<10%) who underwent chemotherapy only⁹.

DIAGNOSTIC ACCURACY

The sensitivity of endoscopic biopsy after nCRT for the detection of residual esophageal cancer (i.e. ypT+) ranged from 12.8% to 58.9% and the specificity from 76.2% to 100% (**Figure 2A**)^{7,9,14-17,20,22,25,48-50}. Pooled sensitivity of endoscopic biopsy was 34.5% (95% CI: 26.0%-44.1%) and pooled specificity was 91.0% (95% CI: 85.6%-94.5%) (**Figure 2A**). The sensitivity of EUS after nCRT for the detection of residual primary tumor (i.e. ypT+) ranged from 80.0% to 100% and the specificity from 0% to 77.8%, with pooled estimates of 96.4% (95% CI: 91.7%-98.5%) and 10.9% (95% CI: 3.5%-29.0%), respectively (**Figure 2B**)^{17,19-21,28,47,51-55}. The sensitivity of EUS after nCRT in the assessment of residual lymph node metastasis (i.e. ypN+) ranged from 25.9% to 93.8% and the specificity from 28.8% to 100%, with pooled estimates of 62.0% (95% CI: 46.0%-75.7%) and 56.7% (95% CI: 41.8%-70.5%), respectively (**Figure 2C**)^{19-21,23,28,46,51,53-55}.

SUBGROUP AND SENSITIVITY ANALYSES

Results from subgroup analyses are presented in **Table 4**. Sensitivity of endoscopic biopsy after nCRT was significantly higher for studies mainly including SCC patients (n=5) compared with studies mainly including AC patients (n=5) (49.3% vs. 23.6%, respectively; $p<0.001$), with similar specificities (90.6% vs. 88.2%, respectively; $p=0.633$). Also, the sensitivity of EUS after nCRT for N-restaging was significantly higher for SCC studies (n=3) compared with AC studies (n=4) (82.7% vs. 44.3%, respectively; $p=0.001$) with similar specificities, although this analysis was based on a small number of studies. As could be expected, the specificity of EUS after nCRT for N-restaging was significantly higher (i.e. less false-positives) when lymph nodes ≥ 10 mm were considered positive compared to using ≥ 5 mm as size criterion (73.5% vs. 31.1%, respectively; $p<0.001$), at the cost of a lower sensitivity (37.9% vs. 58.4%, respectively; $p=0.128$). Sensitivities and specificities of the studied endoscopic modalities after nCRT were not significantly different according to publication year or sample size. Sensitivity analyses demonstrated no clinically relevant changes in pooled sensitivity estimates for endoscopic biopsy (+1.5%), EUS for T-restaging (+0.5%), and EUS for N-restaging (-7.0%), nor in pooled specificity estimates (i.e. -2.6%, -6.4%, and +3.4%, respectively) after excluding respectively 4, 4, and 3 studies with high patient exclusion rates.

IMPLICATIONS OF FINDINGS

Table 5 shows what the implications of the findings would be for a cohort of 1,000 esophageal cancer patients in which clinical decision-making regarding surgical

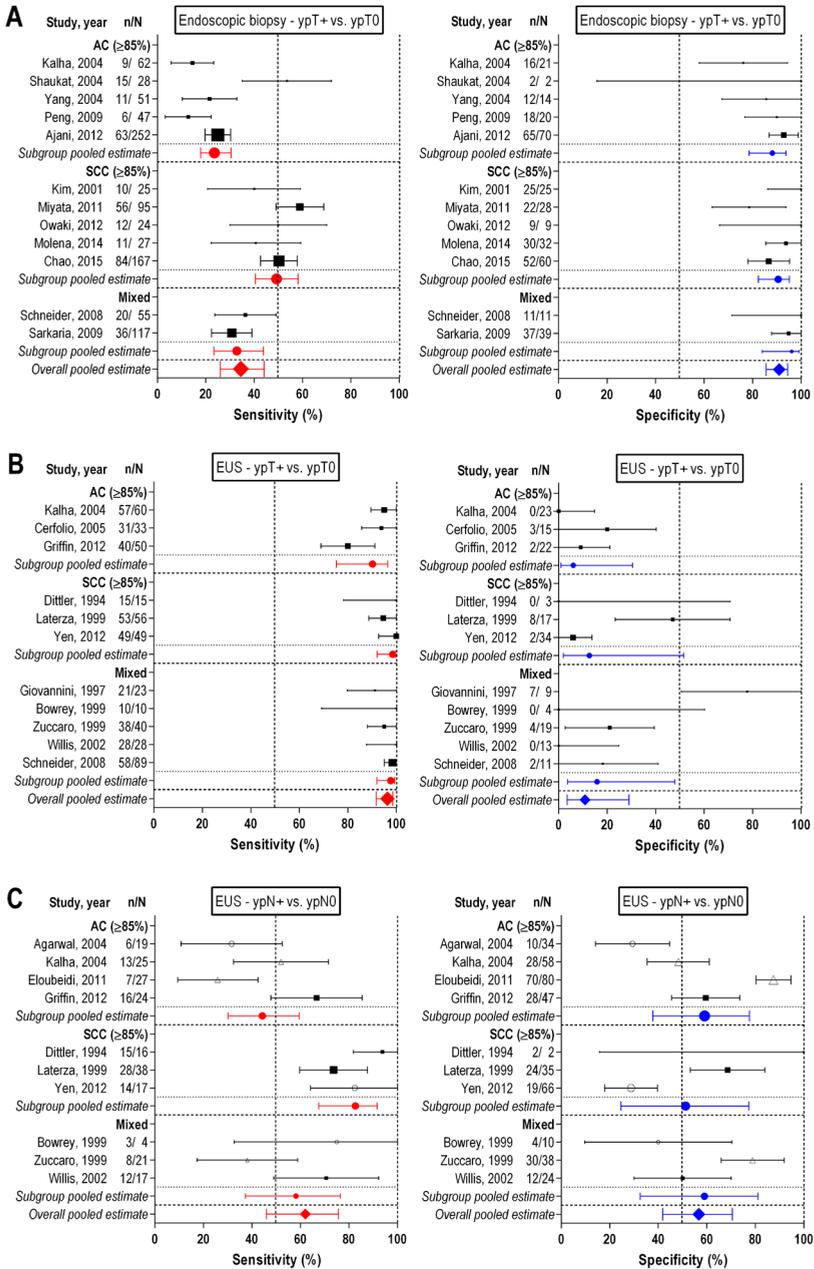


Figure 2 Forest plots demonstrating sensitivities and specificities from individual studies along with pooled estimates of endoscopic biopsy and EUS for detecting residual primary tumor (**A and B, respectively**), and EUS for detecting residual lymph node metastasis (**C**). Subgroups were presented including adenocarcinoma (AC) versus squamous cell carcinoma (SCC) studies (**A-C**), and positive lymph node size criterion of $\geq 5\text{mm}$ (open circles) versus $\geq 10\text{mm}$ (open triangles) (**C**).

resection would be based on the results of endoscopic biopsy or EUS after nCRT according to the CROSS-regimen³. Overall, a negative endoscopic biopsy after nCRT can be expected in the majority of patients (755 of 1,000), of which only 47% (355 of 755) actually have a pathologic complete response (i.e. NPV). Taking into account the results of the subgroup analysis, the NPV of endoscopic biopsy after nCRT for ruling out residual primary tumor is expected to be higher for SCC (72%, 535 of 743) compared to AC (35%, 282 of 802). EUS after nCRT is expected to show a residual primary mass suspected of tumor in 935 of 1,000 patients (93.5%), and from the small minority of patients suspected of a complete response (6.5%, 65 of 1,000), only 66% (43 of 65) would be true pathologic complete responders. The estimated overall NPV of EUS for N-restaging is 77% (391 of 509), which seems lower for the subgroup of AC (65%, 378 of 579) as opposed to SCC (92%, 410 of 445).

Table 4 Results from study-level subgroup analyses for sensitivity and specificity

| Factors | Endoscopic biopsy - ypT+ vs. ypT0 | | | | |
|-----------------------------|-----------------------------------|---------------------------|---------|---------------------------|---------|
| | n [†] | Sensitivity,% (95% CI) | p value | Specificity,% (95% CI) | p value |
| Tumor type: | | | <0.001 | | 0.633 |
| AC (≥85%) | 5 | 23.6 (17.9-30.5) | | 88.2 (78.6-93.8) | |
| SCC (≥85%) | 5 | 49.3 (40.5-58.2) | | 90.6 (82.4-95.2) | |
| Publication year: | | | 0.434 | | 0.636 |
| Before 2005 | 4 | 29.4 (17.1-45.6) | | 89.1 (75.3-95.6) | |
| In or after 2005 | 8 | 36.8 (26.8-48.2) | | 91.3 (85.6-94.9) | |
| Sample size: | | | 0.982 | | 0.076 |
| <70 patients | 5 | 34.6 (22.6-48.9) | | 87.9 (81.1-92.4) | |
| ≥70 patients | 7 | 34.4 (23.2-47.6) | | 95.0 (88.3-97.9) | |
| +Lnn size criterion: | | | | | |
| ≥5 mm | | NA | | NA | |
| ≥10 mm | | NA | | NA | |

AC: adenocarcinoma. CRT: chemoradiotherapy. EUS: endoscopic ultrasound. +Lnn: positive lymph node. NA: not applicable. Ref: reference. SCC: squamous cell carcinoma. 95% CI: 95% confidence interval. †: number of studies.

Table 4 (continued I)

| Factors | EUS - ypT+ vs. ypT0 | | | | |
|-----------------------------|---------------------|---------------------------|---------|---------------------------|---------|
| | n [†] | Sensitivity,% (95% CI) | p value | Specificity,% (95% CI) | p value |
| Tumor type: | | | 0.056 | | 0.559 |
| AC (≥85%) | 3 | 90.2 (75.3-96.5) | | 6.0 (0.9-30.4) | |
| SCC (≥85%) | 3 | 98.5 (92.1-99.7) | | 12.6 (1.9-51.5) | |
| Publication year: | | | 0.556 | | 0.902 |
| Before 2005 | 7 | 97.0 (91.4-99.0) | | 11.7 (2.6-40.2) | |
| In or after 2005 | 4 | 95.3 (85.8-98.5) | | 10.3 (2.1-37.9) | |
| Sample size: | | | 0.497 | | 0.779 |
| <70 patients | 6 | 97.4 (90.7-99.3) | | 12.8 (2.6-44.3) | |
| ≥70 patients | 5 | 95.5 (88.0-98.4) | | 9.7 (2.2-33.3) | |
| +Lnn size criterion: | | | | | |
| ≥5 mm | | NA | | NA | |
| ≥10 mm | | NA | | NA | |

Table 4 (continued II)

| Factors | EUS - ypN+ vs. ypN0 | | | | |
|-----------------------------|---------------------|---------------------------|---------|---------------------------|---------|
| | n [†] | Sensitivity,% (95% CI) | p value | Specificity,% (95% CI) | p value |
| Tumor type: | | | 0.001 | | 0.670 |
| AC (≥85%) | 4 | 44.3 (30.1-59.5) | | 59.1 (37.7-77.6) | |
| SCC (≥85%) | 3 | 82.7 (67.6-91.6) | | 51.3 (24.6-77.3) | |
| Publication year: | | | 0.818 | | 0.635 |
| Before 2005 | 7 | 63.2 (44.0-78.9) | | 54.1 (36.0-71.2) | |
| In or after 2005 | 3 | 59.3 (31.5-82.2) | | 61.5 (36.9-81.3) | |
| Sample size: | | | 0.478 | | 0.119 |
| <70 patients | 4 | 68.8 (42.6-86.7) | | 40.7 (20.3-64.9) | |
| ≥70 patients | 6 | 57.6 (38.3-74.8) | | 63.6 (47.8-76.9) | |
| +Lnn size criterion: | | | 0.128 | | <0.001 |
| ≥5 mm | 3 | 58.4 (37.9-76.3) | | 31.1 (18.3-47.6) | |
| ≥10 mm | 3 | 37.9 (23.7-54.5) | | 73.5 (59.5-84.0) | |

Table 5 Implications of findings: number of results per 1,000 patients undergoing endoscopic restaging after neoadjuvant chemoradiotherapy according to the CROSS-regimen³

| Test result | Endoscopic biopsy - ypT+ vs. ypT0 | | EUS - ypT+ vs. ypT0 | | EUS - ypN+ vs. ypN0 | |
|---|---|--|--|---|---|--|
| | Overall population Prevalence ypT+ of 61% | Adenocarcinoma* Prevalence ypT+ of 68% | Squamous cell carcinoma* Prevalence ypT+ of 41% | Overall population Prevalence ypT+ of 61% | Overall population Prevalence ypN+ of 31% | Squamous cell carcinoma* Prevalence ypN+ of 20% |
| Test positive | | | | | | |
| True positives <i>Justified surgery</i> | 210 per 1,000 (159 to 269) | 160 per 1,000 (122 to 207) | 202 per 1,000 (166 to 239) | 588 per 1,000 (559 to 601) | 192 per 1,000 (143 to 235) | 159 per 1,000 (135 to 183) |
| False positives <i>Unnecessary surgery</i> | 35 per 1,000 (21 to 56) | 38 per 1,000 (20 to 68) | 55 per 1,000 (28 to 104) | 347 per 1,000 (277 to 376) | 299 per 1,000 (204 to 402) | 390 per 1,000 (192 to 613) |
| Test negative | | | | | | |
| True negatives <i>Justified omission of surgery</i> | 355 per 1,000 (334 to 369) | 282 per 1,000 (252 to 300) | 535 per 1,000 (486 to 562) | 43 per 1,000 (14 to 113) | 391 per 1,000 (288 to 486) | 378 per 1,000 (241 to 497) |
| False negatives <i>Unjustified omission of surgery</i> | 400 per 1,000 (341 to 451) | 520 per 1,000 (473 to 558) | 208 per 1,000 (171 to 244) | 22 per 1,000 (9 to 51) | 118 per 1,000 (75 to 167) | 201 per 1,000 (146 to 252) |

Note. Data in parentheses are 95% confidence intervals. *: Pooled results from subgroup analyses were used to calculate separate diagnostic performances for adenocarcinoma and squamous cell carcinoma.

DISCUSSION

Accurate determination of residual cancer status after nCRT for esophageal cancer may assist in selecting the optimal treatment strategy, especially if withholding surgery is contemplated in complete responders. This meta-analysis demonstrates that endoscopic biopsy after nCRT is a specific (pooled estimate: 91.0%) but not a sensitive method (pooled estimate: 34.5%) for detecting residual cancer, with false-negative findings (i.e. missing the presence of actual residual cancer) as typical error resulting in a low negative predictive value. EUS after nCRT yields a high sensitivity (pooled estimate: 96.4%) but a very poor specificity (pooled estimate: 10.9%) for residual cancer at the primary tumor site. Furthermore, EUS is negative in only a limited number of patients, with still a substantial false-negative rate in this group. EUS yields a moderate sensitivity (pooled estimate: 62.0%) and specificity (pooled estimate: 56.7%) for detecting residual lymph node metastasis after nCRT. Therefore, complete reliance on negative endoscopic biopsy findings for deciding to withhold surgery would likely result in local recurrences in the majority of patients, and in the small group of patients with negative post-nCRT EUS results local and regional recurrences are also likely to occur in a substantial proportion.

A positive endoscopic biopsy after nCRT predicts residual cancer in the resection specimen in almost all cases. However, this finding does not change current practice of performing surgery after nCRT in all eligible patients. As of now, the more important negative biopsy findings after nCRT seem not reliable enough to change clinical decision-making. Endoscopic sampling error due to the irradiated luminal surface with remaining small tumor foci combined with inflammation and fibrosis/scarring, and the presence of non-mucosal residual cancer in deeper esophageal wall layers are thought to account for the high false-negative rate^{8,9,16,25,42,49}. In order to improve the sensitivity of endoscopic biopsy after nCRT, extensive sampling protocols and deeper bite-on-bite submucosal biopsies have been suggested in recent studies^{8,42}. These protocols require further investigation with special caution regarding the potential risk of esophageal perforations.

After nCRT, EUS is not able to reliably distinguish between disruption of the esophageal wall due to residual tumor and disruption secondary to inflammation and fibrosis/scarring from nCRT, resulting in a high false-positive rate^{20,21,29}. This is supported by the frequently reported finding that overstaging is the most common error of EUS in the assessment of tumor stage after nCRT^{21,29}. Because successful eradication of malignant disease in the esophagus by nCRT is generally not

accompanied by restoration of the esophageal wall architecture^{29,51,56}, alternatives to the T-classification have been reported for predicting pathologic response. Several investigators have advocated defining the tumor by its (change in) maximum tumor thickness^{24,28,44} or cross-sectional area^{55,57,58}. In a recent prospective multicenter study an EUS-based maximum tumor thickness after nCRT of >6 mm appeared promising for detecting residual cancer (ypT+) as opposed to a pathologic complete response (ypT0) with a sensitivity of 86% and specificity of 64%²⁴. These findings suggest that this method is superior to the diagnostic performance resulting from this meta-analysis on EUS-based T-restaging, but the reported method and threshold have not yet been validated and further studies are required.

Even among ypT0 patients, 10% to 25% demonstrate residual lymph node metastasis at histopathology (i.e. ypT0N1)^{3,59,60}. Therefore, before considering an expectant management when a complete response at the primary tumor site (ypT0) is found after nCRT, one should also be able to accurately rule out the presence of persistent malignant lymphadenopathy⁴⁶. This is supported by the fact that patients with residual lymph node metastasis after nCRT (i.e. ypN+) have a worse prognosis following surgery even in patients with ypT0⁶⁰.

A meta-analysis in patients treated with primary surgery without neoadjuvant treatment reported a pooled sensitivity of EUS for baseline N-staging of 80% (95% CI: 75%-84%) and a pooled specificity 70% (95% CI: 65%-75%)¹¹. Apparently, the diagnostic accuracy of EUS for N-staging decreases after nCRT as is shown in the current meta-analysis with pooled estimates for sensitivity of 62.0% and for specificity of 56.7%. The moderate sensitivity is caused by the failure of EUS to identify patients with microscopic residual nodal metastasis, whereas the poor specificity is mainly attributed to EUS being unable to distinguish between metastatic involvement of the regional lymph nodes and inflammation or fibrosis associated with nodal tumor response^{20,21,29}. The additive value of EUS with fine-needle aspiration (FNA) after nCRT was studied in only a few studies, but has shown potential advantages with regard to accuracy^{23,46}. However, the limited evidence regarding EUS-FNA in this setting so far warrants further studies.

For clinical interpretation of the results of this meta-analysis it should be acknowledged that since (negative) predictive values can change dramatically depending on disease prevalences⁶¹, and prevalences of both ypT0 and ypN0 in the CROSS trial were high compared to other common regimens, the aforementioned NPVs are likely overestimated if other regimens would have been applied. Second, the consequences of a false-negative test result with unjustified

withholding of surgery should be considered. In this context, salvage surgery is often advocated in patients with residual locoregional disease after nCRT which was not detected after completion of treatment and therefore was followed by an expectant follow-up policy¹⁵. However, significant concerns have been raised that salvage esophagectomy is associated with increased morbidity⁶²⁻⁶⁴. Therefore, it is mandatory that better clinical tools for the prediction of a pathologic complete response are developed before a paradigm shift in the management of esophageal cancer can be advocated^{15-17,39,49,65,66}. Unfortunately, so far alternative diagnostic modalities including computed tomography (CT) and ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) have also not been able to accurately predict which patients will achieve a pathologic complete response^{17,67-70}. Diffusion-weighted magnetic resonance imaging (DW-MRI) seems a promising new imaging modality for this purpose in recent pilot studies, but requires validation in larger series^{71,72}.

A few limitations apply to this meta-analysis. Some unexplained heterogeneity between studies beyond chance and subgroup analyses remained (particularly in the N-restaging analysis), which may impair the strength and interpretation of the pooled estimates to some extent. Unfortunately, possible causes of heterogeneity were not eligible for exploration in subgroup analysis because subgroups were too small (e.g. prospective vs. retrospective) or detailed reporting was not performed in a sufficient number of studies (e.g. timing of the index test). Other potential causes of heterogeneity that could not be extracted from the studies or could not be accounted for in subgroup analyses include variation in population characteristics, experience of the endoscopist and interpretation of shape, echogenicity, and margins of lymph nodes. In addition, the authors were not able to account for the fact that the pathologic N+ stage may not have been consistent with the clinical N+ stage as determined by EUS in studies, because the location of the surgically resected positive lymph nodes may have been different from the nodes detected by restaging EUS.

In conclusion, based on the current evidence with reasonable methodological quality, endoscopic biopsy after nCRT is a specific but not sensitive method for detecting residual esophageal cancer. Although EUS after nCRT yields a high sensitivity, the number of patients with negative findings on EUS is limited, while a considerable proportion of these “negative” patients turn out to have residual cancer (i.e. false-negatives). Therefore, endoscopic biopsy and EUS should currently not be used in routine clinical practice after nCRT to triage test-negative patients for withholding surgery. In particular, the time is not yet ready to recommend patients

with a negative endoscopic biopsy or EUS after nCRT to withhold surgical resection with curative intent. Compared to esophageal AC, in SCC the pre-test probability of ypT0N0 is higher using modern nCRT-regimens³, and the sensitivities of both endoscopic biopsy for T-restaging and EUS for N-restaging also appear higher in subgroup analyses. As both these findings contribute to higher negative predictive values, the reported potential improvements in endoscopic protocols deserve further investigation particularly patients with a diagnosis of esophageal SCC.

ACKNOWLEDGEMENTS

The authors would like to thank professor J.J.B. van Lanschot from the Department of Surgery, Erasmus Medical Center, Rotterdam, The Netherlands, who kindly provided the authors with specific prevalences of interest on behalf of the CROSS-group.

REFERENCES

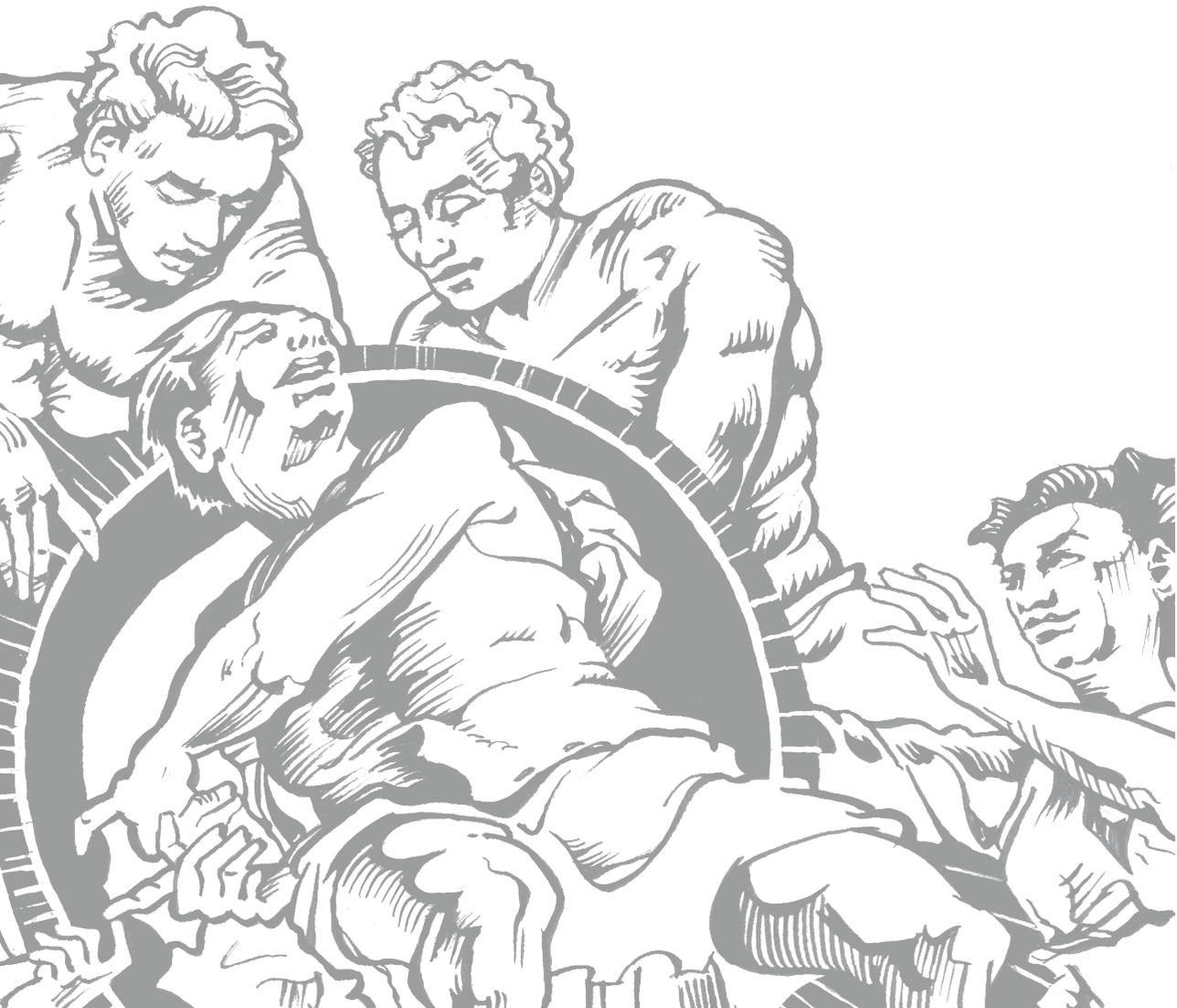
1. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. *Lancet* 2013;381:400-12
2. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011;12:681-92
3. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
4. Chirieac LR, Swisher SG, Ajani JA, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. *Cancer* 2005;103:1347-55
5. Berger AC, Farma J, Scott WJ, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. *J Clin Oncol* 2005;23:4330-7
6. Donahue JM, Nichols FC, Li Z, et al. Complete pathologic response after neoadjuvant chemoradiotherapy for esophageal cancer is associated with enhanced survival. *Ann Thorac Surg* 2009;87:392-8; discussion 398-9
7. Ajani JA, Correa AM, Hofstetter WL, et al. Clinical parameters model for predicting pathologic complete response following preoperative chemoradiation in patients with esophageal cancer. *Ann Oncol* 2012;23:2638-42
8. Shapiro J, ten Kate FJ, van Hagen P, et al. Residual esophageal cancer after neoadjuvant chemoradiotherapy frequently involves the mucosa and submucosa. *Ann Surg* 2013;258:678-88; discussion 688-9
9. Yang Q, Cleary KR, Yao JC, et al. Significance of post-chemoradiation biopsy in predicting residual esophageal carcinoma in the surgical specimen. *Dis Esophagus* 2004;17:38-43
10. Kim TJ, Kim HY, Lee KW, et al. Multimodality assessment of esophageal cancer: preoperative staging and monitoring of response to therapy. *Radiographics* 2009;29:403-21
11. van Vliet EP, Heijnenbroek-Kal MH, Hunink MG, et al. Staging investigations for oesophageal cancer: a meta-analysis. *Br J Cancer* 2008;98:547-57
12. van Vliet EP, Eijkemans MJ, Kuipers EJ, et al. Publication bias does not play a role in the reporting of the results of endoscopic ultrasound staging of upper gastrointestinal cancers. *Endoscopy* 2007;39:325-32
13. Puli SR, Reddy JB, Bechtold ML, et al. Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. *World J Gastroenterol* 2008;14:1479-90
14. Miyata H, Yamasaki M, Takiguchi S, et al. Prognostic value of endoscopic biopsy findings after induction chemoradiotherapy with and without surgery for esophageal cancer. *Ann Surg* 2011;253:279-84
15. Molena D, Sun HH, Badr AS, et al. Clinical tools do not predict pathological complete response in patients with esophageal squamous cell cancer treated with definitive chemoradiotherapy. *Dis Esophagus* 2014;27:355-9

16. Sarkaria IS, Rizk NP, Bains MS, et al. Post-treatment endoscopic biopsy is a poor-predictor of pathologic response in patients undergoing chemoradiation therapy for esophageal cancer. *Ann Surg* 2009;249:764-7
17. Schneider PM, Metzger R, Schaefer H, et al. Response evaluation by endoscopy, rebiopsy, and endoscopic ultrasound does not accurately predict histopathologic regression after neoadjuvant chemoradiation for esophageal cancer. *Ann Surg* 2008;248:902-8
18. Heinzow HS, Seifert H, Tsepetonidis S, et al. Endoscopic ultrasound in staging esophageal cancer after neoadjuvant chemotherapy--results of a multicenter cohort analysis. *J Gastrointest Surg* 2013;17:1050-7
19. Griffin JM, Reed CE, Denlinger CE. Utility of restaging endoscopic ultrasound after neoadjuvant therapy for esophageal cancer. *Ann Thorac Surg* 2012;93:1855-9; discussion 1860
20. Kalha I, Kaw M, Fukami N, et al. The accuracy of endoscopic ultrasound for restaging esophageal carcinoma after chemoradiation therapy. *Cancer* 2004;101:940-7
21. Yen TJ, Chung CS, Wu YW, et al. Comparative study between endoscopic ultrasonography and positron emission tomography-computed tomography in staging patients with esophageal squamous cell carcinoma. *Dis Esophagus* 2012;25:40-7
22. Owaki T, Matsumoto M, Okumura H, et al. Endoscopic ultrasonography is useful for monitoring the tumor response of neoadjuvant chemoradiation therapy in esophageal squamous cell carcinoma. *Am J Surg* 2012;203:191-7
23. Eloubeidi MA, Cerfolio RJ, Bryant AS, et al. Efficacy of endoscopic ultrasound in patients with esophageal cancer predicted to have N0 disease. *Eur J Cardiothorac Surg* 2011;40:636-41
24. Jost C, Binek J, Schuller JC, et al. Endosonographic radial tumor thickness after neoadjuvant chemoradiation therapy to predict response and survival in patients with locally advanced esophageal cancer: a prospective multicenter phase II study by the Swiss Group for Clinical Cancer Research (SAKK 75/02). *Gastrointest Endosc* 2010;71:1114-21
25. Chao YK, Yeh CJ, Lee MH, et al. Factors associated with false-negative endoscopic biopsy results after neoadjuvant chemoradiotherapy in patients with esophageal squamous cell carcinoma. *Medicine (Baltimore)* 2015;94:e588
26. Noordman BJ, Shapiro J, Spaander MC, et al. Accuracy of Detecting Residual Disease After Cross Neoadjuvant Chemoradiotherapy for Esophageal Cancer (preSANO Trial): Rationale and Protocol. *JMIR Res Protoc* 2015;4:e79
27. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529-36
28. Bowrey DJ, Clark GW, Roberts SA, et al. Serial endoscopic ultrasound in the assessment of response to chemoradiotherapy for carcinoma of the esophagus. *J Gastrointest Surg* 1999;3:462-7
29. Beseth BD, Bedford R, Isacoff WH, et al. Endoscopic ultrasound does not accurately assess pathologic stage of esophageal cancer after neoadjuvant chemoradiotherapy. *Am Surg* 2000;66:827-31

30. Reitsma JB, Glas AS, Rutjes AW, et al. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005;58:982-90
31. Rice TW, Boyce GA, Sivak MV, et al. Esophageal carcinoma: esophageal ultrasound assessment of preoperative chemotherapy. *Ann Thorac Surg* 1992;53:972-7
32. Ribeiro A, Franceschi D, Parra J, et al. Endoscopic ultrasound restaging after neoadjuvant chemotherapy in esophageal cancer. *Am J Gastroenterol* 2006;101:1216-21
33. Kroep JR, Van Groenigen CJ, Cuesta MA, et al. Positron emission tomography using 2-deoxy-2-[18F]-fluoro-D-glucose for response monitoring in locally advanced gastroesophageal cancer; a comparison of different analytical methods. *Mol Imaging Biol* 2003;5:337-46
34. Mesenas S, Vu C, McStay M, et al. A large series, resection controlled study to assess the value of radial EUS in restaging gastroesophageal cancer following neoadjuvant chemotherapy. *Dis Esophagus* 2008;21:37-42
35. Misra S, Choi M, Livingstone AS, et al. The role of endoscopic ultrasound in assessing tumor response and staging after neoadjuvant chemotherapy for esophageal cancer. *Surg Endosc Interv Tech* 2012;26:518-22
36. Machlenkin S, Melzer E, Idelevich E, et al. Endoscopic ultrasound: doubtful accuracy for restaging esophageal cancer after preoperative chemotherapy. *Isr Med Assoc J* 2009;11:166-9
37. Ota M, Murata Y, Ide H, et al. Useful endoscopic ultrasonography to assess the efficacy of neoadjuvant therapy for advanced esophageal carcinoma: Based on the response evaluation criteria in solid tumors. *Dig Endosc* 2005;17:59-63
38. Cheedella NKS, Suzuki A, Correa AM, et al. Association of clinical complete response (cCR) after preoperative chemoradiation and pathological complete response (pathCR) in patients with gastroesophageal cancer (GEC) and indispensability of trimodality therapy (TMT). *J Clin Oncol* 2012;30
39. Cheedella NK, Suzuki A, Xiao L, et al. Association between clinical complete response and pathological complete response after preoperative chemoradiation in patients with gastroesophageal cancer: analysis in a large cohort. *Ann Oncol* 2013;24:1262-6
40. Giacoia A, Thomas P, Giovannini M, et al. Endosonography in the preoperative evaluation of cancers of the esophagus. *Ann Chir* 1997;51:1077-83
41. Giacoia A, Thomas P, Giovannini M, et al. Ecoendoscopy in the assessment of esophageal neoplasms. *Acta Gastroenterol Latinoam* 1998;28:299-304
42. Chao YK, Tsai CY, Chang HK, et al. A pathological study of residual cancer in the esophageal wall following neoadjuvant chemoradiotherapy: focus on esophageal squamous cell carcinoma patients with false negative preoperative endoscopic biopsies. *Ann Surg Oncol* 2015;22:3647-52
43. Brown WA, Thomas J, Gotley D, et al. Use of oesophagogastrosocopy to assess the response of oesophageal carcinoma to neoadjuvant therapy. *Br J Surg* 2004;91:199-204
44. Swisher SG, Maish M, Erasmus JJ, et al. Utility of PET, CT, and EUS to identify pathologic responders in esophageal cancer. *Ann Thorac Surg* 2004;78:1152-60.
45. Adelstein DJ, Rice TW, Boyce GA, et al. Adenocarcinoma of the esophagus and gastroesophageal junction. Clinical and pathologic assessment of response to induction chemotherapy. *Am J Clin Oncol* 1994;17:14-8

46. Agarwal B, Swisher S, Ajani J, et al. Endoscopic ultrasound after preoperative chemoradiation can help identify patients who benefit maximally after surgical esophageal resection. *Am J Gastroenterol* 2004;99:1258-66
47. Cerfolio RJ, Bryant AS, Ohja B, et al. The accuracy of endoscopic ultrasonography with fine-needle aspiration, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy. *J Thorac Cardiovasc Surg* 2005;129:1232-41
48. Kim JH, Choi EK, Kim SB, et al. Preoperative hyperfractionated radiotherapy with concurrent chemotherapy in resectable esophageal cancer. *Int J Radiat Oncol Biol Phys* 2001;50:1-12
49. Shaukat A, Mortazavi A, Demmy T, et al. Should preoperative, post-chemoradiotherapy endoscopy be routine for esophageal cancer patients? *Dis Esophagus* 2004;17:129-35
50. Peng HQ, Halsey K, Sun CC, et al. Clinical utility of postchemoradiation endoscopic brush cytology and biopsy in predicting residual esophageal adenocarcinoma. *Cancer* 2009;117:463-72
51. Dittler HJ, Fink U, Siewert GR. Response to chemotherapy in esophageal cancer. *Endoscopy* 1994;26:769-71
52. Giovannini M, Seitz JF, Thomas P, et al. Endoscopic ultrasonography for assessment of the response to combined radiation therapy and chemotherapy in patients with esophageal cancer. *Endoscopy* 1997;29:4-9
53. Laterza E, de Manzoni G, Guglielmi A, et al. Endoscopic ultrasonography in the staging of esophageal carcinoma after preoperative radiotherapy and chemotherapy. *Ann Thorac Surg* 1999;67:1466-9
54. Zuccaro G, Rice TW, Goldblum J, et al. Endoscopic ultrasound cannot determine suitability for esophagectomy after aggressive chemoradiotherapy for esophageal cancer. *Am J Gastroenterol* 1999;94:906-12
55. Willis J, Cooper GS, Isenberg G, et al. Correlation of EUS measurement with pathologic assessment of neoadjuvant therapy response in esophageal carcinoma. *Gastrointest Endosc* 2002;55:655-61
56. Giovannini M, Bardou VJ, Moutardier V, et al. Relation between endoscopic ultrasound evaluation and survival of patients with inoperable thoracic squamous cell carcinoma of the oesophagus treated by combined radio- and chemotherapy. *Ital J Gastroenterol Hepatol* 1999;31:593-7
57. Isenberg G, Chak A, Canto MI, et al. Endoscopic ultrasound in restaging of esophageal cancer after neoadjuvant chemoradiation. *Gastrointest Endosc* 1998;48:158-63
58. Hirata N, Kawamoto K, Ueyama T, et al. Using endosonography to assess the effects of neoadjuvant therapy in patients with advanced esophageal cancer. *Am J Roentgenol* 1997;169:485-91
59. Blom RL, Steenbakkers IR, Lammering G, et al. PET/CT-based metabolic tumour volume for response prediction of neoadjuvant chemoradiotherapy in oesophageal carcinoma. *Eur J Nucl Med Mol Imaging* 2013;40:1500-6

60. Kim MP, Correa AM, Lee J, et al. Pathologic T0N1 esophageal cancer after neoadjuvant therapy and surgery: an orphan status. *Ann Thorac Surg* 2010;90:884-90; discussion 890-1
61. Altman DG, Bland JM. Diagnostic tests 2: Predictive values. *BMJ* 1994;309:102
62. Miyata H, Yamasaki M, Takiguchi S, et al. Salvage esophagectomy after definitive chemoradiotherapy for thoracic esophageal cancer. *J Surg Oncol* 2009;100:442-6
63. Tachimori Y, Kanamori N, Uemura N, et al. Salvage esophagectomy after high-dose chemoradiotherapy for esophageal squamous cell carcinoma. *J Thorac Cardiovasc Surg* 2009;137:49-54
64. Swisher SG, Wynn P, Putnam JB, et al. Salvage esophagectomy for recurrent tumors after definitive chemotherapy and radiotherapy. *J Thorac Cardiovasc Surg* 2002;123:175-83
65. Piessen G, Petyt G, Duhamel A, et al. Ineffectiveness of ¹⁸F-fluorodeoxyglucose positron emission tomography in the evaluation of tumor response after completion of neoadjuvant chemoradiation in esophageal cancer. *Ann Surg* 2013;258:66-76
66. Piessen G, Messenger M, Mirabel X, et al. Is there a role for surgery for patients with a complete clinical response after chemoradiation for esophageal cancer? An intention-to-treat case-control study. *Ann Surg* 2013;258:793-9; discussion 799-800
67. Kwee RM. Prediction of tumor response to neoadjuvant therapy in patients with esophageal cancer with use of ¹⁸F FDG PET: a systematic review. *Radiology* 2010;254:707-17
68. Westerterp M, van Westreenen HL, Reitsma JB, et al. Esophageal cancer: CT, endoscopic US, and FDG PET for assessment of response to neoadjuvant therapy--systematic review. *Radiology* 2005;236:841-51
69. van Rossum PS, van Hillegersberg R, Lever FM, et al. Imaging strategies in the management of oesophageal cancer: what's the role of MRI? *Eur Radiol* 2013;23:1753-65
70. van Rossum PS, van Lier AL, Lips IM, et al. Imaging of oesophageal cancer with FDG-PET/CT and MRI. *Clin Radiol* 2015;70:81-95
71. van Rossum PS, van Lier AL, van Vulpen M, et al. Diffusion-weighted magnetic resonance imaging for the prediction of pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer. *Radiother Oncol* 2015;115:163-70
72. De Cobelli F, Giganti F, Orsenigo E, et al. Apparent diffusion coefficient modifications in assessing gastro-oesophageal cancer response to neoadjuvant treatment: comparison with tumour regression grade at histology. *Eur Radiol* 2013;23:2165-74



Chapter 10

The incremental value of subjective and quantitative assessment of ^{18}F -FDG PET for the prediction of pathologic complete response to preoperative chemoradiotherapy in esophageal cancer

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ABSTRACT

A reliable prediction of a pathologic complete response (pathCR) to chemoradiotherapy before surgery for esophageal cancer would enable investigators to study the feasibility and outcome of an organ-preserving strategy after chemoradiotherapy. So far no clinical parameters or diagnostic studies are able to accurately predict which patients will achieve a pathCR. The aim of this study was to determine whether subjective and quantitative assessment of baseline and post-chemoradiation ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET) can improve the accuracy of predicting pathCR to preoperative chemoradiotherapy in esophageal cancer beyond clinical predictors.

METHODS

This retrospective study was approved by the IRB, and the need for written informed consent was waived. Clinical parameters along with subjective and quantitative parameters from baseline and post-chemoradiation ^{18}F -FDG PET were derived from 217 esophageal adenocarcinoma patients that underwent chemoradiotherapy followed by surgery. The associations between these parameters and pathCR were studied in univariable and multivariable logistic regression analysis. Four prediction models were constructed and internally validated using bootstrapping to study the incremental predictive values of subjective assessment of ^{18}F -FDG PET, conventional quantitative metabolic features, and comprehensive ^{18}F -FDG PET texture/geometry features, respectively. The clinical benefit of ^{18}F -FDG PET was determined using decision-curve analysis.

RESULTS

A pathCR was found in 59 (27%) patients. A clinical prediction model (corrected *c*-index 0.67) was improved by adding ^{18}F -FDG PET-based subjective assessment of response (corrected *c*-index 0.72). This latter model was slightly improved by the addition of one conventional quantitative metabolic feature only (i.e. post-chemoradiation total lesion glycolysis; corrected *c*-index 0.73), and even more by subsequently adding four comprehensive ^{18}F -FDG PET texture/geometry features (corrected *c*-index 0.77). However, at a decision-threshold of 0.9 or higher, representing a clinically relevant predictive value for pathCR at which one may be willing to omit surgery, there was no clear incremental value.

CONCLUSION

Subjective and quantitative assessment of ^{18}F -FDG PET provides statistical incremental value for predicting pathCR after preoperative chemoradiotherapy in esophageal cancer. However, the discriminatory improvement beyond clinical predictors does not translate into a clinically relevant benefit that could change decision-making.

INTRODUCTION

Preoperative chemoradiotherapy followed by surgery is increasingly applied as standard treatment with curative intent for patients with resectable non-metastatic esophageal cancer¹. A pathologic complete response (pathCR) to chemoradiotherapy is observed in approximately 25% to 30% of esophageal cancer patients¹⁻⁴. Many studies have reported that pathCR is associated with favorable overall survival rates²⁻⁴. Whether or not surgery can be safely omitted in patients who achieve a pathCR is an important focus of research, but determining pathCR is very difficult without performing surgery⁵. A reliable prediction of pathCR before surgery would enable investigators to study the feasibility and outcome of an organ-preserving strategy after chemoradiotherapy that includes omission of surgery and close clinical follow-up. Unfortunately, so far no clinical parameters or diagnostic studies are able to accurately predict which patients will achieve a pathCR⁶⁻⁹. Therefore, seeking more powerful predictors for pathCR is of high relevance to modern personalized cancer care where the aim is to tailor treatment to the individual patient.

¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET) is a well-established imaging modality for the initial staging of esophageal cancer and restaging after preoperative chemoradiotherapy for the detection of distant (interval) metastases¹⁰⁻¹². The value of ¹⁸F-FDG PET to predict response to preoperative chemoradiotherapy in patients with esophageal cancer has been studied extensively with wide varying methodologies and conflicting results^{6,10,13}. Some investigators examined the value of a (subjective) determination of clinical response by experienced nuclear medicine physicians based on ¹⁸F-FDG PET scanning after chemoradiotherapy^{11,12,14}. Most other ¹⁸F-FDG PET studies evaluated the value of quantitative metabolic parameters such as the mean standardized uptake value (SUV_{mean}) or maximum SUV (SUV_{max}) within a tumor for assessment of response^{5,6,12,13,15}. A few studies evaluated more advanced ¹⁸F-FDG PET-based metabolic parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) for response prediction¹⁶⁻¹⁸. Unfortunately, all these methods have not shown sufficient capability of ¹⁸F-FDG PET to predict response and guide clinical decision-making.

More recently, ¹⁸F-FDG PET image texture analysis has been proposed to characterize heterogeneity of intratumoral ¹⁸F-FDG uptake, which may provide a useful representation of underlying biologic tumor characteristics¹⁹. Texture analysis refers to a variety of computational methods that describe the relationships between the intensity of voxels and their position within an

image²⁰. Although ¹⁸F-FDG PET texture features are not routinely used in clinical evaluation of ¹⁸F-FDG PET images, there is increasing recognition that a potential complementary role may exist for prediction of treatment response and prognosis in several cancers²⁰. The aim of this diagnostic study was to develop and internally validate multivariable prediction models to determine the *incremental* value of baseline and post-chemoradiation ¹⁸F-FDG PET scanning for predicting pathCR after chemoradiotherapy in esophageal cancer beyond clinical predictive factors. In a large cohort, the added predictive values of subjective assessment of ¹⁸F-FDG PET scans, conventional quantitative metabolic parameters, and comprehensive quantitative ¹⁸F-FDG PET texture/geometry features for pathCR were evaluated, respectively.

MATERIALS AND METHODS

This retrospective study has been approved by the Institutional Review Board of the MD Anderson Cancer Center (MDACC), and the need for written informed consent was waived. The study was conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA), the checklist from the STAndards for the Reporting of Diagnostic accuracy studies (STARD) statement (<http://www.stard-statement.org>)²¹, and the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement (<http://www.tripod-statement.org>)²².

STUDY POPULATION

All consecutive patients with a biopsy-proven resectable adenocarcinoma of the esophagus or gastro-esophageal junction and no distant metastases that underwent preoperative chemoradiotherapy followed by surgery at MDACC from January 2006 to October 2013 were extracted from a prospective database. Patients were included only if results from baseline ¹⁸F-FDG PET, post-chemoradiation ¹⁸F-FDG PET, and post-chemoradiation endoscopic biopsy were available. Exclusion criteria were non-availability of a baseline ¹⁸F-FDG PET scan acquired at MDACC, non-FDG avidity of the tumor at baseline, Siewert type 3 gastro-esophageal junction tumors, and an esophageal stent in situ at the time of ¹⁸F-FDG PET scanning. In addition, patients with a time interval between completion of chemoradiotherapy and surgery of less than 5 weeks or more than 14 weeks - indicating urgent and salvage resections, respectively - were excluded. A detailed description of the treatment regimen and ¹⁸F-FDG PET image acquisition is provided in Supplementary Data A (online).

HISTOPATHOLOGIC ASSESSMENT

The degree of histopathologic tumor regression in the resected specimen was assigned to one of four tumor regression grades (TRGs) by experienced pathologists: complete absence of residual cancer (i.e. pathCR), 1-10% residual carcinoma, 11-50% residual carcinoma, and >50% residual carcinoma². PathCR (i.e. TRG 1) as opposed to any grade of residual carcinoma (i.e. TRG 2-4) was considered the reference standard. Another commonly made distinction between TRG 1-2 (i.e. 0-10% residual carcinoma) and TRG 3-4 (i.e. ≥11% residual carcinoma) was not made, since this distinction is rather arbitrary in terms of inter-pathologist reproducibility and overall survival^{2,4,23}, and the potential clinical consequences of such a distinction are unclear.

QUANTITATIVE IMAGE ANALYSIS

Only the primary esophageal tumors were considered for imaging analysis, since texture analysis cannot be reliably performed on small lesions (such as nodal metastases) due to the small number of voxels^{24,25}. The primary tumor volume was defined as the volume of interest (VOI) and delineated using a semi-automatic gradient-based delineation method²⁶ from commercially available software (MIM Software, Cleveland [OH], USA), followed by manual editing by one reader. A rationale for using this method is provided in Supplementary Data B (online). The reader was blinded to other clinical information and to the reference standard. Contours were extracted and quantitative ¹⁸F-FDG PET analysis was performed using the Imaging Biomarker Explorer (IBEX) software package²⁷ built in-house with commercial software (Matlab version 8.4; The MathWorks Inc, Natick [MA], USA).

TEST-RETEST ANALYSIS

The authors recognized that not all ¹⁸F-FDG PET features are sufficiently robust^{28, 29}, and therefore aimed to only include features that have sufficient robustness in the prediction modeling. To fulfill this goal, ¹⁸F-FDG PET scans taken outside MDACC (with different type of scanners and scan protocols) were used and compared to diagnostic ¹⁸F-FDG PET scans taken within MDACC. A subgroup of 7 patients was identified that underwent this form of double baseline scanning, with an average separation between the two scans of 31 days (range: 11 to 42 days). A single observer contoured the tumor volumes for the test-retest scans on separate occasions. In this way, both robustness and intra-observer contour variability was incorporated in test-retest analysis. For each image-derived

parameter the intraclass correlation coefficient (ICC) was calculated - using an absolute agreement definition in a two-way mixed effects model³⁰- to quantify the relatedness of the two scans per parameter.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS 20.0 (IBM Corp., Armonk, NY) and R 3.1.2 open-source software (<http://www.R-project.org>). A p-value <0.05 was considered statistically significant.

Model development

A detailed description on the studied parameters, standardized pre-selection of variables for multivariable analysis, multivariable model development, model performance tests and validation, is provided in Supplementary Data C (online). The association between clinical parameters and pathCR was studied univariably. A chi-square test or Fisher's exact test (in case of small cell count) was used for categorical variables and a Student's T-test or Mann-Whitney U test for parametric or non-parametric continuous clinical variables. The predictive value of each ¹⁸F-FDG PET-based parameter for pathCR was quantified using univariable logistic regression analysis providing odds ratios (ORs) with 95% confidence intervals (CIs). Various features were logarithmically transformed to improve on the assumption of linearity on the logit scale.

Because many potential predictors were studied in univariable analysis, a standardized pre-selection of variables for multivariable analysis was performed taking into account test-retest robustness and (multi)collinearity between parameters (Supplementary Data C; online). Four multivariable logistic regression models were constructed using stepwise backward elimination to study the value of clinical parameters (Model 1), the added value of subjective assessment of ¹⁸F-FDG PET (Model 2), and the subsequent added value of conventional and comprehensive quantitative ¹⁸F-FDG PET parameters (Model 3 and 4, respectively), for the prediction of pathCR.

Model performance and validation

Model discrimination and calibration results were evaluated for all four models using c-indexes and visual inspection of model calibration plots, respectively. Internal validation using the bootstrap method with 1000 repetitions was carried out to provide insight into potential over-fitting and optimism in model performance. Bootstrapping allowed for calculation of bias-corrected c-indexes of the four models, and provided shrinkage factors that were used to adjust the estimated regression coefficients in the final four models for over-fitting and

miscalibration³¹. A sensitivity analysis was performed on a subcohort of tumors with an initial MTV above 10 mL, because a recent study suggested that texture analysis may only provide valuable complementary information in tumors larger than 10 mL²⁴. In addition, the influence of including cases with 2D acquisition ¹⁸F-FDG PET scans (besides 3D acquisition ¹⁸F-FDG PET scans) in the model development set was determined by sensitivity analysis.

Clinical benefit

Because traditional accuracy metrics - such as the c-index - have limited value for clinical decision-making in the individual patient, the incremental clinical value of ¹⁸F-FDG PET analysis was determined using decision-curve analysis³². In this net benefit assessment the adverse effect of falsely predicting pathCR in non-pathCR patients (e.g. false-positives) is incorporated. In fact, a personal decision threshold can be chosen according to the willingness of risking a false positive result. In the context of predicting pathCR in esophageal cancer a false positive result could result in omission of surgery in a patient with residual disease, which is potentially hazardous^{14,33} and therefore the decision threshold should be high (i.e. ~0.9). To evaluate the incremental value of a model including ¹⁸F-FDG PET information, the net benefit (demonstrated on the y-axis) of the model should be higher compared to the model without that information. Divergence of a model's decision curve from another model's decision curve indicates difference in net benefit, but it depends on the personal decision threshold whether this is of clinical relevance. The decision curves of the four models used in the present study are presented together with the net benefit of making the same decision for all patients (e.g. performing surgery in all patients or omitting surgery in all patients). Additional explanation on the decision-curve analysis is provided in Supplementary Data C (online).

RESULTS

From 324 patients with an esophageal adenocarcinoma that met the pre-specified inclusion criteria, 107 patients were excluded because of non-availability of a baseline ¹⁸F-FDG PET scan acquired at MDACC (n=48), non-FDG avidity at baseline (n=18), a Siewert type 3 gastro-esophageal junction tumor (n=15), an esophageal stent in situ at the time of ¹⁸F-FDG PET scanning (n=1), or a time interval between completion of chemoradiotherapy and surgery of less than 5 weeks (n=1) or more than 14 weeks (n=24). A pathCR was found in 59 (27%) of the 217 eligible patients. Patients in the pathCR group had a mean age of 59 years, and 92% (n=54) of them were male, whereas patients with residual carcinoma had a mean age of 60 years, and 94% of them were male (**Table 1**).

Table 1 Clinical baseline and treatment-related characteristics

| Characteristic | PathCR (n=59) | No pathCR (n=158) | p value |
|---|------------------|----------------------|---------|
| Male gender | 54 (91.5) | 148 (93.7) | 0.558 |
| Age (y) [†] | 58.8 ± 12.3 | 60.1 ± 9.9 | 0.440 |
| BMI (kg/m ²) [†] | 29.5 ± 5.3 | 29.8 ± 5.2 | 0.632 |
| Hypertension | 29 (49.2) | 90 (57.0) | 0.304 |
| Cardiac co-morbidity | 14 (23.7) | 24 (15.2) | 0.141 |
| Diabetes mellitus | 12 (20.3) | 31 (19.6) | 0.906 |
| COPD | 4 (6.8) | 8 (5.1) | 0.739 |
| Smoking | 13 (22.0) | 38 (24.1) | 0.755 |
| Karnofsky performance status [‡] | 86.4 ± 6.9 | 85.5 ± 6.6 | 0.362 |
| Tumor location | | | 0.324 |
| Middle third of esophagus | 2 (3.4) | 1 (0.6) | |
| Distal third of esophagus | 52 (88.1) | 143 (90.5) | |
| Gastro-esophageal junction | 5 (8.5) | 14 (8.9) | |
| EUS-based tumor length (cm) [‡] | 5.0 ± 2.4 | 5.9 ± 2.7 | 0.034* |
| Histologic differentiation grade | | | 0.055 |
| Moderate | 34 (57.6) | 68 (43.0) | |
| Poor | 25 (42.4) | 90 (57.0) | |
| Signet ring cell adenocarcinoma | 5 (8.5) | 30 (19.0) | 0.061 |
| Clinical T-stage | | | 0.006* |
| cT2 | 14 (23.7) | 15 (9.5) | |
| cT3 | 45 (76.3) | 143 (90.5) | |
| Clinical N-stage | | | 0.450 |
| cN0 | 18 (30.5) | 58 (36.7) | |
| cN+ | 39 (66.1) | 98 (62.0) | |
| Missing | 2 (3.4) | 2 (1.3) | |
| Induction chemotherapy | 28 (47.5) | 50 (31.6) | 0.031* |
| Total radiation dose | | | 0.466 |
| 45.0 Gy | 4 (6.8) | 6 (3.8) | |
| 50.4 Gy | 55 (93.2) | 152 (96.2) | |
| Radiation treatment modality | | | 0.405 |
| 3D conformal radiation therapy | 1 (1.7) | 1 (0.6) | |
| Intensity modulated radiotherapy | 38 (64.4) | 111 (70.3) | |
| Proton therapy | 20 (33.9) | 46 (29.1) | |
| Chemotherapy regimen | | | 0.940 |
| Oxaliplatin / 5-fluorouracil | 25 (42.4) | 64 (40.5) | |
| Docetaxel / 5-fluorouracil | 25 (42.4) | 67 (42.4) | |
| Other | 9 (15.3) | 27 (17.1) | |

Table 1 (continued)

| Characteristic | PathCR (n=59) | No pathCR (n=158) | p value |
|--|------------------|----------------------|---------|
| Post-chemoradiation endoscopic biopsy | | | 0.023* |
| No residual cancer | 55 (93.2) | 126 (79.7) | |
| Residual cancer | 4 (6.8) | 32 (20.3) | |
| Days from completion CRT to surgery [†] | 61.5 ± 20.4 | 58.3 ± 19.3 | 0.285 |
| Year of patient accrual | | | 0.072 |
| 2006-2007 | 10 (16.9) | 47 (29.7) | |
| 2008-2010 | 26 (44.1) | 63 (39.9) | |
| 2011-2013 | 23 (39.0) | 48 (30.4) | |

Data are presented as numbers with percentages in parentheses.

[†]: Expressed as mean ± SD.

*: Significant difference between the pathologic complete response group and the pathologic non-complete response group ($p < 0.05$).

COPD: chronic obstructive pulmonary disease. CRT: chemoradiotherapy. EUS: endoscopic ultrasound. PathCR: pathologic complete response.

UNIVARIABLE ANALYSIS

Smaller EUS-based tumor length and less advanced depth of tumor infiltration (i.e. clinical stage T2 vs. T3) were significantly associated with a higher chance of pathCR ($p=0.034$ and $p=0.006$, respectively). The subgroup of 78 patients (36%) that underwent induction chemotherapy prior to trimodality therapy showed a significantly higher pathCR rate compared to the group without induction chemotherapy (36% vs. 22%, respectively; $p=0.031$). The post-chemoradiation endoscopic biopsy result was significantly associated with pathCR ($p=0.023$), although the predictive value of an endoscopic biopsy-based complete response for pathCR was only 30% (55 of 181).

Univariable analysis of subjective assessment and conventional quantitative features of ¹⁸F-FDG PET for predicting pathCR is presented in **Table 2**. Similar to endoscopic biopsy, subjective assessment of the post-chemoradiation ¹⁸F-FDG PET scan was significantly associated with pathCR ($p < 0.001$), but only 27 of 60 patients (45%) with a clinical complete response on ¹⁸F-FDG PET had a true pathCR. There was a trend towards a lower baseline SUV_{max} in pathologic complete responders ($p=0.087$). Some of the conventional quantitative features on the post-chemoradiation ¹⁸F-FDG PET scan were significantly related to a higher chance of pathCR including lower SUV_{max} ($p=0.015$), lower MTV ($p < 0.001$), and lower TLG ($p < 0.001$).

Table 2 Univariable analysis of subjective and conventional quantitative assessment of ^{18}F -FDG PET for predicting pathCR

| Characteristic | Number | Univariable analysis | | |
|---|--------|----------------------|-------------|----------------|
| | | OR | 95% CI | <i>p</i> value |
| Subjective assessment ^{18}F -FDG PET | | | | 0.001* |
| Clinical complete response | 60 | 1.0 (ref) | | |
| No clinical complete response | 157 | 0.30 | 0.15 – 0.59 | |
| Baseline SUV_{max} (<i>log</i>) | 217 | 0.63 | 0.37 – 1.07 | 0.087 |
| Baseline SUV_{mean} (<i>log</i>) | 217 | 0.60 | 0.32 – 1.13 | 0.112 |
| Baseline MTV (<i>log</i>) | 217 | 0.85 | 0.57 – 1.26 | 0.408 |
| Baseline TLG (<i>log</i>) | 217 | 0.82 | 0.61 – 1.10 | 0.181 |
| Post-chemoradiation SUV_{max} (<i>log</i>) | 217 | 0.32 | 0.13 – 0.80 | 0.015* |
| Post-chemoradiation SUV_{mean} (<i>log</i>) | 217 | 0.64 | 0.22 – 1.89 | 0.420 |
| Post-chemoradiation MTV (<i>log</i>) | 217 | 0.34 | 0.21 – 0.53 | <0.001* |
| Post-chemoradiation TLG (<i>log</i>) | 217 | 0.41 | 0.28 – 0.61 | <0.001* |
| $\Delta\text{SUV}_{\text{max}}$ (%) | 217 | 1.00 | 0.99 – 1.01 | 0.701 |
| $\Delta\text{SUV}_{\text{mean}}$ (%) | 217 | 1.01 | 1.00 – 1.02 | 0.146 |
| ΔMTV (%) | 217 | 1.00 | 0.99 – 1.00 | 0.142 |
| ΔTLG (%) | 217 | 1.00 | 0.99 – 1.00 | 0.301 |

*: Significant difference between the pathologic complete response group and the pathologic non-complete response group ($p < 0.05$).

CI: confidence interval. MTV: metabolic tumor volume. OR: odds ratio. SUV: standardized uptake value. TLG: total lesion glycolysis. Δ : Relative change between baseline and post-chemoradiation ^{18}F -FDG PET scans.

Test-retest relatedness of the conventional ^{18}F -FDG PET features was good (ICCs of SUV_{max} , SUV_{mean} , MTV, and TLG were 0.86, 0.87, 0.99, and 0.96, respectively). For each comprehensive ^{18}F -FDG PET feature, the ICCs resulting from test-retest analysis along with univariable analyses for predicting pathCR are presented in Supplementary Tables 1 and 2 (online). In general, test-retest relatedness was excellent for geometry features (median ICC 0.92), good for first-, second- and regional higher-order texture features (median ICC 0.86, 0.83, and 0.85, respectively), and poor for local higher-order texture features (median ICC 0.69).

MULTIVARIABLE ANALYSIS

Table 3 shows the finalized multivariable analysis of the four prediction models. In the clinical model (Model 1) four variables remained associated with a higher chance of pathCR (EUS-based tumor length, clinical T-stage, induction chemotherapy,

Table 3 Finalized prediction models for pathCR using multivariable logistic regression analysis with stepwise backward elimination

| Characteristic | Model 1 | | | Model 2 | | | Model 3 | | | Model 4 | | |
|---|------------------|---------|--|------------------|---------|--|------------------|---------|--|------------------|---------|--|
| | OR (95% CI) | p value | | OR (95% CI) | p value | | OR (95% CI) | p value | | OR (95% CI) | p value | |
| EUS-based tumor length (log) | 0.48 (0.24–0.95) | 0.034* | | 0.50 (0.24–1.01) | 0.054 | | 0.55 (0.57–1.14) | 0.107 | | 0.46 (0.19–1.11) | 0.085 | |
| Clinical T-stage | | 0.077 | | | 0.046* | | | 0.185 | | | 0.239 | |
| cT2 | 1.0 (ref) | | |
| cT3 | 0.45 (0.19–1.09) | | | 0.39 (0.15–0.98) | | | 0.53 (0.20–1.36) | | | 0.54 (0.19–1.51) | | |
| Induction chemotherapy | | 0.008* | | | 0.012* | | | 0.022* | | | 0.008* | |
| No | 1.0 (ref) | | |
| Yes | 2.44 (1.26–4.74) | | | 2.40 (1.21–4.77) | | | 2.26 (1.12–4.54) | | | 2.80 (1.31–5.98) | | |
| Post-CRT endoscopic biopsy | | 0.035* | | | 0.047* | | | 0.057 | | | 0.073 | |
| No residual cancer | 1.0 (ref) | | |
| Residual cancer | 0.30 (0.10–0.92) | | | 0.32 (0.10–0.98) | | | 0.32 (0.10–1.04) | | | 0.31 (0.08–1.12) | | |
| Subjective assessment ¹⁸ F-FDG PET | Not entered | - | | Not entered | 0.001* | | Not entered | 0.043* | | Not entered | 0.113 | |
| Clinical complete response | | | | 1.0 (ref) | | | 1.0 (ref) | | | 1.0 (ref) | | |
| No clinical complete response | | | | 0.30 (0.15–0.59) | | | 0.45 (0.21–0.98) | | | 0.52 (0.23–1.17) | | |
| Post-CRT TLG (log) | Not entered | - | | Not entered | - | | 0.57 (0.37–0.88) | 0.011* | | 0.76 (0.41–1.39) | 0.370 | |
| Baseline Cluster shade (log) | Not entered | - | | Not entered | - | | Not entered | - | | 0.19 (0.03–1.03) | 0.054 | |
| ΔRun percentage | Not entered | - | | Not entered | - | | Not entered | - | | 1.07 (1.02–1.11) | 0.004* | |
| ΔICM Entropy | Not entered | - | | Not entered | - | | Not entered | - | | 0.97 (0.94–0.99) | 0.044* | |
| Post-CRT Roundness (log) | Not entered | - | | Not entered | - | | Not entered | - | | 0.10 (0.03–0.42) | 0.001* | |

Entered variables that were eliminated based on redundancy were year of patient accrual, histologic differentiation grade and signet ring cell adenocarcinoma [Model 1]; baseline SUV_{max} and ΔMetabolic tumor volume [Model 3]; and baseline Maximum probability (log), ΔBusyness, ΔCumulative histogram, post-chemoradiation Skewness and post-chemoradiation Long run high intensity emphasis (log) [Model 4]. EUS: endoscopic ultrasound. CI: confidence interval. CRT: chemoradiotherapy. OR: odds ratio. TLG: total lesion glycolysis.

and post-chemoradiation endoscopic biopsy). Adding the subjective assessment of response on post-chemoradiation ^{18}F -FDG PET to the clinical model significantly improved the model (Model 2). Although 8 conventional quantitative ^{18}F -FDG PET features showed a p-value of ≤ 0.25 in univariable analysis, only 4 (baseline SUV_{max} , ΔMTV , post-chemoradiation SUV_{max} , and post-treatment TLG) were pre-selected

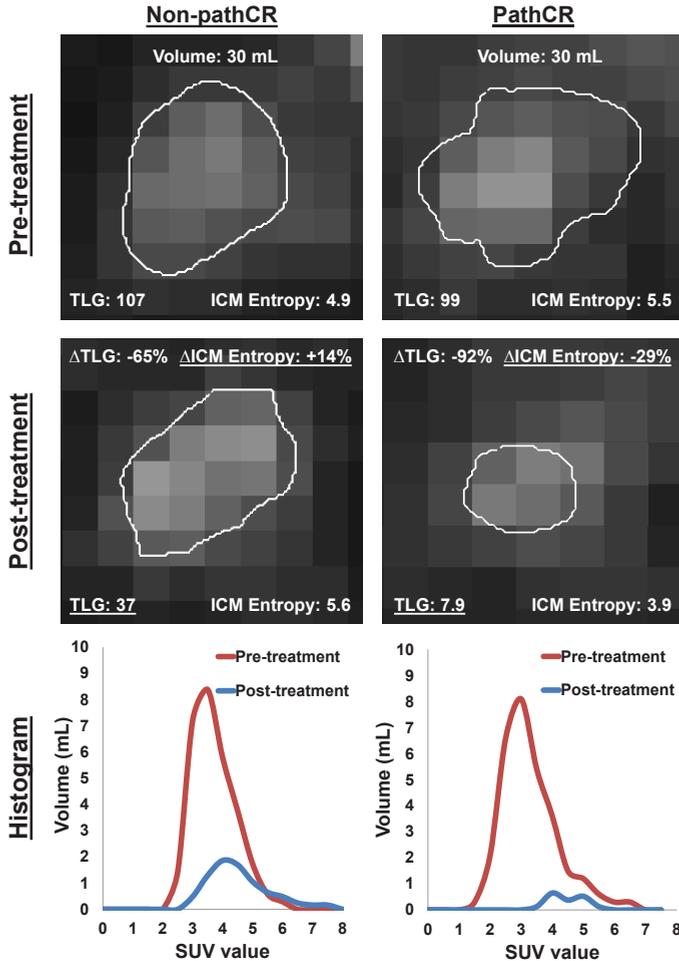


Figure 1 Examples of representative transverse slices of ^{18}F -FDG PET scans before and after chemoradiotherapy in a patient with no pathCR (i.e. non-pathCR) and in a patient with a pathCR. These patients initially had a comparable tumor volume, TLG, and local tumor texture (as expressed by the ICM entropy metric). However, in the complete responder the ΔICM entropy metric decreased and the post-treatment TLG was markedly lower (*underlined*), which represent two of the important predictors in models 3 and 4. Histograms illustrate the three-dimensional FDG-uptake within the volumes of interest.

for multivariable analysis due to several strong inter-parameter correlations (i.e. multicollinearity). After stepwise elimination, only post-treatment TLG appeared to provide significant model improvement (Model 3).

Many geometry and first- and second-order texture features from the post-chemoradiation ¹⁸F-FDG PET appeared significantly associated with pathCR in univariable analysis (Supplementary Table 1; online). However, most of these features were highly correlated with post-chemoradiation TLG (e.g. did not provide additional information, but would increase the risk of multicollinearity) and were not pre-selected for multivariable analysis. Subsequently, 9 comprehensive ¹⁸F-FDG PET features that met the pre-selection criteria were added to Model 3 in order to construct Model 4. Four of these features remained significantly important to the model after stepwise elimination (i.e. baseline cluster shade, Δ run percentage, Δ ICM entropy, and post-chemoradiation roundness). Examples of ¹⁸F-FDG PET scans before and after chemoradiotherapy in patients with and without a pathCR are provided in **Figure 1**.

MODEL PERFORMANCE

Measures of the performance of each model are presented in **Table 4**. Discrimination was moderate to good for all four models with c-indexes ranging from 0.71 for the clinical model to 0.75, 0.77 and 0.82 for the more complex models including subjective assessment of ¹⁸F-FDG PET, conventional and comprehensive quantitative ¹⁸F-FDG PET features, respectively (**Figure 2**). After internal validation, the corrected c-indexes appeared slightly lower (0.67, 0.72, 0.73, and 0.77 for Models 1-4, respectively), indicating a limited degree of (a combination of) over-fitting and bias due to the predictor selection process.

Table 4 Estimates of model performance for the four prediction models

| Model number/ Type | Discrimination | |
|---|-------------------|---------------------|
| | Apparent c-index* | Corrected c-index*† |
| 1/ Clinical model | 0.71 (0.64–0.79) | 0.67 (0.60–0.75) |
| 2/ + Subjective assessment ¹⁸ F-FDG PET | 0.75 (0.68–0.82) | 0.72 (0.65–0.79) |
| 3/ + Conventional ¹⁸ F-FDG PET features | 0.77 (0.70–0.84) | 0.73 (0.66–0.80) |
| 4/ + Comprehensive ¹⁸ F-FDG PET features | 0.82 (0.75–0.88) | 0.77 (0.70–0.83) |

* Data in parentheses are 95% confidence intervals.

† Correction after internal validation for both optimism and bias from the predictor selection process.

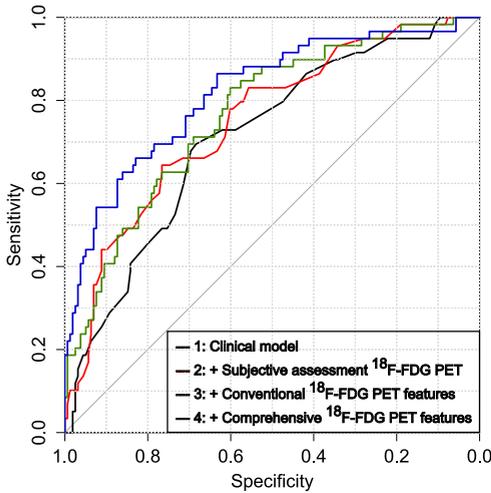


Figure 2 ROC curve analysis of the four models indicating their ability to discriminate between pathCR and non-pathCR patients.

Visual inspection of the consecutive model calibration plots showed a good overall fit (**Figure 3**). In general, the models tended to slightly overestimate the incidence of pathCR and underestimate the incidence of residual cancer as a result of minimal over-fitting (**Figure 3**). In Supplementary Table 3 (online), the logistic regression formulas of the four models are presented in which the minimal over-fitting and miscalibration were taken into account by applying a shrinkage factor that was obtained by bootstrapping.

Sensitivity analysis demonstrated no relevant change in discrimination after excluding 45 cases with initial tumor volumes below 10 mL (corrected c-indexes 0.67, 0.70, 0.72, and 0.78 for Models 1-4, respectively) or after excluding 65 cases with 2D acquisition ^{18}F -FDG PET scans (corrected c-indexes 0.69, 0.69, 0.71, 0.74 for Models 1-4, respectively).

CLINICAL BENEFIT

The decision curves of the models for the prediction of pathCR are displayed in **Figure 4**. At decision-thresholds ranging from ~ 0.3 to ~ 0.7 some incremental value of ^{18}F -FDG PET-based analyses (i.e. Models 2-4) beyond clinical predictors (i.e. Model 1) was suggested by the divergence between the decision curves. However, at a decision-threshold of 0.9 or higher - representing a clinically relevant predictive value for pathCR of $\geq 90\%$ at which one may be willing to omit surgery - there was no clear incremental value of the prediction models (net benefit: 0% for Models 1-3, and 1.8% for Model 4).

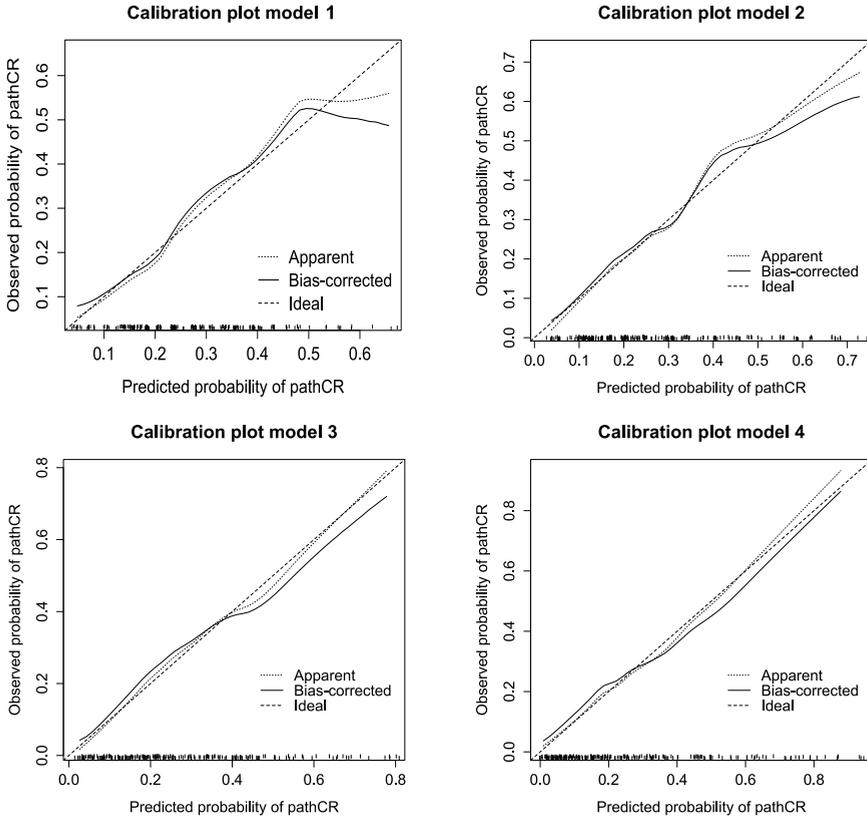


Figure 3 Calibration plots of the four models demonstrating the agreement between the predicted probability of pathCR by the model and the observed incidence.

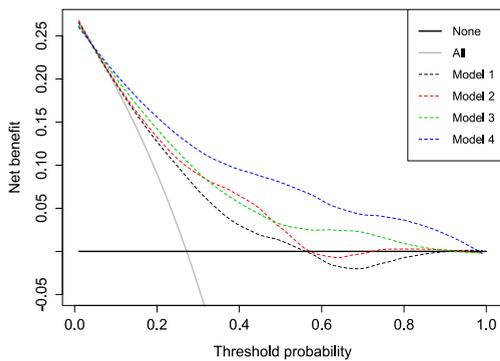


Figure 4 Decision curves graphically representing the net benefit (y-axis) for the four models at a range of decision-thresholds (i.e. minimum probabilities of pathologic complete response at which one would be willing to change clinical decision-making; x-axis). The black and grey solid lines represent making the same decision in all patients (i.e. omitting surgery in none or all of the patients, respectively).

DISCUSSION

This study demonstrates incremental value of baseline and post-chemoradiation ^{18}F -FDG PET scanning for predicting pathCR after preoperative chemoradiotherapy in esophageal cancer beyond clinical predictive factors in terms of discrimination. A clinical prediction model (corrected c-index 0.67) was improved by adding the subjective assessment of response by an experienced nuclear medicine physician on a post-chemoradiation ^{18}F -FDG PET (corrected c-index 0.72), and even more by subsequently adding comprehensive quantitative ^{18}F -FDG PET features analysis (corrected c-index 0.77). In terms of clinical benefit, however, both the clinical and the more complex ^{18}F -FDG PET-based multivariable models were not able to provide reliable predictive values for pathCR of $\sim 90\%$ or more, which was supported by the lack of net benefit (0% to 1.8%) in decision-curve analysis at this clinically relevant decision threshold. In our opinion, these findings suggest that adding simple or complex ^{18}F -FDG PET analyses to clinical parameters for the prediction of pathCR do not aid the clinician to such reliable extent that one may be willing to omit surgery in predicted complete responders.

The recent recognition that medical images may contain more useful information than can be perceived with the naked eye led to the field of ‘radiomics’, in which comprehensive features can be extracted by computational post-processing algorithms²⁰. Evidence is slowly emerging that these comprehensive texture and geometry features may yield additional predictive and prognostic information in several solid tumors²⁰. Although a single feature is not directly linked to a specific biologic process, investigators assume that a combination of image-derived textural (and geometry) features may be closely related to underlying biologic processes such as vascularization, cell density, tumor aggressiveness, or hypoxia^{20,34}; which in turn may be related to the degree of chemoradiation-resistance. In accordance with what one could reasonably expect, a tumor exhibiting a heterogeneous – compared with a homogeneous – ^{18}F -FDG distribution at baseline (i.e. higher ‘cluster shade’) was less likely to reach pathCR in our analysis. Similarly, a larger change towards a more homogeneous ^{18}F -FDG uptake and a greater loss in the amount of information (or unpredictability) as a result of chemoradiotherapy – as reflected by ‘ Δ run percentage’ and ‘ Δ ICM entropy’, respectively – resulted in a higher chance of pathCR. After chemoradiotherapy, more roundly shaped ^{18}F -FDG uptake with higher total lesion glycolysis (TLG) were more likely to represent residual cancer.

Several investigators have studied the predictive value of baseline or post-chemoradiation ^{18}F -FDG uptake for treatment response in esophageal cancer.

Large recent studies (n=88 to n=284) reported that the predictive value of a clinical complete response based on post-chemoradiation ¹⁸F-FDG PET (either or not combined with endoscopic biopsy) for pathCR is very low (range: 20%-64%)^{11,12,14}; a finding that was confirmed in the current study (45%). In other studies, pathologic response was variably found to be associated with image-derived quantitative parameters such as baseline SUV_{max}³⁵ and MTV¹⁷, or post-chemoradiation SUV_{max}⁵ and SUV_{mean}³⁶, or the relative change in SUV_{max}, MTV and TLG^{16,37}. In the current study, a similar trend – although non-significant – was observed for baseline SUV_{max} (p=0.087), whereas post-chemoradiation SUV_{max}, MTV and TLG were significantly associated with pathCR (p=0.015, p<0.001, and p<0.001, respectively). Importantly, however, in former studies as well as the current study, these subjective and quantitative ¹⁸F-FDG PET parameters did not allow differentiating pathCR from non-pathCR with high accuracy; a distinction that could be useful for clinical decision-making. This emphasizes the difference between a significant association of a parameter with pathologic response and a true predictive value in terms of discrimination or incremental value beyond other predictors. To this regard, we encourage investigators to study new potential diagnostic (bio)markers not only for their univariable association with pathologic response, but also for their predictive value and incremental value using a multivariable approach.

In esophageal cancer, four recent pilot studies from two research groups observed that ¹⁸F-FDG PET texture features seemed more informative than conventional metabolic parameters for the prediction of response to chemoradiotherapy (**Table 5**)^{29,34,38,39}. However, these studies were generally limited by small sample size (n=20 to n=50), heterogeneity of included tumor types and stages, lack of internal validation, and high likeliness of model over-fitting and over-optimism of reported results. Also, the used reference standard was suboptimally defined according to the ‘Response Evaluation Criteria In Solid Tumors’ (RECIST) criteria^{29,34} - which is known to correlate poorly with pathologic response⁸ - or ‘pathCR’ was mixed together as one group with ‘microscopic residual disease’^{38,39} while these groups are considered different entities associated with different survival rates^{2,4}. In addition, the studies differed from the current study regarding the used delineation method. All these substantial differences with the current study compromise proper comparison.

Table 5 Overview of studies on ¹⁸F-FDG PET texture analysis in esophageal cancer for treatment response assessment

| Study, year (reference) | n | Tumor type(s) | Tumor stages | Timing of ¹⁸ F-FDG PET | Outcome associated with tumor texture |
|-----------------------------------|-----|---------------|--------------|-----------------------------------|--|
| Tixier et al, 2011 ^{34*} | 41 | AC, SCC | I-IV | Pre-CRT | Clinical response (according to RECIST) |
| Hatt et al. 2013 ^{29*} | 50 | AC, SCC | I-IV | Pre-CRT | Clinical response (according to RECIST) |
| Tan et al, 2013 ^{38†} | 20 | AC, SCC | II-III | Pre- and post-CRT | Pathologic response (TRG 1+2 vs. 3+4) |
| Zhang et al, 2014 ^{39†} | 20 | AC, SCC | II-III | Pre- and post-CRT | Pathologic response (TRG 1+2 vs. 3+4) |
| Current study | 217 | AC | II-III | Pre- and post-CRT | Pathologic complete response (TRG 1 vs. 2-4) |

*: Significant overlap of study populations. †: Complete overlap of study populations. AC: adenocarcinoma. CRT: chemoradiotherapy. RECIST: Response Evaluation Criteria In Solid Tumors. TRG: tumor regression grade according to Chirieac et al.². SCC: squamous cell carcinoma.

The reported influences of clinical parameters - including pre-treatment EUS-based tumor length and T-stage, and post-treatment endoscopic biopsy - on the probability of pathCR in our study were in accordance with existing literature^{5,40,41}. The finding that induction chemotherapy before chemoradiotherapy was associated with a significantly higher rate of pathCR in the current series was in line with a recent phase II randomized trial at MDACC that did report a difference in pathCR rate in favor of induction chemotherapy (26% vs. 13%), but this difference was not statistically significant in that trial ($p=0.094$)⁴². The difference in significance and non-significance of the influence of induction chemotherapy on pathCR between the current study and the randomized trial cannot be fully explained. Potential explanations are possible selection bias through selecting operated patients in the current study only or a lack of statistical power (i.e. sample size) in the randomized trial. However, in the current study the significant difference between the two groups was considered not negligible, and induction chemotherapy was therefore entered into the multivariable prediction modeling process.

Several limitations apply to this study. First, slight model over-fitting occurred despite the large sample size. Therefore, we reported optimism-corrected model performance estimates resulting from internal validation in addition to apparent estimates. In addition, external validation of the prediction models would be

necessary to determine the residual overestimation of generalizability caused by the issue of multiple testing that was inherent to the explorative character of this study. Second, pathologic response in the primary tumor alone was examined, while a pathCR of the primary tumor may not completely exclude residual lymph node involvement¹⁷, and potentially useful information provided by ¹⁸F-FDG PET on lymph node involvement and response could have been missed. Particularly in patients with large lymphadenopathies, texture analysis could potentially provide valuable complementary information^{24,25}. Third, it should be acknowledged that the MTV threshold of 10 mL used for sensitivity analysis may not have been perfectly chosen, as it was based on a previous study that applied slightly different calculation methods for the texture features²⁴. Fourth, the metabolic tumor volume on the post-chemoradiation scan was small in many cases, which could have compromised the reliability of the texture features analysis of these scans. Finally, inherently to the retrospective character of this study the authors could not determine whether more modern reconstruction protocols using smaller voxel sizes, smaller post-reconstruction filtering methods and isotropic rather than anisotropic voxels⁴³ could potentially provide incremental information on tumor heterogeneity. However, our analysis was strengthened by using a prospectively maintained database, including clinical parameters that are practical, restricting analysis to robust features only, studying incremental rather than isolated predictive values, performing internal validation of the developed models, assessing added value in terms of clinical benefit, and providing novel findings.

No comparison with diffusion-weighted magnetic resonance imaging (DW-MRI) was performed in this study. However, in a recent prospective explorative study our group found that the treatment-induced change in the median tumor apparent diffusion coefficient (ADC) during the first 2-3 weeks of preoperative chemoradiotherapy as determined on DW-MRI seems highly predictive of pathCR⁴⁴. We believe that in future research a multimodality imaging approach - rather than using ¹⁸F-FDG PET alone - might prove to provide sufficient incremental predictive value for pathCR beyond clinical predictors to safely guide treatment decision-making. Therefore, in a recently embarked multicenter study we aim to evaluate the potential complementary value of DW-MRI in addition to ¹⁸F-FDG PET for predicting pathCR by performing both DW-MRI and ¹⁸F-FDG PET before, during, and after preoperative chemoradiotherapy in patients with esophageal cancer.

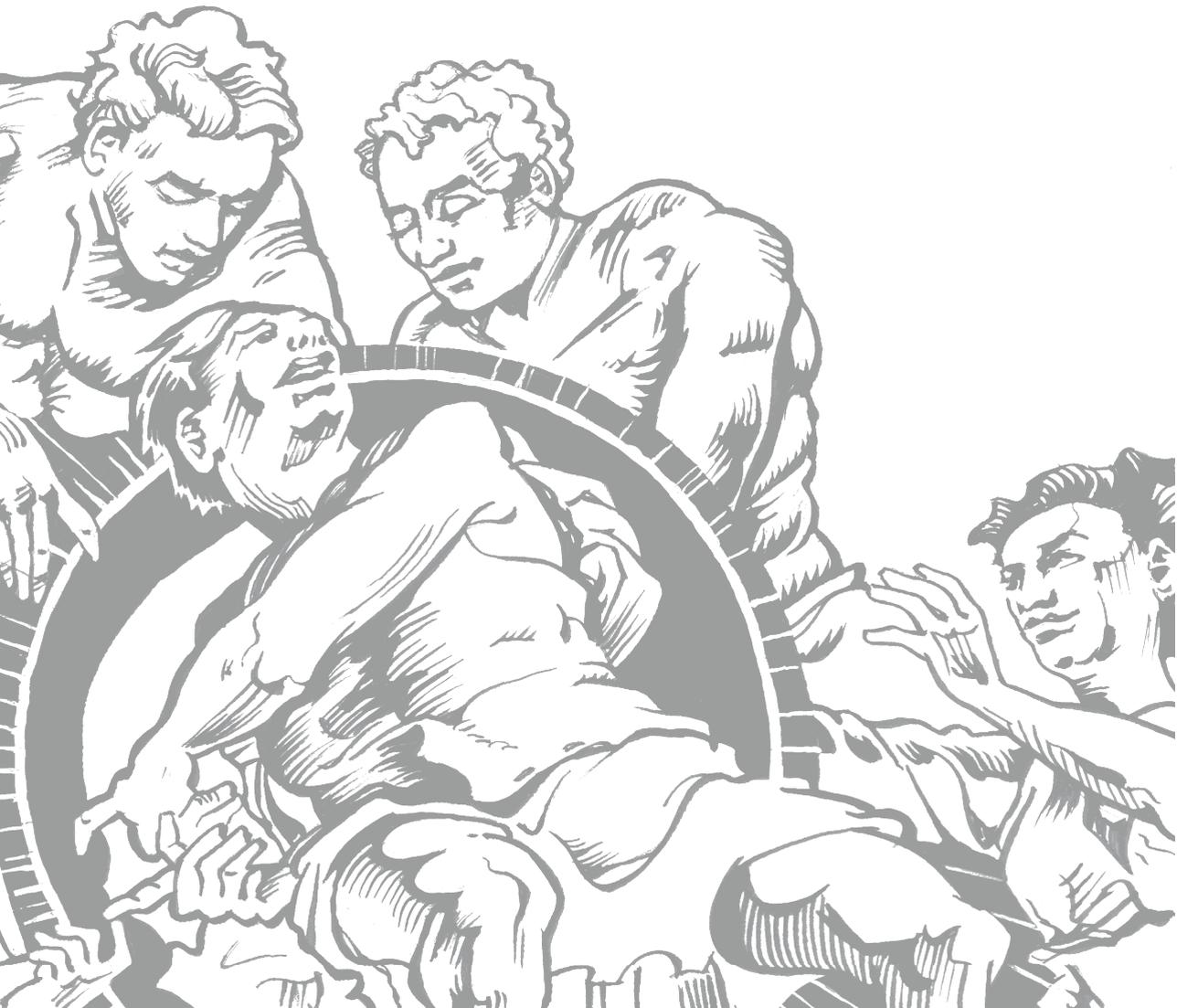
In conclusion, this study demonstrates that subjective and quantitative assessment of baseline and post-chemoradiation ^{18}F -FDG PET provides statistical –but currently not clinically relevant– incremental value for predicting pathologic complete response after preoperative chemoradiotherapy in esophageal cancer. The statistical discriminatory improvement beyond clinical predictors did not translate into a clinically relevant benefit that could change clinical decision-making in terms of safely omitting surgery in predicted complete responders. This particular clinical dilemma demands a very high predictive accuracy before clinical decision-making can be influenced, warranting improvement, development and validation of current and new imaging- or biomarkers.

REFERENCES

1. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
2. Chirieac LR, Swisher SG, Ajani JA, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. *Cancer* 2005;103:1347-55
3. Berger AC, Farma J, Scott WJ, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. *J Clin Oncol* 2005;23:4330-7
4. Donahue JM, Nichols FC, Li Z, et al. Complete pathologic response after neoadjuvant chemoradiotherapy for esophageal cancer is associated with enhanced survival. *Ann Thorac Surg* 2009;87:392-8
5. Ajani JA, Correa AM, Hofstetter WL, et al. Clinical parameters model for predicting pathologic complete response following preoperative chemoradiation in patients with esophageal cancer. *Ann Oncol* 2012;23:2638-42
6. Kwee RM. Prediction of tumor response to neoadjuvant therapy in patients with esophageal cancer with use of ¹⁸F FDG PET: a systematic review. *Radiology* 2010;254:707-17
7. Schneider PM, Metzger R, Schaefer H, et al. Response evaluation by endoscopy, rebiopsy, and endoscopic ultrasound does not accurately predict histopathologic regression after neoadjuvant chemoradiation for esophageal cancer. *Ann Surg* 2008;248:902-8
8. Westerterp M, van Westreenen HL, Reitsma JB, et al. Esophageal cancer: CT, endoscopic US, and FDG PET for assessment of response to neoadjuvant therapy--systematic review. *Radiology* 2005;236:841-51
9. van Rossum PS, van Hillegersberg R, Lever FM, et al. Imaging strategies in the management of oesophageal cancer: what's the role of MRI? *Eur Radiol* 2013;23:1753-65
10. van Rossum PS, van Lier AL, Lips IM, et al. Imaging of oesophageal cancer with FDG-PET/CT and MRI. *Clin Radiol* 2015;70:81-95
11. Bruzzi JE, Swisher SG, Truong MT, et al. Detection of interval distant metastases: clinical utility of integrated CT-PET imaging in patients with esophageal carcinoma after neoadjuvant therapy. *Cancer* 2007;109:125-34
12. Elliott JA, O'Farrell NJ, King S, et al. Value of CT-PET after neoadjuvant chemoradiation in the prediction of histological tumour regression, nodal status and survival in oesophageal adenocarcinoma. *Br J Surg* 2014;101:1702-11
13. Chen YM, Pan XF, Tong LJ, et al. Can ¹⁸F-fluorodeoxyglucose positron emission tomography predict responses to neoadjuvant therapy in oesophageal cancer patients? A meta-analysis. *Nucl Med Commun* 2011;32:1005-10
14. Cheedella NK, Suzuki A, Xiao L, et al. Association between clinical complete response and pathological complete response after preoperative chemoradiation in patients with gastroesophageal cancer: analysis in a large cohort. *Ann Oncol* 2013;24:1262-6

15. Ott K, Weber WA, Lordick F, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. *J Clin Oncol* 2006;24:4692-8
16. Roedl JB, Colen RR, Holalkere NS, et al. Adenocarcinomas of the esophagus: response to chemoradiotherapy is associated with decrease of metabolic tumor volume as measured on PET-CT: comparison to histopathologic and clinical response evaluation. *Radiother Oncol* 2008;89:278-86
17. Blom RL, Steenbakkers IR, Lammering G, et al. PET/CT-based metabolic tumour volume for response prediction of neoadjuvant chemoradiotherapy in oesophageal carcinoma. *Eur J Nucl Med Mol Imaging* 2013;40:1500-6
18. Hatt M, Visvikis D, Pradier O, et al. Baseline ¹⁸F-FDG PET image-derived parameters for therapy response prediction in oesophageal cancer. *Eur J Nucl Med Mol Imaging* 2011;38:1595-1606
19. El Naqa I, Grigsby P, Apte A, et al. Exploring feature-based approaches in PET images for predicting cancer treatment outcomes. *Pattern Recognit* 2009;42:1162-71
20. Chicklore S, Goh V, Siddique M, et al. Quantifying tumour heterogeneity in ¹⁸F-FDG PET/CT imaging by texture analysis. *Eur J Nucl Med Mol Imaging* 2013;40:133-40
21. Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ* 2003;326:41-4
22. Moons KG, Altman DG, Reitsma JB, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 2015;162:W1-73
23. Karamitopoulou E, Thies S, Zlobec I, et al. Assessment of tumor regression of esophageal adenocarcinomas after neoadjuvant chemotherapy: comparison of 2 commonly used scoring approaches. *Am J Surg Pathol* 2014;38:1551-6
24. Hatt M, Majdoub M, Vallieres M, et al. ¹⁸F-FDG PET uptake characterization through texture analysis: investigating the complementary nature of heterogeneity and functional tumor volume in a multi-cancer site patient cohort. *J Nucl Med* 2015;56:38-44
25. Brooks FJ, Grigsby PW. The effect of small tumor volumes on studies of intratumoral heterogeneity of tracer uptake. *J Nucl Med* 2014;55:37-42
26. Werner-Wasik M, Nelson AD, Choi W, et al. What is the best way to contour lung tumors on PET scans: multiobserver validation of a gradient-based method using a NSCLC digital PET phantom. *Int J Radiat Oncol Biol Phys* 2012;82:1164-71
27. Zhang L, Fried DV, Fave XJ, et al. IBEX: an open infrastructure software platform to facilitate collaborative work in radiomics. *Med Phys* 2015;42:1341-53
28. Tixier F, Hatt M, Le Rest CC, et al. Reproducibility of tumor uptake heterogeneity characterization through textural feature analysis in ¹⁸F-FDG PET. *J Nucl Med* 2012;53:693-700
29. Hatt M, Tixier F, Le Rest CC, et al. Robustness of intratumour ¹⁸F-FDG PET uptake heterogeneity quantification for therapy response prediction in oesophageal carcinoma. *Eur J Nucl Med Mol Imaging* 2013;40:1662-71
30. McGraw KO, Wong SP. Forming inferences about some intraclass correlation coefficients. *Psychological Methods* 1996;1:30-46

31. Moons KG, Kengne AP, Woodward M, et al. Risk prediction models: i. development, internal validation, and assessing the incremental value of a new (bio)marker. *Heart* 2012;98:683-90
32. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making* 2006;26:565-74
33. Piessen G, Messager M, Mirabel X, et al. Is there a role for surgery for patients with a complete clinical response after chemoradiation for esophageal cancer: an intention-to-treat case-control study. *Ann Surg* 2013;258:793-9
34. Tixier F, Le Rest CC, Hatt M, et al. Intra-tumor heterogeneity characterized by textural features on baseline ¹⁸F-FDG PET images predicts response to concomitant radiochemotherapy in esophageal cancer. *J Nucl Med* 2011;52:369-78
35. Rizk NP, Tang L, Adusumilli PS, et al. Predictive value of initial PET-SUV_{max} in patients with locally advanced esophageal and gastroesophageal junction adenocarcinoma. *J Thorac Oncol* 2009;4:875-9
36. Swisher SG, Erasmus J, Maish M, et al. 2-Fluoro-2-deoxy-D-glucose positron emission tomography imaging is predictive of pathologic response and survival after preoperative chemoradiation in patients with esophageal carcinoma. *Cancer* 2004;101:1776-85
37. Stiekema J, Vermeulen D, Vegt E, et al. Detecting interval metastases and response assessment using ¹⁸F-FDG PET/CT after neoadjuvant chemoradiotherapy for esophageal cancer. *Clin Nucl Med* 2014;39:862-7
38. Tan S, Kligerman S, Chen W, et al. Spatial-temporal [¹⁸F]FDG-PET features for predicting pathologic response of esophageal cancer to neoadjuvant chemoradiation therapy. *Int J Radiat Oncol Biol Phys* 2013;85:1375-82
39. Zhang H, Tan S, Chen W, et al. Modeling pathologic response of esophageal cancer to chemoradiation therapy using spatial-temporal ¹⁸F-FDG PET features, clinical parameters, and demographics. *Int J Radiat Oncol Biol Phys* 2014;88:195-203
40. Chao YK, Tseng CK, Wen YW, et al. Using pretreatment tumor depth and length to select esophageal squamous cell carcinoma patients for nonoperative treatment after neoadjuvant chemoradiotherapy. *Ann Surg Oncol* 2013;20:3000-8
41. Huang RW, Chao YK, Wen YW, et al. Predictors of pathologic complete response to neoadjuvant chemoradiotherapy for esophageal squamous cell carcinoma. *World J Surg Oncol* 2014;12:170-6
42. Ajani JA, Xiao L, Roth JA, et al. A phase II randomized trial of induction chemotherapy versus no induction chemotherapy followed by preoperative chemoradiation in patients with esophageal cancer. *Ann Oncol* 2013;24:2844-9
43. Vallières M, Freeman CR, Skamene SR, et al. A radiomics model from joint FDG-PET and MRI texture features for the prediction of lung metastases in soft-tissue sarcomas of the extremities. *Phys Med Biol* 2015;60:5471-96
44. van Rossum PS, van Lier AL, van Vulpen M, et al. Diffusion-weighted magnetic resonance imaging for the prediction of pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer. *Radiother Oncol* 2015;115:163-70



Chapter 11

Diffusion-weighted MRI for the prediction of pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer

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Radiotherapy & Oncology 2015;115:163-70

ABSTRACT

PURPOSE

To explore the value of diffusion-weighted magnetic resonance imaging (DW-MRI) for the prediction of pathologic response to neoadjuvant chemoradiotherapy (nCRT) in esophageal cancer.

MATERIAL AND METHODS

In 20 patients receiving nCRT for esophageal cancer DW-MRI scanning was performed before nCRT, after 8-13 fractions, and before surgery. The median tumor apparent diffusion coefficient (ADC) was determined at these three time points. The predictive potential of initial tumor ADC, and change in ADC (Δ ADC) during and after treatment for pathologic complete response (pathCR) and good response was assessed. Good response was defined as pathCR or near-pathCR (tumor regression grade [TRG] 1 or 2).

RESULTS

A pathCR after nCRT was found in 4 of 20 patients (20%), and 8 patients (40%) showed a good response to nCRT. The Δ ADC_{during} was significantly higher in pathCR vs. non-pathCR patients ($34.6\% \pm 10.7\%$ [mean \pm SD] vs. $14.0\% \pm 13.1\%$, $p=0.016$), as well as in good vs. poor responders ($30.5\% \pm 8.3\%$ vs. $9.5\% \pm 12.5\%$, $p=0.002$). The Δ ADC_{during} was predictive for residual cancer at a threshold of 29% (sensitivity 100%, specificity 75%, PPV 94%, and NPV 100%), and for poor pathologic response at a threshold of 21% (sensitivity 82%, specificity 100%, PPV 100%, and NPV 80%).

CONCLUSIONS

In this explorative study, the treatment-induced change in ADC during the first 2-3 weeks of nCRT for esophageal cancer seemed highly predictive for histopathologic response. Larger series are warranted to verify these results.

INTRODUCTION

The addition of neoadjuvant chemoradiotherapy (nCRT) to surgery for the treatment of resectable esophageal cancer has improved locoregional control and overall survival rates^{1,2}. Neoadjuvant chemoradiotherapy can induce significant tumor downstaging before surgery, even resulting in a pathologic complete response (pathCR) in approximately 30% of patients². This complete disappearance of viable tumor cells is associated with a favorable long-term prognosis and it is speculated that surgery might be safely omitted in this selected group of patients with a complete response³⁻⁷. In rectal cancer studies, authors have reported encouraging results with regard to feasibility and outcome of such a wait-and-see policy that includes omission of surgery and close clinical follow-up^{8,9}. On the other hand, patients with a poor pathologic response to nCRT may benefit less from nCRT but are exposed to its toxicity. Accurate identification of poor responders before or early during treatment could potentially allow for early modification or discontinuation of nCRT. However, in order to safely and effectively guide patient-tailored strategies in the management of esophageal cancer, a reliable tool that accurately assesses response to treatment is warranted first.

All studied modalities - including endoscopy with or without biopsy, endoscopic ultrasonography (EUS), computed tomography (CT), and ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) - yield unsatisfactory results in the assessment of response to nCRT so far¹⁰⁻¹³. Therefore, guiding neoadjuvant treatment decisions based on treatment response monitoring remains unjustified in current practice. The inability of size-related (dimensional) criteria to detect small tumor masses or underlying submucosal extent of residual tumor, and the difficulty of differentiating residual tumor mass from inflammation and fibrosis result in a low negative predictive value (NPV)¹³. Metabolic and functional imaging modalities allow for biologic and microstructural characterization of tumors and may visualize treatment-induced changes before volumetric changes become apparent^{14,15}. Two meta-analyses on the value of ¹⁸F-FDG PET(/CT) for response evaluation suggested that the decrease in mean or maximum metabolic activity within the first two weeks of nCRT is the best available predictor of pathCR so far, although still insufficient, with pooled sensitivities and specificities of 67% to 70% (95% confidence intervals ranging from 62% to 76%)^{10,11}.

Diffusion-weighted MRI (DW-MRI) is a functional imaging modality that allows for tissue characterization by deriving image contrast from variations in the free diffusion (i.e. random mobility or Brownian motion) of water molecules between

tissues which is a marker for microstructural density¹⁶. The apparent diffusion coefficient (ADC) can be calculated to quantify these differences in diffusion or microstructural density in a certain volume of interest¹⁴. The ADC is inversely correlated with tissue cellularity and as chemoradiotherapy can result in the loss of cell membrane integrity, tumor response can be detected as an increase in tumor ADC¹⁷. The predictive value of ADC in the assessment of response to (chemo) radiotherapy has previously been described in several malignancies including brain, head-and-neck, breast, prostate, and rectal cancer with promising results^{15,18-23}.

The primary aim of this study was to explore the value of diffusion-weighted magnetic resonance imaging (DW-MRI) for the prediction and assessment of pathologic response to neoadjuvant chemoradiotherapy (nCRT) in patients with esophageal cancer. In order to elaborate on our understanding of the biologic meaning of the ADC value in esophageal tumors a secondary aim was to study the relation between pre-treatment DW-MRI measurements and histopathologic tumor characteristics.

MATERIALS AND METHODS

STUDY POPULATION

This prospective study was approved by our institutional review board and all patients provided written informed consent. Patients presented at our tertiary referral center from May 2013 until May 2014 with newly diagnosed biopsy-proven esophageal cancer that were planned to receive nCRT followed by surgery were eligible for inclusion. In the Netherlands, neoadjuvant chemoradiotherapy is currently considered the standard of treatment with curative intent, rather than neoadjuvant chemotherapy, for both adenocarcinomas and squamous cell carcinomas². Patients with contraindications for MRI were excluded. Besides endoscopy with biopsy, the diagnostic work-up consisted of EUS, ultrasonography of the neck, and either standalone diagnostic CT or integrated ¹⁸F-FDG PET/CT scan for clinical staging.

TREATMENT PROTOCOL

The neoadjuvant treatment regimen consisted of weekly intravenous administration of carboplatin (area under the curve of 2 mg/mL per minute) and paclitaxel (50 mg/m² body-surface area) for 5 weeks with concurrent radiotherapy (41.4 Gy in 23 fractions of 1.8 Gy)². Here, the gross tumor volume (GTV) was defined by the primary tumor and any suspicious regional lymph nodes determined using

all available information (physical examination, endoscopy, EUS, CT-thorax/abdomen, and ^{18}F -FDG PET if available). The clinical target volume (CTV) was created by expanding the GTV with a proximal and distal margin of 3 cm - in case of tumor extension into the stomach a distal margin of 2 cm was chosen - and a radial margin of 5 mm adjusted for anatomical structures. The planning target volume (PTV) consisted of the CTV plus a margin of 1 cm in all directions. All patients were treated with an IMRT technique obeying the following constraints for the heart and lung tissue: $V_{\text{heart}} 40\text{Gy} \leq 30\%$ and $V_{\text{lung}} 20\text{Gy} \leq 35\%$. Five to ten weeks after completion of nCRT (median: 8.6 weeks) all patients underwent transhiatal or transthoracic esophagectomy with en-bloc two-field lymphadenectomy and gastric conduit reconstruction with cervical anastomosis.

IMAGE ACQUISITION

Patients underwent MRI scanning with anatomical T2-weighted and functional DW-MRI sequences within two weeks (median: 4 days) before nCRT (MRI_{pre}), after 8-13 radiotherapy fractions at 10-15 days after initiation of treatment (median: 8 fractions or 10 days after initiation of treatment) ($\text{MRI}_{\text{during}}$), and three to nine weeks (median: 5.7 weeks) after completion of nCRT, prior to surgery (MRI_{post}). The timing of the scan in the second or third week after initiation of nCRT was based on ^{18}F -FDG PET studies in esophageal cancer demonstrating a potential superior diagnostic accuracy at this time point as opposed to a pre- and post-treatment assessment only^{11,24}. These studies proposed that the second or third week may be an optimal time point in which significant tumor regression can already be found in responders while the image interpretation may not yet be influenced by radiation esophagitis, which generally occurs after the first few weeks of treatment.

The MRI examinations were performed on one 1.5T scanner equipped with a 16-element phased-array receive coil for thoracic imaging (Achieva; Philips Medical Systems, Best, The Netherlands). Patients were scanned in supine position. No anti-peristaltic agents were administered. Sagittal and transverse T2-weighted images were obtained with a navigator that monitors the position of the diaphragm using a fast 1D-MRI acquisition in order to trigger scanning exclusively during the expiration position of the diaphragm²⁵. Transverse DW images were obtained under free breathing conditions. Diffusion-weighted images were acquired using three different diffusion-sensitizing gradients ($b = 0, 200$ and 800 s/mm^2). Detailed scan parameters are presented in **Supplementary Table 1**.

IMAGE ANALYSIS*ADC calculation and measurements*

Imaging analysis including primary tumor delineations and automatic calculation of tumor ADC values was performed using our image analysis software package Volumetool developed in-house²⁶. The DW-MR images with b-values of 0, 200, and 800 s/mm² were used to generate ADC maps¹⁶. ADC values were calculated using a linear regression for the logarithmically transformed signal intensity (S_b) obtained with a certain diffusion-weighting b , according to the following equation: $\ln(S_b) = \ln(S_0) - b * ADC$, where S_0 is the signal intensity without diffusion-weighting.

The whole primary tumor was manually delineated on the DW-MR images with a b-value of 800 s/mm² before, during, and after nCRT by one reader (P.S.N.v.R.). The reader was blinded to patient-related characteristics and clinical outcome in terms of histopathologic response. The scans performed at different time points were registered per patient using mutual information, allowing for direct comparison of the delineated volumes. In case no residual tumor was identified on the post-treatment images, the apparent tumor bed - consisting of residual esophageal wall thickening on the T2-weighted images within the cranio-caudal boundaries defined on the DW-based tumor delineation before and during treatment - was delineated based on the T2-weighted images^{27,28}. From the drawn volumes of interest (VOIs), the median ADC values per VOI were extracted from the ADC map using Volumetool software. The percentage change in tumor ADC (ΔADC) between the initial and follow-up time points was expressed as: $\Delta ADC_n = (ADC_n - ADC_{pre}) / ADC_{pre} * 100\%$, where n is the time point during or after nCRT.

HISTOPATHOLOGIC ASSESSMENT

Histopathologic examination of the resection specimen was performed by two experienced pathologists who were blinded for the results of the MRI scans. The resection specimen was evaluated using a standardized protocol in accordance with the 7th edition of the International Union Against Cancer protocol for ypTNM-classification²⁹. The macroscopic identifiable tumor or the area of scarring at the site of previous tumor was embedded in total in order to adequately judge tumor residue and neoadjuvant treatment effects. Tissue sections were stained with hematoxylin and eosin. In cases of initial failure to detect residual tumor cells, additional sections were collected to confirm pathCR.

The degree of histopathologic tumor regression was considered the reference standard and graded according to the system proposed by Mandard et al³⁰. PathCR was defined as tumor regression grade (TRG) 1 representing complete absence of residual cancer cells. Good response was defined as either TRG 1 (e.g. pathCR) or TRG 2 (e.g. near-pathCR) which is indicated by rare residual cancer cells scattered throughout fibrosis. A poor pathologic response was indicated by TRG 3 representing residual cancer cells outgrown by fibrosis, TRG 4 with residual cancer cells outgrowing fibrosis, or TRG 5 in case no sign of tumor regression was found³⁰.

The authors chose to provide separate analyses on two different ways of dividing the outcome measure. The first studied outcome measure consisted of pathCR (i.e. TRG 1) versus non-pathCR (i.e. TRG ≥ 2) in order to explore the potential value of DW-MRI to aid in clinical decision-making regarding omission of surgery in anticipated complete responders. In a second and separate analysis the outcome measure consisted of good response (i.e. TRG 1-2) versus poor response (i.e. TRG ≥ 3). This alternative subdivision was made because it may be more relevant with regard to future considerations of modifying or discontinuing nCRT early during treatment if a poor response (as opposed to a good response) could be accurately predicted.

STATISTICAL ANALYSIS

First, the Mann-Whitney U test was used to compare the initial tumor ADC value and Δ ADC during and after nCRT between patients with a pathCR versus patients with no pathCR, and between good responders (i.e. with TRG 1 or 2) versus poor responders (i.e. with TRG ≥ 3). Receiver operating characteristics (ROC) analysis was used to assess the potential of initial tumor ADC value and Δ ADC to discriminate pathologic complete responders from pathologic non-complete responders, and good responders from poor responders. Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated for optimal thresholds that were determined by giving equal weight to sensitivity and specificity on the ROC curves.

Second, correlations between the ADC measurements and the TRG score (as a continuous outcome rather than a dichotomized outcome) were assessed by Spearman's rank correlation tests. Spearman's correlation coefficient ρ can be interpreted as follows: a positive or negative correlation coefficient of 0.80 to 1.00 is considered very strong; 0.60 to 0.79, strong; 0.40 to 0.59, moderate; 0.20 to 0.39, weak; and 0 to 0.20, very weak.

Third, the initial tumor ADC was compared between squamous cell carcinomas and adenocarcinomas, and between moderately and poorly differentiated tumors, using the Mann-Whitney U test. Furthermore, the Kruskal-Wallis test was used to compare the initial tumor ADC values among different clinical T-stages as determined by EUS. This pilot study was explorative by nature; therefore no formal sample size calculation has been performed. Statistical analysis was performed using SPSS 20.0 (SPSS Inc, Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

RESULTS

From a total of 23 consecutively included patients, two patients (9%) were excluded because the diagnostic quality of the pre-treatment DW-MRI scans was insufficient for further analysis due to severe cardiopulmonary motion artifacts. In addition, one patient was excluded due to the discovery of unexpected distant metastatic disease after completion of nCRT, impeding surgical resection. The remaining 20 patients with a total of 56 MRI scans were eligible for further analysis. Pre-treatment MRI scans were available in all patients. One MRI scan during nCRT and three MRI scans after completion of nCRT were missing due to patient's refusal associated with illness during or after treatment (n=3) or impracticality caused by an unexpectedly antedated operation date for logistic reasons (n=1).

Patients had a mean age of 61.3 years (range: 49 to 73 years), and 17 (85%) of them were male. Histopathologic tumor type consisted of either adenocarcinoma (n=15, 75%) or squamous cell carcinoma (n=5, 25%). Patient and tumor-related characteristics are summarized in **Table 1**. Histopathologic assessment of the resection specimens after surgery revealed a pathCR after nCRT in 4 patients (20%). A total of 8 patients (40%) showed a good response to nCRT. Examples of MRI scans from a patient with a pathCR and from a patient with a poor response are presented in **Figures 1 and 2**, respectively.

Table 1 Patient and tumor-related characteristics

| Characteristic | n (%) |
|---|--------------|
| Gender | |
| Male | 17 (85%) |
| Female | 3 (15%) |
| Age (years)^a | 61.3 ± 7.1 |
| Histologic tumor type | |
| Adenocarcinoma | 15 (75%) |
| Squamous cell carcinoma | 5 (25%) |
| Histologic tumor grade | |
| Moderate differentiation | 11 (55%) |
| Poor differentiation | 9 (45%) |
| Tumor location | |
| Proximal third | 2 (10%) |
| Middle third | 2 (10%) |
| Distal third | 13 (65%) |
| Gastro-esophageal junction | 3 (15%) |
| Clinical T-stage | |
| cT2 | 2 (10%) |
| cT3 | 16 (80%) |
| cT4a | 1 (5%) |
| cT4b | 1 (5%) |
| Clinical N-stage | |
| cN0 | 7 (35%) |
| cN1 | 8 (40%) |
| cN2 | 4 (20%) |
| cN3 | 1 (5%) |
| Histopathologic T-stage | |
| ypT0 | 4 (20%) |
| ypT1b | 2 (10%) |
| ypT2 | 8 (40%) |
| ypT3 | 6 (30%) |
| Histopathologic N-stage | |
| ypN0 | 13 (65%) |
| ypN1 | 6 (30%) |
| ypN2 | 0 (0%) |
| ypN3 | 1 (5%) |
| Histopathologic tumor regression | |
| TRG 1 (pathCR) | 4 (20%) |
| TRG 2 | 4 (20%) |
| TRG 3 | 10 (50%) |
| TRG 4 | 2 (10%) |
| TRG 5 | 0 (0%) |

^a Data presented as mean ± standard deviation.

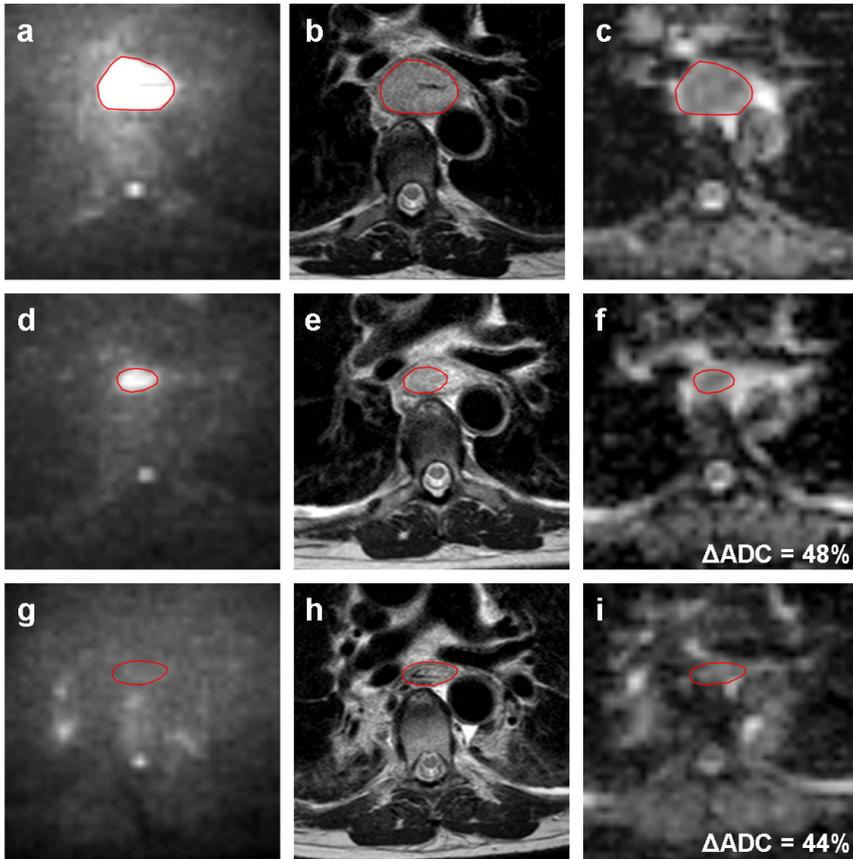


Figure 1 Patient with a cT4aN2M0 mid-esophageal squamous cell carcinoma with a complete histopathologic response to treatment (TRG 1) (red contours). High b-value ($b=800 \text{ s/mm}^2$) diffusion-weighted images (a,d,g), corresponding T2-weighted MR images (b,e,h), and corresponding ADC maps (c,f,i) before neoadjuvant chemoradiotherapy (nCRT) (a-c), during nCRT (d-f), and after nCRT (g-i). ADC calculations revealed an ADC increase of 48% after 2 weeks of nCRT and an increase of 44% 7 weeks after nCRT.

The course of the median tumor ADC before, during, and after nCRT averaged over all patients is shown in **Supplementary Figure 1**. The associations of initial ADC and ΔADC with the histopathologic tumor regression are presented in **Table 2**.

During nCRT, the relative increase in tumor ADC ($\Delta\text{ADC}_{\text{during}}$) was significantly higher in pathCR patients compared with patients without pathCR ($34.6\% \pm 10.7\%$ [mean \pm SD] vs. $14.0\% \pm 13.1\%$, $p=0.016$) (**Figure 3a**). Also, a significantly higher

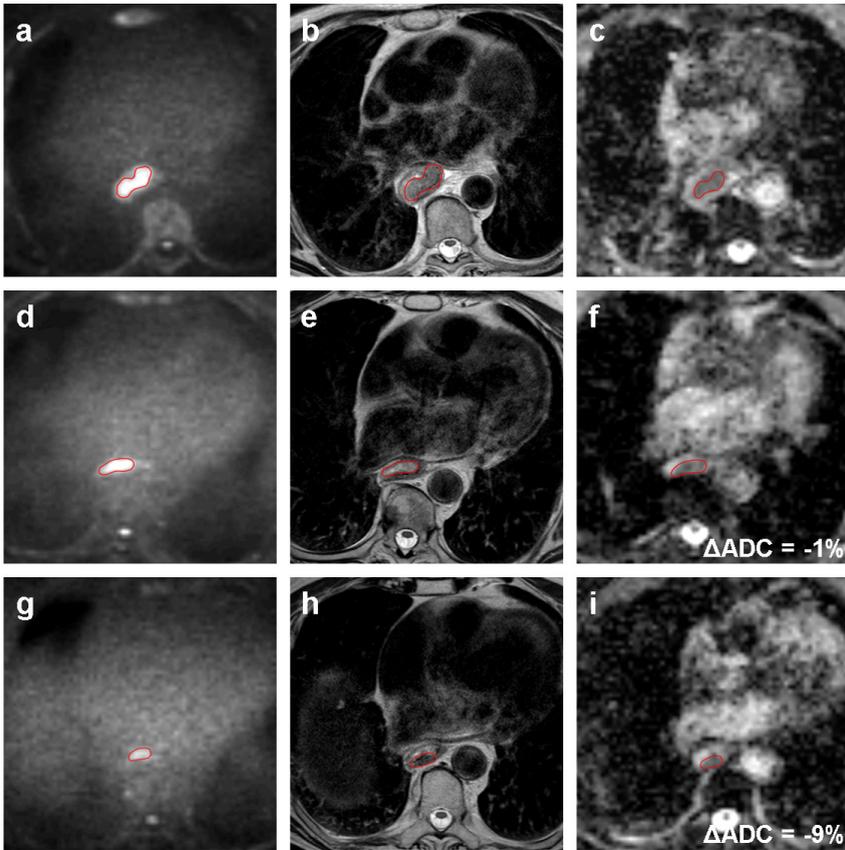


Figure 2 Patient with a cT3N2M0 adenocarcinoma of the distal esophagus with a poor histopathologic response to treatment (TRG4) (red contours). High b-value ($b=800 \text{ s/mm}^2$) diffusion-weighted images (a,d,g), corresponding T2-weighted MR images (b,e,h), and corresponding ADC maps (c,f,i) before nCRT (a-c), during nCRT (d-f), and after nCRT (g-i). ADC calculations revealed an ADC decrease of 1% after 2 weeks of nCRT and a decrease of 9% 4 weeks after nCRT.

$\Delta\text{ADC}_{\text{during}}$ was found in patients with a good response compared with poor responders ($30.5\pm 8.3\%$ vs. $9.5\pm 12.5\%$, $p=0.002$) (Figure 3b). Initial tumor ADC and the change in ADC after completion of nCRT ($\Delta\text{ADC}_{\text{post}}$) were not significantly related to any definition of pathologic response (Figure 3c-d).

Results of ROC analyses on the value of ADC measurements in the prediction of pathologic response are outlined in Supplementary Table 2. ROC analysis for $\Delta\text{ADC}_{\text{during}}$ resulted in an AUC of 0.90 for discriminating pathCR from no pathCR.

Table 2 Association between ADC measurements and histopathologic tumor regression

| MRI measurement | PathCR (n=4) | No pathCR (n=16) | <i>p</i> value | GR (n=8) | No GR (n=12) | <i>p</i> value |
|---|-----------------|--------------------------|----------------|-------------|--------------------------|----------------|
| Initial ADC (*10 ⁻³ mm ² /s) | 1.71 ± 0.32 | 1.84 ± 0.24 | 0.299 | 1.75 ± 0.29 | 1.86 ± 0.24 | 0.316 |
| ΔADC _{during} (%) | 34.6 ± 10.7 | 14.0 ± 13.1 ^a | 0.016* | 30.5 ± 8.3 | 9.5 ± 12.5 ^a | 0.002** |
| ΔADC _{post} (%) | 38.9 ± 45.7 | 18.9 ± 34.6 ^b | 0.258 | 36.3 ± 34.3 | 12.3 ± 37.3 ^b | 0.178 |

Data presented as mean ± standard deviation.

ADC: apparent diffusion coefficient. PathCR: pathologic complete response (i.e. TRG 1). GR: good response (i.e. TRG 1 or 2).

* Significant difference between pathologic complete and non-complete responders ($p < 0.05$).

** Significant difference between pathologic good and poor responders ($p < 0.05$).

^a Data based on all but one patient due to patient's refusal of planned MRI during neoadjuvant treatment.

^b Data based on all but three patients due to patient's refusal ($n = 2$) or logistic impracticality ($n = 1$) of the planned MRI after neoadjuvant treatment.

An optimal cut-off value of 29% yielded a sensitivity of 100%, specificity of 75%, accuracy of 95%, PPV of 94%, and NPV of 100% for predicting residual cancer (i.e. no pathCR). For discriminating good responders from poor responders, ΔADC_{during} showed an AUC of 0.92 with an optimal cut-off value of 21% resulting in a sensitivity of 82%, specificity of 100%, accuracy of 89%, PPV of 100%, and NPV of 80%. ROC analyses for initial ADC, and ΔADC_{post} showed inferior AUC values in comparison with ΔADC_{during}.

A strong inverse and significant correlation was found between TRG score and ΔADC_{during} ($\rho = -0.71$, $p = 0.001$). **Supplementary Figure 2** shows the lower ΔADC_{during} with increasing TRG score. Weak to very weak non-significant correlations were found between TRG (score 1 to 4 in this series) and both initial ADC ($\rho = 0.32$, $p = 0.174$), and ΔADC_{post} ($\rho = -0.38$, $p = 0.130$).

Initial ADC was significantly related to histologic tumor type (in *10⁻³ mm²/s: 1.58±0.20 in squamous cell carcinomas vs. 1.89±0.23 in adenocarcinomas, $p = 0.016$), and histologic tumor grade (in *10⁻³ mm²/s: 1.68±0.22 in moderately differentiated tumors vs. 1.97±0.21 in poorly differentiated tumors, $p = 0.009$). Although on average the initial tumor ADC was lower with increasing clinical T-stage, this relation did not reach statistical significance ($p = 0.180$). The association between initial ADC and histopathologic tumor characteristics is presented in **Supplementary Figure 3**.

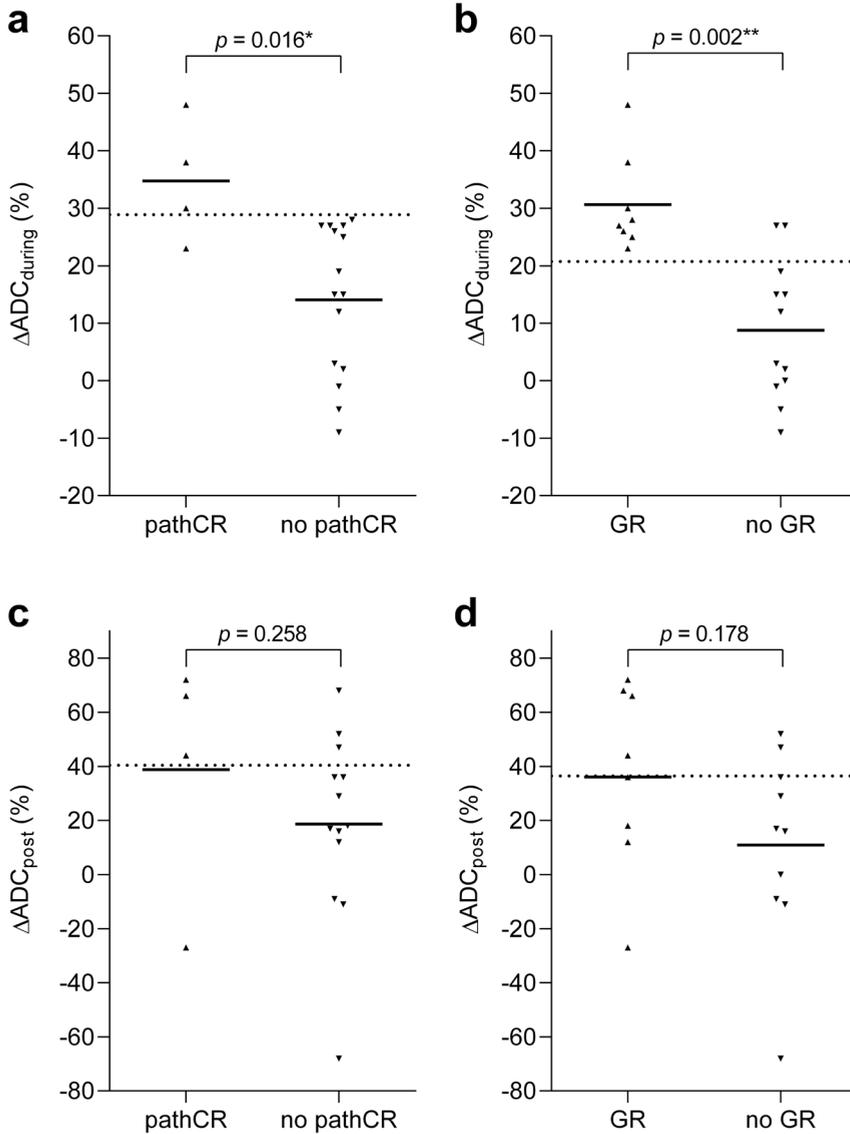


Figure 3 Scatter plots demonstrating the percentage of change in tumor ADC value during chemoradiotherapy ($\Delta ADC_{\text{during}}$) and after completion of chemoradiotherapy prior to surgery (ΔADC_{post}) for esophageal cancer in pathologic complete responders (pathCR) versus pathologic non-complete responders (no pathCR) (**a and c**), and in good responders (GR) versus poor responders (no GR) (**b and d**). Horizontal continuous and dotted lines represent group means and optimal cut-off levels, respectively.

DISCUSSION

In this study the value of DW-MRI based ADC measurements before, during, and after nCRT for esophageal cancer for the prediction and assessment of response to treatment was investigated. A significant association was found between treatment-induced ADC change during the first two to three weeks of nCRT ($\Delta\text{ADC}_{\text{during}}$) and histopathologic tumor regression defined as pathCR versus residual cancer or as good (TRG 1-2) versus poor pathologic response (TRG 3-5). A low $\Delta\text{ADC}_{\text{during}}$ of less than 29%, indicating a relatively low rate of cell membrane integrity loss early during treatment, predicted residual cancer (e.g. no pathCR) with a sensitivity and NPV of 100%. The high sensitivity and NPV for predicting residual cancer - reflecting the non-occurrence of erroneously predicting a complete response in a patient with residual cancer - are particularly promising when considering a patient-tailored wait-and-see approach with omission of surgery in the future. In addition, a low $\Delta\text{ADC}_{\text{during}}$ of less than 21% predicted a poor pathologic response with a specificity and PPV of 100%. The high specificity and PPV for predicting poor response are particularly promising for future considerations regarding modification or discontinuation of nCRT early during treatment.

Before treatment, the tumor ADC value was not significantly associated with any of the defined pathologic response criteria. This suggests inability of pre-treatment MRI to accurately identify prognostic indicators of treatment response that would allow for guiding individualized treatment decisions from the start. Contradictory results on the value of initial ADC for predicting response have been published in three previous studies with substantial differences in terms of tumor histology, MRI scan protocol, and used reference standard³¹⁻³³. One study reported that esophageal squamous cell carcinoma patients with higher initial ADC showed a better response to chemoradiotherapy³¹, whereas another study contrarily found significantly higher initial ADC values in non-responders³². Similar to our results, a third study found no significant association between initial ADC and response, regardless of a manual or semi-automated ADC measurement in that study³³. However, our explorative study suggests that there is some information to gain from the initial ADC value with regard to primary tumor characteristics. To our knowledge, this is the first study to report on the significant difference in ADC between esophageal adenocarcinomas and squamous cell carcinomas, and between moderately and poorly differentiated tumors. Additionally, we found a decreasing trend in initial tumor ADC with increasing clinical T-stage, which is supported by a previous study in esophageal squamous cell carcinomas³⁴.

Our finding that pathCR or good response status could be predicted by the change in tumor ADC early during neoadjuvant treatment is in line with results of previous studies in rectal, liver, head-and-neck, and brain tumors^{15,17,18,20,35-38}. Our study is the first to demonstrate that early ADC changes during nCRT are more predictive of pathCR than late ADC changes after completion of nCRT in esophageal cancer. This finding has also been recognized in ¹⁸F-FDG PET studies for response assessment in esophageal cancer^{11,24}, and is supported by results from recent DW-MRI studies in rectal cancer^{15,39}. In the first study that reported on MRI scanning before and during nCRT in 11 esophageal cancer patients, no correlation was found between change in mean tumor ADC and the histopathologic TRG³³. However, that study differed from the current study as a smaller sample of patients was studied, a different MRI scan protocol with other b-values was used, other methods for VOI delineation were applied, and patients underwent a different nCRT regimen³³.

After nCRT, the observed relative change in ADC ($\Delta\text{ADC}_{\text{post}}$) in our study was not predictive of response, which could be explained by the observation of a paradoxical decrease in tumor ADC in few of the good responders. This resulted in a relatively large variation in the $\Delta\text{ADC}_{\text{post}}$ value as compared to the variation in the $\Delta\text{ADC}_{\text{during}}$ value (as represented by the standard deviations in **Table 2**). The wide variation of $\Delta\text{ADC}_{\text{post}}$ values subsequently deprived the notable difference in group means (as demonstrated in **Table 2** and **Supplementary Figure 1**) to reach statistical significance. One could speculate that the decrease in tumor ADC in few of the good responders might have been caused by the formation of tissue fibrosis after treatment³³ or by a complicated determination of the VOI in some cases. The latter possibility is supported by our observation that after nCRT no residual high signal intensity was observed on the DW images in three cases, where VOIs were delineated based on the apparent tumor bed on the T2-weighted images^{27,28}. Although the authors expected that these VOIs probably reflected irradiated non-malignant tissue (e.g. fibrosis) with potentially a higher ADC than residual malignancy, histopathology revealed residual cancer with a poor response (i.e. TRG 3) to treatment in one of these three cases. The other two patients did have a pathologic complete response (i.e. TRG 1), but apparently one cannot simply assume absence of residual tumor in this situation. Future studies should point out whether this more problematic analysis of post-treatment images as opposed to images during treatment will continue to provide less reliable predictions for pathologic response.

Several limitations apply to this study. First, the small sample size that comes with the explorative character of this study may cause both over- and underestimation of the true predictive values. We acknowledge that the reported diagnostic performance of $\Delta\text{ADC}_{\text{during}}$ (e.g. sensitivity and NPV of 100% for pathCR; specificity and PPV of 100% for good pathologic response) is likely overestimated to some extent and we emphasize the need for validation in larger cohorts. In addition, the optimal threshold values to discriminate between response groups may vary with different hardware characteristics, used b-values, timing of scans and treatment regimens, warranting further evaluation before considering clinical implementation. Second, two of 23 patients (9%) unfortunately had to be excluded due to insufficient diagnostic quality of the pre-treatment DW-MRI scans caused by severe motion artifacts. This is a commonly reported problem in DW-MRI^{33,40}. Third, although the majority of patients (13 of 19; 68%) underwent the second MRI scan at an identical time point (i.e. after 8 fractions), this scan was performed after 11 or 13 fractions in 6 of 19 patients (32%) due to logistic planning difficulties related to limited MRI scanner capacity at the time, which may have affected the results either positively or negatively. Fourth, ADC measurements were only correlated to histopathologic tumor response. Although studies have shown that histopathologic tumor response is strongly related to disease-free and overall survival in esophageal cancer^{4,5} - and can therefore be regarded as a good surrogate endpoint - it would be interesting to correlate these measurements to survival endpoints after a certain follow-up time has passed.

No comparison with ¹⁸F-FDG PET/CT was performed in this study. Two recent meta-analyses on the value of ¹⁸F-FDG PET(/CT) for response evaluation reported pooled sensitivities and specificities of 67% to 70%^{10,11}. Our findings suggest superiority of DW-MRI to ¹⁸F-FDG PET/CT in the prediction of response to nCRT for esophageal cancer. The apparent insensitivity of DW-MRI to inflammation early during treatment may potentially be a helpful addition to ¹⁸F-FDG PET/CT⁴¹. In a recently embarked multicenter study we aim to determine this potential complementary value of DW-MRI in addition to ¹⁸F-FDG PET/CT for response evaluation by performing both MRI and ¹⁸F-FDG PET/CT before, during, and after nCRT in patients with esophageal cancer.

In conclusion, this initial study suggests that the change of tumor ADC as determined on DW-MRI during the first two to three weeks of neoadjuvant chemoradiotherapy for esophageal cancer may allow for accurate early prediction of histopathologic response. Larger studies are needed to validate our findings and evaluate the distinct and combined predictive value of DW-MRI and ¹⁸F-FDG PET/CT.

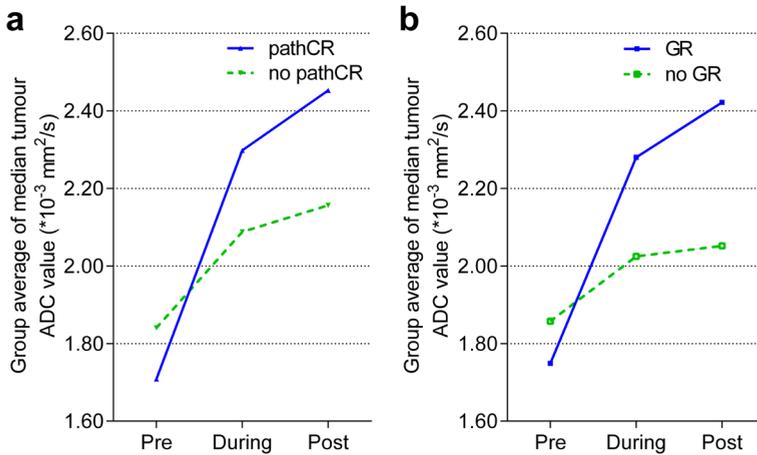
REFERENCES

1. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011;12:681-92
2. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
3. Oppedijk V, van der Gaast A, van Lanschot JJ, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. *J Clin Oncol* 2014;32:385-91
4. Berger AC, Farma J, Scott WJ, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. *J Clin Oncol* 2005;23:4330-7
5. Donahue JM, Nichols FC, Li Z, et al. Complete pathologic response after neoadjuvant chemoradiotherapy for esophageal cancer is associated with enhanced survival. *Ann Thorac Surg* 2009;87:392-8; discussion 398-9
6. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005;23:2310-7
7. Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol* 2007;25:1160-8
8. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg* 2004;240:711-7; discussion 717-8
9. Maas M, Beets-Tan RG, Lambregts DM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. *J Clin Oncol* 2011;29:4633-40
10. Kwee RM. Prediction of tumor response to neoadjuvant therapy in patients with esophageal cancer with use of ¹⁸F FDG PET: a systematic review. *Radiology* 2010;254:707-17
11. Chen YM, Pan XF, Tong LJ, et al. Can ¹⁸F-fluorodeoxyglucose positron emission tomography predict responses to neoadjuvant therapy in oesophageal cancer patients? A meta-analysis. *Nucl Med Commun* 2011;32:1005-10
12. Schneider PM, Metzger R, Schaefer H, et al. Response evaluation by endoscopy, rebiopsy, and endoscopic ultrasound does not accurately predict histopathologic regression after neoadjuvant chemoradiation for esophageal cancer. *Ann Surg* 2008;248:902-8
13. Westerterp M, van Westreenen HL, Reitsma JB, et al. Esophageal cancer: CT, endoscopic US, and FDG PET for assessment of response to neoadjuvant therapy--systematic review. *Radiology* 2005;236:841-51
14. Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. *Am J Roentgenol* 2007;188:1622-35
15. Lambrecht M, Vandecaveye V, De Keyzer F, et al. Value of diffusion-weighted magnetic resonance imaging for prediction and early assessment of response to neoadjuvant radiochemotherapy in rectal cancer: preliminary results. *Int J Radiat Oncol Biol Phys* 2012;82:863-70

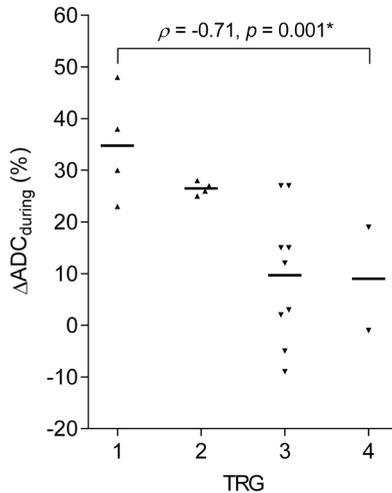
16. Padhani AR, Liu G, Koh DM, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. *Neoplasia* 2009;11:102-25
17. Thoeny HC, Ross BD. Predicting and monitoring cancer treatment response with diffusion-weighted MRI. *J Magn Reson Imaging* 2010;32:2-16
18. Mardor Y, Pfeffer R, Spiegelmann R, et al. Early detection of response to radiation therapy in patients with brain malignancies using conventional and high b-value diffusion-weighted magnetic resonance imaging. *J Clin Oncol* 2003;21:1094-1100
19. Vandecaveye V, Dirix P, De Keyser F, et al. Diffusion-weighted magnetic resonance imaging early after chemoradiotherapy to monitor treatment response in head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2012;82:1098-1107
20. Pickles MD, Gibbs P, Lowry M, et al. Diffusion changes precede size reduction in neoadjuvant treatment of breast cancer. *Magn Reson Imaging* 2006;24:843-7
21. Powell C, Schmidt M, Borri M, et al. Changes in functional imaging parameters following induction chemotherapy have important implications for individualised patient-based treatment regimens for advanced head and neck cancer. *Radiother Oncol* 2013;106:112-7
22. Joye I, Deroose CM, Vandecaveye V, et al. The role of diffusion-weighted MRI and ¹⁸F-FDG PET/CT in the prediction of pathologic complete response after radiochemotherapy for rectal cancer: a systematic review. *Radiother Oncol* 2014;113:158-65
23. Decker G, Murtz P, Gieseke J, et al. Intensity-modulated radiotherapy of the prostate: dynamic ADC monitoring by DWI at 3.0 T. *Radiother Oncol* 2014;113:115-20
24. Ott K, Weber WA, Lordick F, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. *J Clin Oncol* 2006;24:4692-8
25. Lever FM, Lips IM, Crijns SP, et al. Quantification of esophageal tumor motion on cine-magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* 2014;88:419-24
26. Bol GH, Kotte AN, van der Heide UA, et al. Simultaneous multi-modality ROI delineation in clinical practice. *Comput Methods Programs Biomed* 2009;96:133-40
27. Lambregts DM, Beets GL, Maas M, et al. Tumour ADC measurements in rectal cancer: effect of ROI methods on ADC values and interobserver variability. *Eur Radiol* 2011;21:2567-74
28. Intven M, Reerink O, Philippens ME. Diffusion-weighted MRI in locally advanced rectal cancer: pathological response prediction after neo-adjuvant radiochemotherapy. *Strahlenther Onkol* 2013;189:117-22
29. Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC Cancer Staging Manual: esophagus and esophagogastric junction. *Ann Surg Oncol* 2010;17:1721-4
30. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer* 1994;73:2680-6

31. Aoyagi T, Shuto K, Okazumi S, et al. Apparent diffusion coefficient values measured by diffusion-weighted imaging predict chemoradiotherapeutic effect for advanced esophageal cancer. *Dig Surg* 2011;28:252-7
32. De Cobelli F, Giganti F, Orsenigo E, et al. Apparent diffusion coefficient modifications in assessing gastro-oesophageal cancer response to neoadjuvant treatment: comparison with tumour regression grade at histology. *Eur Radiol* 2013;23:2165-74
33. Kwee RM, Dik AK, Sosef MN, et al. Interobserver reproducibility of diffusion-weighted MRI in monitoring tumor response to neoadjuvant therapy in esophageal cancer. *PLoS One* 2014;9:e92211
34. Aoyagi T, Shuto K, Okazumi S, et al. Evaluation of the clinical staging of esophageal cancer by using diffusion-weighted imaging. *Exp Ther Med* 2010;1:847-51
35. Vandecaveye V, Dirix P, De Keyzer F, et al. Predictive value of diffusion-weighted magnetic resonance imaging during chemoradiotherapy for head and neck squamous cell carcinoma. *Eur Radiol* 2010;20:1703-14
36. Kim S, Loevner L, Quon H, et al. Diffusion-weighted magnetic resonance imaging for predicting and detecting early response to chemoradiation therapy of squamous cell carcinomas of the head and neck. *Clin Cancer Res* 2009;15:986-94
37. Theilmann RJ, Borders R, Trouard TP, et al. Changes in water mobility measured by diffusion MRI predict response of metastatic breast cancer to chemotherapy. *Neoplasia* 2004;6:831-7
38. Cui Y, Zhang XP, Sun YS, et al. Apparent diffusion coefficient: potential imaging biomarker for prediction and early detection of response to chemotherapy in hepatic metastases. *Radiology* 2008;248:894-900
39. Sun YS, Zhang XP, Tang L, et al. Locally advanced rectal carcinoma treated with preoperative chemotherapy and radiation therapy: preliminary analysis of diffusion-weighted MR imaging for early detection of tumor histopathologic downstaging. *Radiology* 2010;254:170-8
40. Le Bihan D, Poupon C, Amadon A, et al. Artifacts and pitfalls in diffusion MRI. *J Magn Reson Imaging* 2006;24:478-88
41. Park SH, Moon WK, Cho N, et al. Comparison of diffusion-weighted MR imaging and FDG PET/CT to predict pathological complete response to neoadjuvant chemotherapy in patients with breast cancer. *Eur Radiol* 2012;22:18-25

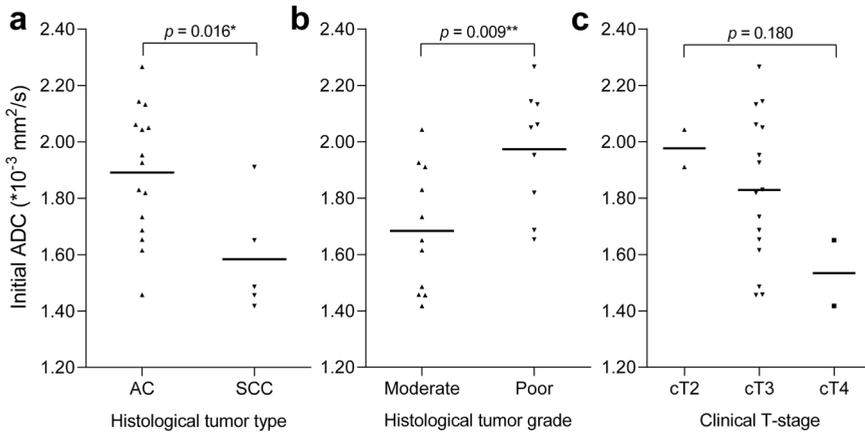
SUPPLEMENTARY DATA



Supplementary Figure 1 Course of median tumor ADC values before, during, and after neoadjuvant chemoradiotherapy for esophageal cancer averaged over all pathologic complete responders (pathCR) versus pathologic non-complete responders (no pathCR) (a) and averaged over all good responders (GR) versus poor responders (no GR) (b).



Supplementary Figure 2 Scatter plot illustrating the correlation between percentage of change in tumor ADC value during chemoradiotherapy ($\Delta\text{ADC}_{\text{during}}$) and histopathologic tumor regression grade (TRG). Horizontal lines represent group means.



Supplementary Figure 3 Scatter plots illustrating the comparison of initial tumor ADC values between (a) adenocarcinomas (AC) and squamous cell carcinomas (SCC), (b) tumors with moderate and poor differentiation grades, and (c) clinical stage T2, T3, and T4. Horizontal lines represent group means.

Supplementary Table 1 Scan parameters of the used MRI protocol

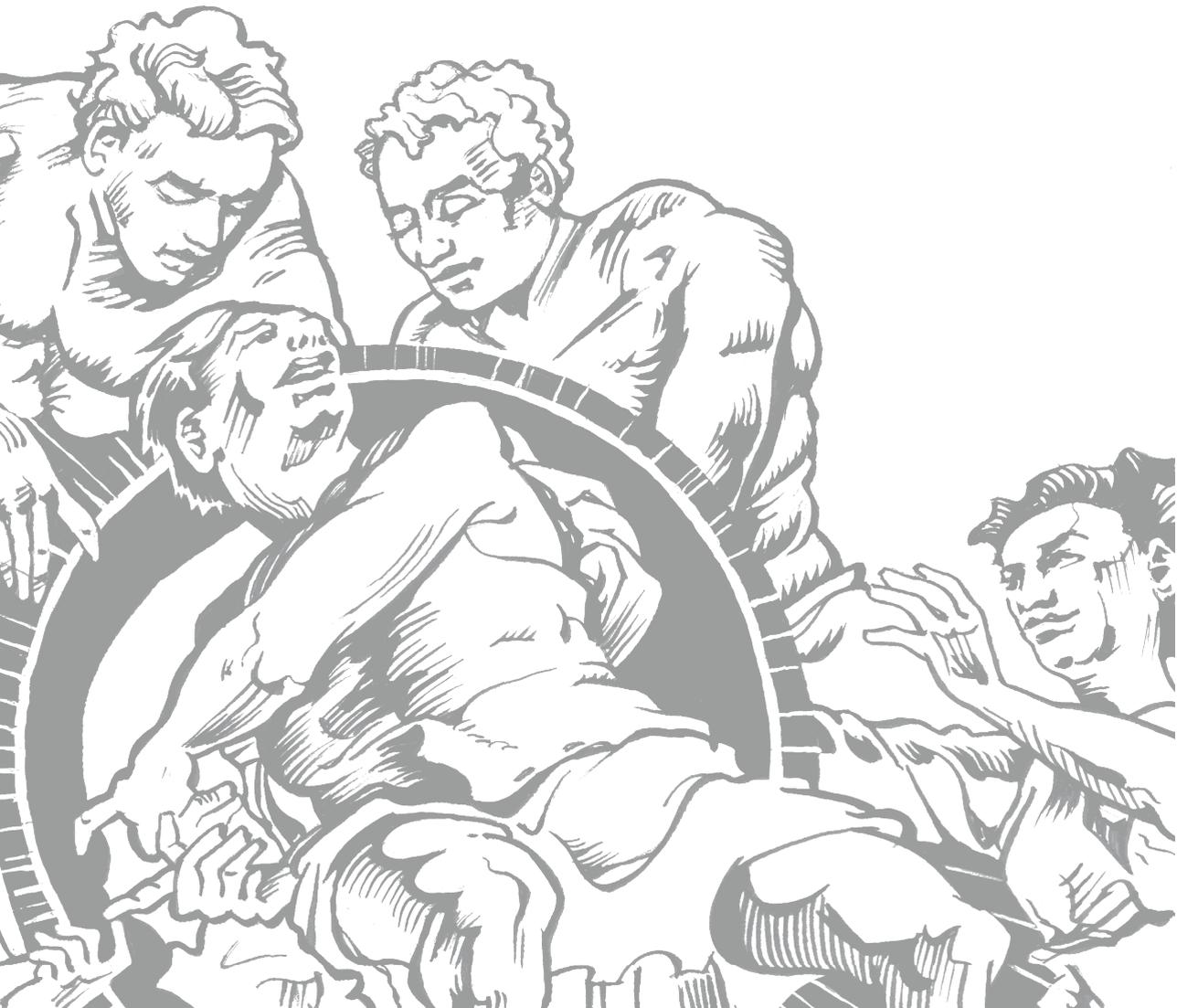
| Scan parameter | Transverse T2-weighted | Sagittal T2-weighted | DWI |
|--|------------------------|----------------------|-------------|
| Imaging plane | Transverse | Sagittal | Transverse |
| TR (ms) | 1454 | 1431 | 7503 |
| TE (ms) | 100 | 100 | 180 |
| Turbo factor | 39 | 22 | NA |
| Echo spacing (ms) | NA | NA | NA |
| Bandwidth (Hz/pixel) | 281 | 191 | 31.9 |
| B-value (s/mm ²) | NA | NA | 0, 200, 800 |
| NSA | 4 | 4 | 4,4,12 |
| Number of slices | 28 | 14 | 50 |
| FOV (mm) | 225x225 | 225x148 | 260x560 |
| Slice thickness (mm) | 4 | 3 | 4 |
| Voxel size (mm) | 0.67 | 0.70 | 3.25 |
| Acquisition time (min:sec) | 5:00 | 2:36 | 6:37 |
| Respiratory triggering using navigator | Yes | Yes | No |

DWI: diffusion-weighted imaging. FOV: field of view. NA: not applicable. NSA: number of signal averages. TE: echo time. TR: repetition time.

Supplementary Table 2 Diagnostic performance of ADC measurements

| | Diagnosing n on-pathCR vs. pathCR | | | Diagnosing poor vs. good response | | |
|-----------------|--|--------------------------------|------------------------------|--|--------------------------------|------------------------------|
| | Initial ADC | Δ ADC _{during} | Δ ADC _{post} | InitialADC | Δ ADC _{during} | Δ ADC _{post} |
| Cut-off value | $1.55 * 10^{-3} \text{ mm}^2/\text{s}$ | 29% | 40% | $1.63 * 10^{-3} \text{ mm}^2/\text{s}$ | 21% | 36% |
| AUC | 0.67 | 0.90 | 0.69 | 0.64 | 0.92 | 0.69 |
| Sensitivity (%) | 88 | 100 | 77 | 92 | 82 | 78 |
| Specificity (%) | 50 | 75 | 75 | 50 | 100 | 63 |
| Accuracy (%) | 80 | 95 | 77 | 63 | 89 | 71 |
| PPV (%) | 88 | 94 | 91 | 73 | 100 | 70 |
| NPV (%) | 50 | 100 | 50 | 80 | 80 | 71 |

ADC: apparent diffusion coefficient. AUC: area under the receiver operating characteristic (ROC) curve. NPV: negative predictive value. PPV: positive predictive value.



Chapter 12

Dynamic contrast-enhanced MRI for treatment response assessment in patients with esophageal cancer receiving neoadjuvant chemoradiotherapy

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ABSTRACT

PURPOSE

To explore and evaluate the potential value of dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) for the prediction of pathologic response to neoadjuvant chemoradiotherapy (nCRT) in esophageal cancer.

MATERIAL AND METHODS

Twenty-six patients underwent DCE-MRI before, during (week 2-3) and after nCRT, but before surgery (pre/per/post, respectively). Histopathologic tumor regression grade (TRG) was assessed after esophagectomy. Tumor area-under-the-concentration time curve (AUC), time-to-peak (TTP) and slope were calculated. The ability of these DCE-parameters to distinguish good responders (GR, TRG 1-2) from poor responders (noGR, TRG \geq 3), and pathologic complete responders (pCR) from no-pCR was assessed.

RESULTS

Twelve patients (48%) showed GR of which 8 patients (32%) pCR. Analysis of AUC change throughout treatment, $AUC_{\text{per-pre}}$, was most predictive for GR, at a threshold of 22.7% resulting in a sensitivity of 92%, specificity of 77%, PPV of 79%, and a NPV of 91%. $AUC_{\text{post-pre}}$ was most predictive for pCR, at a threshold of -24.6% resulting in a sensitivity of 83%, specificity of 88%, PPV of 71%, and a NPV of 93%. TTP and slope were not associated with pathologic response.

CONCLUSIONS

This study demonstrates that changes in AUC throughout treatment are promising for prediction of histopathologic response to nCRT for esophageal cancer.

INTRODUCTION

Worldwide, esophageal cancer is the eight most common cancer and the incidence rate is rapidly increasing¹. Esophageal cancer has a poor prognosis with 5-year overall survival rates ranging from 15 to 25%². Esophagectomy with en-bloc lymphadenectomy for patients with resectable non-metastatic disease results in 5-year survival rates of 34% to 36%^{3,4}. Neoadjuvant chemoradiotherapy (nCRT) increases these rates by approximately 13% as was consistently shown in recent trials and a meta-analysis^{3,5,6}. Therefore nCRT is currently considered as the standard treatment with curative intent for both adenocarcinomas (AC) and squamous cell carcinomas (SCC). However, not all patients benefit equally, as patient outcome depends heavily on the response to chemo(radio)therapy^{5,7,8}. In 29% of the patients pathologic complete response (pCR) to nCRT is found, with increased 5-year overall survival rates up to 48-65%^{3,7,9,10}.

With accurate response prediction before surgery the treatment strategy could potentially be improved. Depending on patient outcome, adaptive approaches could be explored such as an organ-preserving wait-and-see approach, modification of nCRT or termination of neoadjuvant therapy to initiate surgery sooner¹¹.

Endoscopic biopsy and/or ultrasonography and ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET) have been extensively studied for neoadjuvant treatment response assessment in esophageal cancer¹²⁻¹⁶. Unfortunately, these imaging modalities yield insufficient accuracies in the prediction of pathologic response^{17,18}. Among the studied modalities ¹⁸F-FDG PET seems the best so far. Two meta-analyses on treatment response monitoring, found that scans from the first two weeks of nCRT were most predictive for pathologic response, showing similar or superior diagnostic accuracy as opposed to pre- and post-treatment scanning only^{13,14,19}. Accordingly, investigators proposed that the second week might be optimal, because significant tumor regression can already be found in responders while the image interpretation may not yet be influenced by radiation esophagitis¹⁴. Overall pooled sensitivities and specificities were, however, still insufficient to justify changes in clinical decision-making with values ranging from 67% to 70%^{13,14}. Also non-image based methods using molecular biomarkers and clinical parameters have shown potential for response prediction²⁰⁻²².

Recently, diffusion-weighted magnetic resonance imaging (DW-MRI) was described as a potential method for treatment response monitoring and prediction in esophageal cancer^{18,23}. It was reported that the change in apparent diffusion coefficient (ADC) measured prior and during nCRT is predictive for response.

The reported sensitivity and specificity were higher than for the aforementioned methods, showing the potential of MRI-based techniques for early treatment response assessment and prediction.

Pilot studies on dynamic contrast-enhanced (DCE-)MRI demonstrated the feasibility for esophageal cancer imaging^{24,25}. However, the use of DCE-MRI to measure (early) response of esophageal tumors to nCRT with histopathology as reference standard has not previously been described. Therefore, the purpose of this study was to investigate the potential of nonparametric analysis of DCE-MRI for the (early) prediction of pathologic response to nCRT in patients with esophageal cancer. Since DCE-MRI visualizes different physiological properties (perfusion and vascular permeability in tumor microenvironment) compared to DW-MRI (diffusion in tissues), it could potentially provide complementary information beyond DW-MRI. In this exploratory study, not only pre- and post-treatment measurements were obtained, but also approximately two weeks after initiation of treatment, enabling comparison of the predictive potential of perfusion parameters at three different time points.

MATERIALS AND METHODS

STUDY POPULATION

This prospective study was approved by the local medical ethical committee and written informed consent was obtained from all patients. Patients with contraindications for MRI with contrast agent were not eligible for inclusion. Six patients who participated in the study but did not receive all three MRI scans due to patient's wish of discontinuation (n=5) or urgent non-elective surgery (n=1), were excluded. In addition, one patient was excluded due to a technical failure during MR acquisition. Twenty-six consecutive patients with biopsy-proven esophageal cancer who received nCRT followed by surgery, and completed all three MRI studies in our institutes (University Medical Center Utrecht [UMCU], n=19; and the Netherlands Cancer Institute [NKI], n=7) from August 2013 to January 2015, were included. One patient with severe pneumonia on the initial MRI, with an infiltrate adjacent to the tumor, was excluded for further analysis.

All patients received five weeks of neoadjuvant treatment, involving weekly intravenous administration of carboplatin (area under the curve of 2mg/mL per minute) and paclitaxel (50 mg/m² body-surface area) with concurrent radiotherapy (41.4 Gy in 23 fractions of 1.8 Gy)³. Five to ten weeks after completion of nCRT all patients underwent esophagectomy with en-bloc two-field lymphadenectomy

and gastric conduit reconstruction with cervical anastomosis. After resection, pathologic assessment of the resection specimen included determination of the tumor regression grade (TRG) according to Mandard, using an identical protocol in both institutes²⁶.

MRI ACQUISITION

MR images were acquired at the following three time points: prior to treatment (pre), after 8-13 fractions nCRT (per) and 3-9 weeks after completion of treatment, prior to surgery (post). All MR images were acquired with 1.5T systems Philips Achieva or Philips Ingenia (Best, the Netherlands), using the Torso coil (16 channel) or Anterior/Posterior (28 channel) receive coils, respectively. For anatomical verification, a T2-weighted scan was performed with a multi-slice turbo spin echo sequence (TR/TE = 1983/100ms, resolution = 0.67x0.67x4 mm³), using a navigator for respiratory triggering¹⁸. A DCE-MRI serie of 62 images was acquired using a three-dimensional spoiled gradient echo sequence (TR/TE = 3.43/1.53ms, flip angle = 20°, matrix size = 432x432x33, reconstructed image voxel size = 1.18x1.18x3 mm³), with a 3-second interval. After the 10th image, the contrast agent (CA) gadobutrol (Gd-BT-DO3A, Gadovist; Schering AG, Berlin, Germany) was injected at a dose of 0.1mmol/kg of body weight with an automatic syringe pump at a flow rate of 1ml/sec followed by saline injection. The scanned volume included the heart in order to prevent artefacts in the aorta due to pulsatile flow. In both institutes the same imaging protocol was used. However, at the NCI a different CA was used, Dotarem (Gadoteric acid, 0.5mM; Guerbet, Paris, France), with a fixed dose of 7.5mmol for each patient.

Prior to the dynamic series, five acquisitions for varying flip angles ($\alpha = 2^\circ/6^\circ/10^\circ/12^\circ/16^\circ$) with identical scanning properties were acquired for determination of pre-contrast T1 values. This flip angle series was chosen to be sensitive to a large range of tissue T1 values. Additionally, DW-MRI scans were acquired with b-values of 0, 200 and 800 s/mm² (STIR fat suppression, resolution = 3.5x3.5x4 mm³)¹⁸.

IMAGE PROCESSING

Delineation of the primary tumor on the T2-weighted scans was divided over two clinicians (P.S.N.v.R and I.M.L.). The delineation was adapted in the scans obtained during and after nCRT to account for tumor alterations. For definition of the cranio-caudal tumor length the DW-MRI with b=800 s/mm² was used. A radiation oncologist (O.R.), with over 10 years of experience, verified all delineations. To

account for breathing motion within the DCE-MRI series, scans were rigidly registered to a scan after contrast-enhancement, which led to the best retrospective motion compensation (**Supplementary Figure 1**)²⁷. Finally, the delineation was cropped with an isotropic margin of 2 mm to account for the conversion from T2-weighted scan to the DCE-MRI, residual motion and partial volume effects.

IMAGE ANALYSIS

In order to enable comparison of scans between different sessions in time, independent of MRI scaling settings, institute, MRI scanner or CA, the image intensity was converted to concentration. For this purpose, T1 pre-contrast relaxation times were calculated with in-house developed software using multiple flip angle sequences. Relaxivity values of 4.7 and 3.6 L mmol⁻¹ s⁻¹ for Gadovist and Dotarem, respectively, were used²⁸.

A nonparametric approach was chosen for the analysis of DCE-MRI throughout time, as studies in different tumor sites indicate that this approach has an increased prognostic ability compared to parametric measures²⁹. No analysis was performed per tumor subtype, as the subgroups of SCC and adenosquamous carcinoma (ASC) were too small. For analysis, the initial area-under-the-concentration versus time curve (AUC) was calculated (**Supplementary Figure 1**). The AUC reflects blood flow, vascular permeability and the fraction of interstitial space³⁰. In addition, it is a relatively straight-forward model-free parameter, which can provide information about tumor vascular changes. The time-to-peak (TTP) and slope of the concentration-time curve were mapped for each tumor, using a customized sigmoid-curve fitting method in Matlab (The Mathworks Inc, Natick, MA). To account for variations in the moment of contrast injection, the TTP was calculated with respect to the initial arterial CA increase, measured as the TTP in the artery (TTP_{aorta}) (**Supplementary Figure 1**).

The AUC was defined as the trapezoidal integral over the concentration-time curve over a period of 60 seconds after inflow of CA, based on TTP_{aorta}. Within the tumor delineation three percentiles, 25th (P25), median (P50) and 75th (P75), of the AUC were calculated. Additionally, relative differences between time points were calculated with respect to the first MRI scan session (pre):

$$AUC_{t-pre} = \frac{AUC_t - AUC_{pre}}{AUC_{pre}} \times 100\%, \quad (1)$$

with t the second or third scan session (per or post).

STATISTICAL ANALYSIS

This pilot study was of exploratory nature, therefore no formal sample size calculation has been performed. All statistical tests were performed using SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA). Two different approaches were chosen. First, a distinction was made between a group of pathologic good responders (GR), defined as pCR (TRG 1) or near-pCR (TRG 2), and a group of poor responders (noGR) with TRG 3 or higher²⁶. Second, analysis was performed on pCR (TRG 1) versus no-pCR (TRG \geq 2). For both approaches the Mann-Whitney U test was used to compare the various parameters derived from DCE-MRI between the groups (if not stated otherwise). A p-value of <0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was performed. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were estimated for an optimal threshold in which sensitivity and specificity were given equal weight. Correlation between AUC values and TRG scores were assessed by Spearman's rank correlation tests.

RESULTS

In the 25 patients included, assessment of the histopathologic tumor type revealed esophageal AC in 21 patients (84%), SCC in three patients (12%) and ASC in one patient (4%). Patient and tumor-related characteristics for both institutes are presented in **Table 1**. The pathology specimen showed a pathologic good response (i.e. TRG 1-2) to nCRT in 12 of 25 patients (48%), whereas the remaining 13 patients (52%) had a poor pathologic response (i.e. TRG \geq 3). Among the good responders, 8 patients (32%) showed a pCR (i.e. TRG 1), and 4 patients (16%) had a near-pCR (i.e. TRG 2).

The tumor showed a rapid initial contrast-enhancement followed by a plateau over the first minutes (**Figure 1**). The timing of the enhancement closely followed the first-pass peak as observed in the aorta. This reflects the direct vascular connection between the aorta and the esophageal tumor. Small variations in peak height of the arterial input function (AIF) between different time points occurred regularly (also visible in **Figure 1**). However, in three patients with noGR, of which two showed an $AUC_{\text{per-pre}} > 140\%$, an extreme increase was found in peak height in the second acquisition.

In general, the AUC maps showed a heterogeneous uptake within the delineated tumor (**Figure 1**). In three patients, the delineation in the post-treatment scan was too small in cranio-caudal direction to subtract the margin and were therefore excluded from the analysis of this time point.

Table 1 Patient and treatment-related characteristics

| | Study population UMCU | Study population NCI/AVL |
|------------------------------------|--------------------------|-----------------------------|
| Gender | | |
| Male | 17 (94%) | 6 (86%) |
| Female | 1 (5.5%) | 1 (14%) |
| Age, years (at start RT) | 65.1 ± 7.5 | 59.5 ± 13.4 |
| Clinical T-stage | | |
| T2 | 4 (22%) | 1 (14%) |
| T2-3 | 3 (17%) | 0 (0%) |
| T3 | 11 (61%) | 6 (86%) |
| Clinical N-stage | | |
| N0 | 6 (33%) | 4 (57%) |
| N1 | 3 (17%) | 2 (29%) |
| N2 | 8 (44%) | 1 (14%) |
| N3 | 1 (5.5%) | 0 (0%) |
| Type | | |
| SCC | 1 (5.5%) | 2 (29%) |
| AC | 16 (89%) | 5 (71%) |
| ASC | 1 (5.5%) | 0 (0%) |
| Location | | |
| Middle third of esophagus | 1 (5.5%) | 1 (14%) |
| Distal third of esophagus | 13 (72%) | 3 (43%) |
| Gastroesophageal junction | 4 (22%) | 3 (43%) |
| Acquisition, number of days | | |
| Before (before start nCRT) | 5.7 ± 2.9 | 4.4 ± 3.6 |
| During (after start nCRT) | 11.3 ± 2.6 | 12.9 ± 3.0 |
| After (after completion nCRT) | 38.7 ± 13.7 | 46.3 ± 10.2 |

AC: adenocarcinoma. ASC: adenosquamous carcinoma. SCC: squamous cell carcinoma.

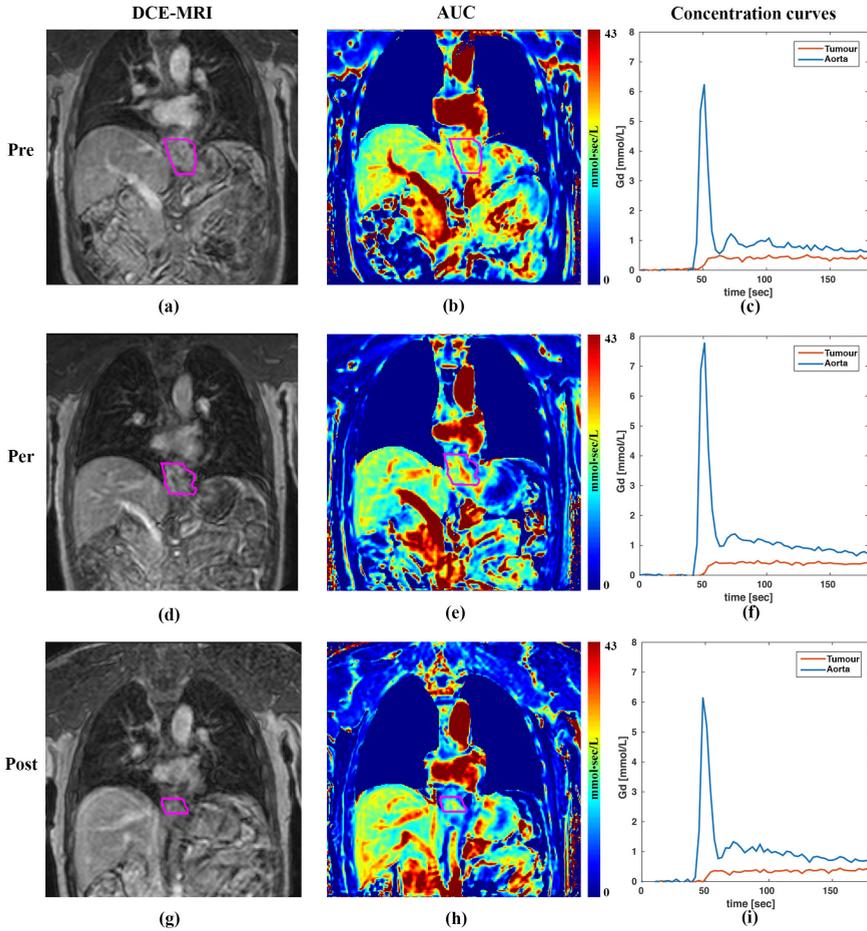


Figure 1 (a) Coronal view of DCE-MRI (after contrast agent injection) of a pathologic complete responder before treatment (pre) with the tumor contour in pink. (b) Corresponding AUC map (60 seconds after contrast inflow). (d,e) Corresponding images after two weeks of nCRT (i.e. during treatment), showing a reduction in tumor AUC values during treatment. (g,h) Corresponding images after treatment, showing further reduction in AUC values along with a decrease in volume. (c,f,i) Corresponding concentration time curves measured in a slice in the aorta and tumor, for pre-, per- and post-treatment scans, respectively.

The association of the measured DCE-MRI parameters with GR versus noGR are presented in **Table 2**. Regarding the analysis of the AUC values for single time points, only the initial scan showed significant differences. The AUC values for all patients at all time points are shown in **Figure 2**. The P25 AUC_{pre} was most significant, showing higher AUC in GR compared to noGR. The TTP and slope were not associated with response. The analysis of changes during treatment, showed in several noGRs an initial increase in AUC after 2 weeks of treatment followed by a decrease, while this was less apparent for GRs (**Figure 2**). Comparing the relative changes with respect to the initial scan session, for GR versus noGR, P75 AUC_{per-pre} was found to be most significant showing higher AUC for noGR (**Table 2, Figure 3a**). The parameters determined at the final scan session before surgery were found to be less associated with pathologic response. The optimal

Table 2 Association between (changes in) DCE-MRI parameters and pathologic good response (GR) versus poor response (noGR)

| | | Time | GR (n=12) | noGR (n=13) | p-value | AUC-ROC | |
|-------------|------------------------------|--|---------------|--------------|-------------|---------|------|
| AUC | P25 [mmol L ⁻¹ s] | Pre | 20.6 ± 5.4 | 16.8 ± 4.8 | 0.03 | 0.76 | |
| | | Per | 21.2 ± 4.6 | 22.0 ± 7.3 | 1.00 | 0.50 | |
| | | Post | 14.3 ± 6.6* | 16.7 ± 7.1 | 0.70 | 0.56 | |
| | ΔMedian (%) | Per-Pre | 4.3 ± 16.3 | 41.0 ± 54.0 | 0.02 | 0.78 | |
| | | Post-Pre | -30.8 ± 34.6* | 2.0 ± 26.0 | 0.05 | 0.75 | |
| | ΔP75 (%) | Per-Pre | 4.9 ± 20.1 | 46.7 ± 55.5 | 0.01 | 0.80 | |
| | | Post-Pre | -37.1 ± 41.8* | 4.0 ± 32.5 | 0.03 | 0.78 | |
| | ΔP25 (%) | Per-Pre | 5.3 ± 17.5 | 36.8 ± 50.7 | 0.08 | 0.71 | |
| | | Post-Pre | -26.0 ± 30.8* | -0.09 ± 20.8 | 0.05 | 0.75 | |
| | Slope | Median [mmol L ⁻¹ s ⁻¹] | Pre | 0.18 ± 0.07 | 0.13 ± 0.08 | 0.09 | 0.71 |
| | | | Per | 0.15 ± 0.06 | 0.17 ± 0.14 | 0.69 | 0.55 |
| | | | Post | 0.09 ± 0.05* | 0.10 ± 0.09 | 0.90 | 0.52 |
| ΔMedian (%) | | Per-Pre | -11.2 ± 38.8 | 34.4 ± 75.1 | 0.12 | 0.69 | |
| | | Post-Pre | -56.3 ± 25.0* | 3.7 ± 80.7 | 0.11 | 0.71 | |
| TTP | | Median [sec] | Pre | 7.8 ± 8.0 | 9.3 ± 5.9 | 0.43 | 0.60 |
| | Per | | 9.3 ± 5.2 | 12.4 ± 9.9 | 0.69 | 0.55 | |
| | Post | | 15.9 ± 13.5* | 17.6 ± 15.5 | 0.79 | 0.53 | |
| | ΔMedian (%) | Per-Pre | 76.0 ± 160.5 | 30.6 ± 65.0 | 0.77 | 0.54 | |
| | | Post-Pre | 239 ± 330* | 416 ± 1042 | 0.13 | 0.70 | |

Note. Data are presented as mean ± SD. For single time point AUC values, only highest significant parameters are presented. Significant p-values (<0.05) are indicated in bold. *n=9 (instead of n=12) for post-treatment scans due to the exclusion of 3 patients as explained in the results.

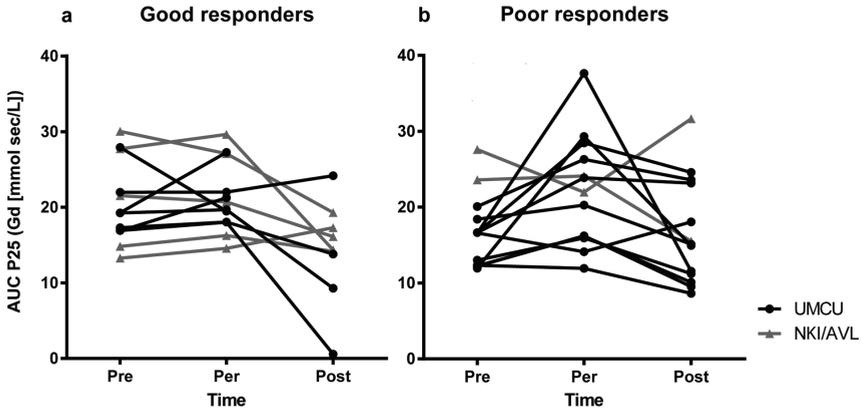


Figure 2 Course of P25 AUC values over time for (a) pathologic good responders and (b) pathologic poor responders. Every line represents a patient, with patients from the UMCU indicated by black circles and patients from the NKI/AVL by grey triangles. In case the delineation was too small the time point was excluded (3 post-treatment scans).

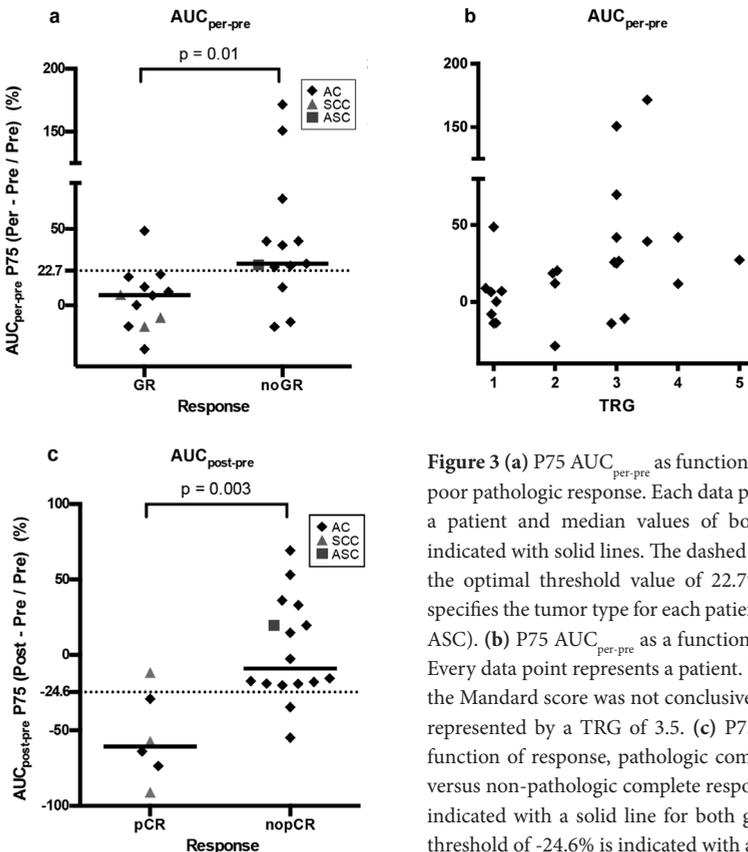


Figure 3 (a) P75 $AUC_{per-pre}$ as function of good versus poor pathologic response. Each data point represents a patient and median values of both groups are indicated with solid lines. The dashed line represents the optimal threshold value of 22.7%. The legend specifies the tumor type for each patient (AC, SCC or ASC). (b) P75 $AUC_{per-pre}$ as a function of TRG score. Every data point represents a patient. In two patients the Mandard score was not conclusive (TRG 3 or 4), represented by a TRG of 3.5. (c) P75 $AUC_{post-pre}$ as function of response, pathologic complete response versus non-pathologic complete response. Median is indicated with a solid line for both groups and the threshold of -24.6% is indicated with a dashed line.

threshold for P75 $AUC_{\text{per-pre}}$ was determined at 22.7%, yielding a sensitivity of 92%, specificity of 77%, PPV of 79% and a NPV of 91%. Comparing P75 $AUC_{\text{per-pre}}$ as a function of the separate TRG scores, a moderate positive correlation was found (Spearman's rank order $\rho=0.53$; $p=0.006$) (**Figure 3b**).

Focusing on the previous significant parameters in the analysis of pCR versus no-pCR changes throughout treatment, several parameters also showed significant difference. The associations of these parameters are presented in **Table 3**. The P75 $AUC_{\text{post-pre}}$ was found to be most predictive showing lower AUC for pCR compared to no-pCR (**Figure 3c**). The optimal threshold of -24.6% yielded a sensitivity of 83%, specificity of 88%, PPV of 71% and a NPV of 93%. The P75 $AUC_{\text{per-pre}}$ was also found to be significant, for an optimal threshold of 10.3%, a sensitivity of 88%, specificity of 82%, PPV of 70% and a NPV of 93% was reached. No significant differences were found in the TTP and slope, as well as in the analysis of single time point AUC.

Table 3 Association between (changes in) DCE-MRI parameters and pathologic complete response (pCR) versus no pathologic complete response (no-pCR)

| | | Time | pCR (n=8) | no-pCR (n=17) | p-value | AUC-ROC |
|-----|---------------------|----------|-------------------|-------------------|-----------------|---------|
| AUC | Δ Median (%) | Per-Pre | 6.3 \pm 15.4 | 31.4 \pm 50.8 | 0.14 | 0.69 |
| | | Post-Pre | -42.6 \pm 26.1* | 0.3 \pm 28.2** | 0.01 | 0.84 |
| | Δ P75 (%) | Per-Pre | 4.5 \pm 20.1 | 37.1 \pm 52.3 | 0.04 | 0.76 |
| | | Post-Pre | -54.4 \pm 29.2* | 2.8 \pm 33.7** | <0.01 | 0.90 |
| | Δ P25 (%) | Per-Pre | 10.2 \pm 16.4 | 27.1 \pm 48.1 | 0.59 | 0.57 |
| | | Post-Pre | -36.3 \pm 26.5* | -1.1 \pm 22.3** | 0.01 | 0.85 |

Note. Data are presented as mean \pm SD. No significant differences were found in the TTP and slope, as well as in the analysis of single time point AUC, therefore this data points are not presented. Significant p-values (<0.05) are indicated in bold. *n=6 (instead of n=8) for post-treatment scans due to the exclusion of 2 patients as explained in the results. **n=16 (instead of n=17) for post-treatment scans due to the exclusion of 1 patient as explained in the results.

DISCUSSION

This prospective study demonstrates the potential of DCE-MRI for treatment response assessment and prediction to nCRT for patients with esophageal cancer. The change during treatment in P75 $AUC_{\text{per-pre}}$ was significantly different between GR and noGR with good diagnostic performance. This is particularly promising for future considerations regarding early modification or discontinuation of nCRT in

anticipated noGRs. Additionally, the change in $P75 AUC_{\text{post-pre}}$ differed significantly between pCR and no-pCR, which could potentially aid in the clinical decision-making regarding the omission of surgery.

This is the first report on (early) response assessment measured by DCE-MRI with pathologic reference in esophageal cancer. In a previous study, a significant change in DCE-MRI parameters was observed in 12 patients with SCC of the esophagus²⁵. However, this feasibility study only performed a limited analysis (before vs. after treatment, single slice analysis, no comparison with pathologic response was given) compared to our study.

The initial scan session showed predictive value for treatment outcome. However, acquiring a second scan after 2 weeks of nCRT added additional diagnostic value compared to pre- and post-treatment scanning only, resulting in higher predictive values. The finding that the change in tumor parameters early during nCRT is predictive for the pathologic outcome in terms of response, is in line with a previous study performed by our group using DW-MRI¹⁸ as well as in other tumor sites using DCE-MRI^{31,32}. The large range in the timing of acquisition of the last scan, together with the fact that tumor delineations after chemoradiotherapy can be challenging, might have influenced the predictive values of the post-treatment scan to an unknown extent. The influence of this variability deserves attention in further studies.

For future studies on therapy adaptation, based on MRI response monitoring, it is advantageous that response can be measured early, on which adaptation could potentially be made in the first stages of neoadjuvant treatment. Furthermore, the scan prior to surgery showed diagnostic value in differentiation between patients with pCR and no-pCR, which could potentially be used in addition to the early differentiation between good and poor response. Equal weight was given to both sensitivity and specificity, but depending on the purpose of the analysis (e.g. changing therapy, omitting surgery) this weight could be varied.

In literature conflicting reports are found with respect to patient outcome and TRG 1 or 2. In terms of 5-year survival rates, some studies report statistically significant differences between patients with TRG 1 versus $TRG \geq 2$ ^{7,9,33}, while in another study survival curves were found to be similar³⁴. At this moment, it is debatable if the presented separation based on DCE-MRI between pCR/ $TRG \geq 2$ or GR/noGR is sufficiently strong to support the decision to omit surgery. Therefore, the use of DCE-MRI (together with other imaging modalities) for treatment adaptations is subject of our ongoing research. In addition to studying the complementary

values of DW-MRI and DCE-MRI, it will become increasingly important to study the complementary values of clinical parameters, other imaging modalities (e.g. ^{18}F -FDG PET), and molecular biomarkers²⁰⁻²². In this light it is promising that in rectal cancer omission of surgery or delayed resection in selected patient groups did not increase the risk of recurrent disease or affect survival compared to immediate surgery^{35,36}.

The tumor contrast uptake curve pattern observed in this study resembles the curve described by Chang et al²⁴, although the AIF differs. The observed AIF, showing a rapid in- and outflow of contrast, is more in line with the standard AIF as reported by Parker et al³⁷. To our knowledge, the trend showing lower $\text{AUC}_{\text{per-pre}}$ values for GR as opposed to noGR has not been reported previously for esophageal cancer. In a review by Li et al³⁸, summarizing various tumor sites, it was found that chemotherapy responders showed a drop in AUC, while radiotherapy responders showed an initial increase in AUC in the first 1-2 weeks, followed by an AUC drop.

In this study a nonparametric approach was chosen, as it is not sensitive to errors arising from inaccurate determination of the AIF. Parametric approaches can be prone to errors due to uncertainty in input parameters, more complex fitting methods and lower reproducibility^{29,38-40}. On the other hand, Roberts et al³⁹ suggested that the reproducibility of AUC and K^{trans} were similar, and therefore the parametric measure may be superior providing greater physiologic insights. In future studies we intend to acquire multiple baseline acquisitions to gain more insight into the true variations and reproducibility of the AIF, to judge whether the use of a parametric model is justified.

As aforementioned, the AUC reflects blood flow and vascular permeability, which is increased in tumor tissue. The fact that P75 AUC resulted in superior predictive values could indicate that it is more sensitive to active (i.e. better perfused or more permeable) areas within the tumor. This could implicate that the delineated tumor is heterogeneous, and thus includes less active regions. In future research we intend to research the possibilities for voxel-based analysis of DCE-MRI.

Some limitations apply to this study. First, the small sample size of this exploratory study may have caused both over- and underestimation of the true predictive values. Therefore, our conclusions require validation in a larger patient cohort. Second, a possible sensitivity of the AUC for the peak height of the AIF was found, which will be investigated by determining the reproducibility of DCE-MRI. This will also give further insight into the robustness of the method. Next, to compensate for organ motion due to respiration, we adopted a retrospective registration strategy. This

improved geometrical overlap between consecutive scans. However, minor motion artefacts were visible in the individual scans. Strategies to compensate for motion prospectively are therefore expected to improve overall quality.

In conclusion, our study showed that analysis of DCE-MRI has potential for treatment response assessment and prediction in patients with esophageal cancer undergoing chemoradiotherapy. Changes in AUC within the tumor throughout the first two to three weeks of treatment were found to differ significantly between good and poor responders potentially allowing for early prediction of treatment response. In addition, the change in AUC prior to surgery was found to differ significantly between pathologic complete responders and non-pathologic complete responders.

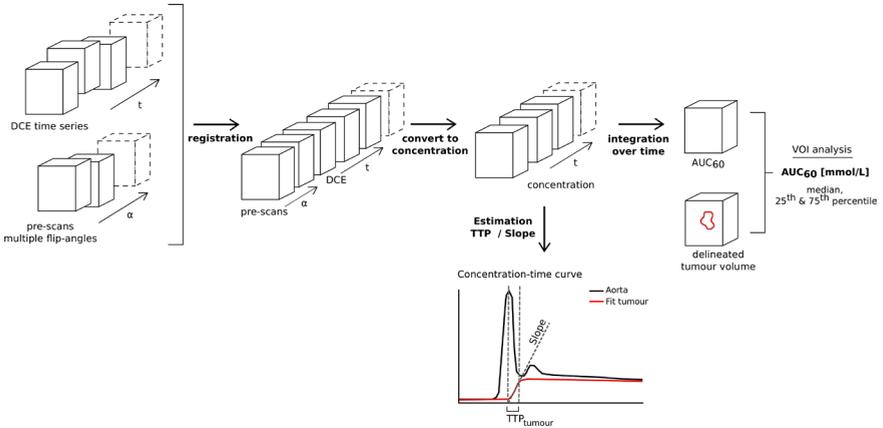
REFERENCES

1. Torre LA, Bray F, Siegel RL, et al. Global Cancer Statistics, 2012. *CA Cancer J Clin* 2015;65:87-108
2. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. *Lancet* 2013;381:400-12
3. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
4. Omloo JM, Lagarde SM, Hulscher JB, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. *Ann Surg* 246:992-1001
5. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011;12:681-92
6. Shapiro J, van Lanschot JJ, Hulshof MC, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): Long-term results of a randomised controlled trial. *Lancet Oncol* 2015;16:1090-8
7. Donahue JM, Nichols FC, Li Z, et al. Complete pathologic response after neoadjuvant chemoradiotherapy for esophageal cancer is associated with enhanced survival. *Ann Thorac Surg* 2009;87:392-9
8. Allum WH, Stenning SP, Bancewicz J, et al. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol* 2009;27:5062-7
9. Chirieac LR, Swisher SG, Ajani JA, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. *Cancer* 2005;103:1347-55
10. Berger AC, Farma J, Scott WJ, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. *J Clin Oncol* 2005;23:4330-7
11. Blazeby JM, Sanford E, Falk SJ, et al. Health-related quality of life during neoadjuvant treatment and surgery for localized esophageal carcinoma. *Cancer* 2005;103:1791-9
12. Brücher BL, Weber W, Bauer M, et al. Neoadjuvant therapy of esophageal squamous cell carcinoma : response evaluation by positron emission tomography. *Ann Surg* 2001;233:300-9
13. Kwee R. Prediction of tumor response to neoadjuvant therapy in patients with esophageal cancer with use of ¹⁸F FDG PET: a systematic review. *Radiology* 2010;254:707-17
14. Chen Y, Pan X, Tong L, et al. Can ¹⁸F-fluorodeoxyglucose positron emission tomography predict responses to neoadjuvant therapy in oesophageal cancer patients? A meta-analysis. *Nucl Med Commun* 2011;32:1005-10
15. Schneider PM, Metzger R, Schaefer H, et al. Response evaluation by endoscopy, rebiopsy, and endoscopic ultrasound does not accurately predict histopathologic regression after neoadjuvant chemoradiation for esophageal cancer. *Ann Surg* 2008;248:902-8

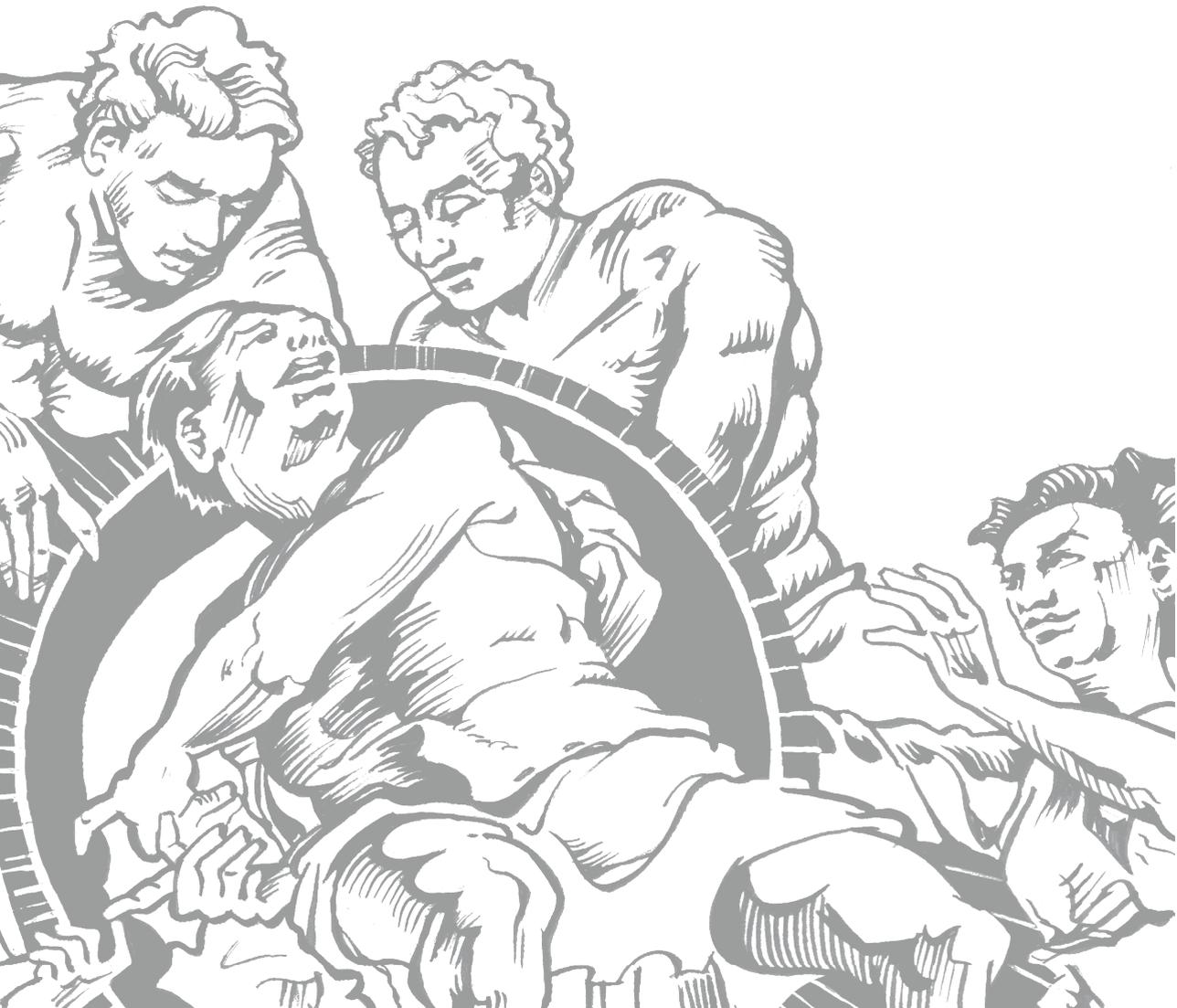
16. Ajani JA, Correa AM, Hofstetter WL, et al. Clinical parameters model for predicting pathologic complete response following preoperative chemoradiation in patients with esophageal cancer. *Ann Oncol* 2012;23:2638–42
17. van Rossum PS, van Hillegersberg R, Lever FM, et al. Imaging strategies in the management of oesophageal cancer: what's the role of MRI? *Eur Radiol* 2013;23:1753–65
18. van Rossum PS, van Lier AL, van Vulpen M, et al. Diffusion-weighted magnetic resonance imaging for the prediction of pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer. *Radiother Oncol* 2015;115:163–70
19. Wieder HA, Ott K, Lordick F, et al. Prediction of tumor response by FDG-PET: comparison of the accuracy of single and sequential studies in patients with adenocarcinomas of the esophagogastric junction. *Eur J Nucl Med Mol Imaging* 2007;34:1925–32
20. Toxopeus ELA, Nieboer D, Shapiro J, et al. Nomogram for predicting pathologically complete response after neoadjuvant chemoradiotherapy for oesophageal cancer. *Radiother Oncol* 2015;115:392–8
21. Honing J, Pavlov KV, Mul VE, et al. CD44, SHH and SOX2 as novel biomarkers in esophageal cancer patients treated with neoadjuvant chemoradiotherapy. *Radiother Oncol* 2015;117:152–8
22. van Olphen SH, Biermann K, Shapiro J, et al. P53 and SOX2 protein expression predicts esophageal adenocarcinoma in response to neoadjuvant chemoradiotherapy. *Ann Surg* 2016 [Epub ahead of print]
23. Imanishi S, Shuto K, Aoyagi T, et al. Diffusion-weighted magnetic resonance imaging for predicting and detecting the early response to chemoradiotherapy of advanced esophageal squamous cell carcinoma. *Dig Surg* 2013;30:240–8
24. Chang EY, Li X, Jerosch-Herold M, et al. The evaluation of esophageal adenocarcinoma using dynamic contrast-enhanced magnetic resonance imaging. *J Gastrointest Surg* 2008;12:166–75
25. Oberholzer K, Pohlmann A, Schreiber W, et al. Assessment of tumor microcirculation with dynamic contrast-enhanced MRI in patients with esophageal cancer: Initial experience. *J Magn Reson Imaging* 2008;27:1296–1301
26. Mandard A, Dalibard F, Mandard J. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer* 1994;73:2680–6
27. Heethuis SE, van Rossum PS, Lips IM, et al. Comparison of image registration strategies to improve DCE-MRI uptake curves in esophageal cancer. 56th Annual Meeting AAPM 2014, Austin, Texas, US. WE-G-18C-4
28. Kanal E, Maravilla K, Rowley HA. Gadolinium contrast agents for CNS imaging: current concepts and clinical evidence. *Am J Neuroradiol* 2014;35:2215–26
29. Joo I, Lee JM, Han JK, et al. Dynamic contrast-enhanced MRI of gastric cancer: correlation of the perfusion parameters with pathological prognostic factors. *J Magn Reson Imaging* 2015;41:1608–14

30. Evelhoch JL, LoRusso PM, He Z, et al. Magnetic resonance imaging measurements of the response of murine and human tumors to the vascular-targeting agent ZD6126. *Clin Cancer Res* 2004;10:3650–7
31. Yuh WTC, Mayr NA, Jarjoura D, et al. Predicting control of primary tumor and survival by DCE MRI during early therapy in cervical cancer. *Invest Radiol* 2009;44:343–50
32. Li X, Arlinghaus LR, Ayers GD, et al. DCE-MRI analysis methods for predicting the response of breast cancer to neoadjuvant chemotherapy: pilot study findings. *Magn Reson Med* 2013;71:1592–602
33. Hermann RM, Horstmann O, Haller F, et al. Histomorphological tumor regression grading of esophageal carcinoma after neoadjuvant radiochemotherapy: which score to use? *Dis Esophagus* 2006;19:329–34
34. Vincent J, Mariette C, Pezet D, et al. Early surgery for failure after chemoradiation in operable thoracic oesophageal cancer. Analysis of the non-randomised patients in FFCD 9102 phase III trial: Chemoradiation followed by surgery versus chemoradiation alone. *Eur J Cancer* 2015;51:1683–93
35. Habr-Gama A, Perez RO, Proscurshim I, et al. Interval between surgery and neoadjuvant chemoradiation therapy for distal rectal cancer: does delayed surgery have an impact on outcome? *Int J Radiat Oncol Biol Phys* 2008;71:1181–8
36. Habr-Gama A, Perez RO, Proscurshim I, et al. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. *J Gastrointest Surg* 2006;10:1319–29
37. Parker GJ, Roberts C, Macdonald A, et al. Experimentally-derived functional form for a population-averaged high-temporal-resolution arterial input function for dynamic contrast-enhanced MRI. *Magn Reson Med* 2006;56:993–1000
38. Li SP, Padhani AR. Tumor response assessments with diffusion and perfusion MRI. *J Magn Reson Imaging* 2012;35:745–63
39. Roberts C, Issa B, Stone A, et al. Comparative study into the robustness of compartmental modeling and model-free analysis in DCE-MRI studies. *J Magn Reson Imaging* 2006;23:554–63
40. Huang W, Li X, Chen Y, et al. Variations of dynamic contrast-enhanced magnetic resonance imaging in evaluation of breast cancer therapy response: a multicenter data analysis challenge. *Transl Oncol* 2014;7:153–66

SUPPLEMENTARY DATA



Supplementary Figure 1 Flowchart of the registration and calculation of the concentration in the DCE-MRI time series. First, rigid registration is performed on the DCE-series as well as on the pre-treatment scans. Second, image intensities are converted to contrast agent concentration values. For analysis, the AUC over 60 seconds is calculated voxelwise, in which tumor median, 25th and 75th percentiles are estimated. TTP and slope are estimated using the concentration-time curves per voxel.



Chapter 13

The value of ^{18}F -FDG PET before and after induction chemotherapy for the early prediction of a poor pathologic response to subsequent preoperative chemoradiotherapy in esophageal adenocarcinoma

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European Journal of Nuclear Medicine and Molecular Imaging 2016 [In press]

ABSTRACT

PURPOSE

To determine the value of ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET) before and after induction chemotherapy in patients with esophageal adenocarcinoma for the early prediction of a poor pathologic response to subsequent preoperative chemoradiotherapy (CRT).

MATERIALS AND METHODS

In 70 consecutive patients receiving a three-step treatment strategy of induction chemotherapy and preoperative chemoradiotherapy followed by surgery for esophageal adenocarcinoma, ^{18}F -FDG PET scans were performed before and after induction chemotherapy (before preoperative CRT). Tumor maximum and mean standardized uptake values (SUV_{max} and SUV_{mean}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were determined at these two time points. The predictive potential of (the change in) these parameters for a poor pathologic response and for progression-free and overall survival was assessed.

RESULTS

A poor pathologic response after induction chemotherapy and preoperative CRT was found in 27 (39%) of 70 patients. Patients with a poor pathologic response experienced less of a reduction in TLG after induction chemotherapy ($p < 0.01$). The change in TLG was predictive for a poor pathologic response at a threshold of -26% (sensitivity 67%, specificity 84%, accuracy 77%, PPV 72%, NPV 80%), yielding an area-under-the-curve of 0.74 in ROC analysis. Also, patients with a decrease in TLG lower than 26% had a significantly worse progression-free survival ($p = 0.02$), but not overall survival ($p = 0.18$).

CONCLUSION

^{18}F -FDG PET appears useful to predict a poor pathologic response as well as progression-free survival early after induction chemotherapy in patients with esophageal adenocarcinoma undergoing a three-step treatment strategy. As such, the early ^{18}F -FDG PET response after induction chemotherapy has the potential to aid in individualizing treatment by modification or withdrawal of subsequent preoperative CRT in poor responders.

INTRODUCTION

The long-term survival of patients with locoregionally advanced esophageal cancer remains quite poor despite considerable advances in surgery, radiotherapy, and chemotherapy, with 5-year survival rates still below 50%^{1,2}. Multimodality treatment strategies have been implemented in an effort to improve the outcome achieved with surgery alone³. Since early studies showed that adjuvant therapy did not improve outcomes^{4,7}, contemporary research mainly focused on neoadjuvant strategies which resulted in improved resection rates, pathologic downstaging, and a reduction in disease recurrences³. As a result, preoperative concurrent chemoradiotherapy (CRT) followed by esophagectomy is commonly applied in clinical practice⁸.

An important observation in patients treated with trimodality therapy (i.e. preoperative CRT followed by esophagectomy) is that the most common pattern of treatment failure is now distant progression^{8,9}. In an attempt to eliminate micrometastases and thereby improve the distant failure rate and overall outcome, additional induction chemotherapy before trimodality therapy has been investigated in the United States and Europe, as well as in Asia¹⁰⁻²⁹. Results of comparative studies have been inconclusive with some studies reporting a benefit of induction chemotherapy^{15,16}, while others were equivocal^{27,29}. Nonetheless, induction chemotherapy is thought to have a number of potential advantages including improvement of swallowing/nutritional status and obviating the need for feeding tubes in patients presenting with dysphagia^{11,12,14,18,19,22,24}. More importantly, it has been suggested that the use of induction chemotherapy may permit early identification of poorly responding patients in whom neoadjuvant treatment is ineffective or even harmful^{24,30-32}.

¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET) is a well-established imaging modality for initial staging and re-staging after preoperative CRT for the detection of distant (interval) metastases³³⁻³⁷. ¹⁸F-FDG PET has been shown to be more accurate than other modalities in predicting pathologic response to neoadjuvant chemotherapy or CRT for esophageal cancer^{38,39}. However, current evidence is limited with regard to the value of ¹⁸F-FDG PET for response prediction in the setting of a three-step strategy of induction chemotherapy and preoperative CRT followed by esophagectomy. Therefore, the aim of this study was to determine the value of ¹⁸F-FDG PET scanning at baseline and after induction chemotherapy for the early prediction of a poor versus good pathologic response (i.e. >10% versus ≤10% residual carcinoma) to subsequent preoperative CRT.

MATERIAL AND METHODS

This retrospective study has been approved by our Institutional Review Board, and the need for written informed consent was waived. The study was conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and the checklist from the STAndards for the Reporting of Diagnostic accuracy studies (STARD) statement (<http://www.stard-statement.org>)⁴⁰.

STUDY POPULATION

From a prospectively acquired database, we extracted all consecutive patients with a biopsy-proven potentially resectable adenocarcinoma of the esophagus or gastro-esophageal junction and no distant metastases that underwent a three-step treatment strategy of induction chemotherapy and preoperative chemoradiotherapy followed by surgery at MD Anderson Cancer Center from March 2006 to February 2013. Patients were excluded if one of two ¹⁸F-FDG PET scans of interest were either not available or acquired at another institution. Also, non-FDG-avid tumors at baseline, Siewert type 3 gastro-esophageal junction tumors, and patients with a stent in-situ at the time of scanning were excluded. Finally, patients with a time interval between completion of preoperative chemoradiation and surgery of less than 5 weeks or more than 14 weeks - indicating urgent and salvage resections, respectively - were excluded.

TREATMENT REGIMEN

All patients were treated by induction chemotherapy and subsequent external beam radiation with concurrent chemotherapy. The backbone of induction chemotherapy generally consisted of a fluoropyrimidine (intravenous 5-FU or oral capecitabine) and oxaliplatin, with the addition of either leucovorin (54% of cases) or docetaxel (37% of cases)^{17,27}. Other (sporadic) induction chemotherapy regimens included carboplatin/paclitaxel (3%), cisplatin/paclitaxel (1.5%), cisplatin/irinotecan (1.5%), 5-FU monotherapy (1.5%) and capecitabine/oxaliplatin/epirubicin (1.5%). Radiation therapy consisted of a total radiation dose of 45.0 Gy (4%) or 50.4 Gy (96%) delivered in daily fractions of 1.8 Gy using intensity modulated radiation therapy (IMRT; 69%) or proton therapy (31%). The chemotherapy concurrently administered with radiation generally consisted of a fluoropyrimidine (intravenous or oral) with either a platinum compound (69%) or docetaxel (17%). Other (sporadic) concurrent chemotherapy regimens included carboplatin/paclitaxel (3%), 5-FU/paclitaxel (3%), 5-FU/oxaliplatin/docetaxel (3%), oxaliplatin/docetaxel/irinotecan (3%), oxaliplatin/docetaxel

(1%), and cisplatin/irinotecan (1%). After completion of chemoradiation, either a transthoracic (Ivor-Lewis), transhiatal, total (three-field technique), or minimally invasive esophagectomy was performed with curative intent at the discretion of the treating surgeon.

HISTOPATHOLOGIC ASSESSMENT

Histopathologic examination of the resected specimen was standardized in accordance with the seventh edition of the American Joint Committee on Cancer protocol for TNM-classification⁴¹. The degree of pathologic response to neoadjuvant treatment was graded as follows⁴²: complete absence of residual cancer (tumor regression grade [TRG] 1), 1-10% residual carcinoma (TRG 2), 11-50% residual carcinoma (TRG 3), and >50% residual carcinoma (TRG 4). A poor pathologic response (defined as TRG 3-4) as opposed to a good pathologic response (defined as TRG 1-2) was considered the reference standard of this study.

IMAGE ACQUISITION

¹⁸F-FDG PET/computed tomography (CT) scans were performed on an integrated PET/CT system (Discovery RX, ST, or STE; GE Medical Systems, Milwaukee [WI], USA). Before ¹⁸F-FDG PET, a CT scan was acquired (120 kV peaks, 300 mA, 0.5 seconds rotation, pitch of 1.375, slice thickness 3.75 mm, and slice interval 3.27 mm) for attenuation correction purposes. ¹⁸F-FDG PET scans were acquired 60-90 minutes after administration of ¹⁸F FDG with a dose of 555-740 MBq, in either two-dimensional (2D) or three-dimensional (3D) acquisition mode at 3-5 minutes per bed position. Images were reconstructed using ordered-subset expectation maximization in 2D or iterative reconstruction in 3D images. All analyses were performed on the attenuation-corrected images.

IMAGE ANALYSIS

The primary tumor was defined as the volume of interest (VOI) and delineated on the ¹⁸F-FDG PET scans using a semi-automatic gradient-based delineation method from commercially available software (MIM Software, Cleveland [OH], USA). This contouring method has recently been validated in a multi-observer study that showed superiority over manual and threshold methods⁴³. The following quantitative features were extracted from the VOIs of the ¹⁸F-FDG PET scans at baseline and after induction chemotherapy (before preoperative CRT): maximum and mean standardized uptake value (SUV_{max} and SUV_{mean}), metabolic tumor volume (MTV) and total lesion glycolysis (TLG). The MTV was automatically

calculated by the software by summing up the areas within each two-dimensional transverse tumor contour multiplied by the corresponding slice thickness. The TLG was calculated by multiplying MTV by SUV_{mean}^{44} . In addition, the relative changes (in %) of these parameters between ^{18}F -FDG PET at baseline and ^{18}F -FDG PET after induction chemotherapy were calculated and included in the analysis.

STATISTICAL ANALYSIS

First, the association between clinical parameters and poor versus good pathologic response was studied using the chi-square test (or Fisher's exact test in case of small cell count) for categorical parameters, and the Student's T-test for parametric continuous parameters. The association between the quantitative ^{18}F -FDG PET parameters and pathologic response was quantified using logistic regression analysis providing odds ratios (ORs) with 95% confidence intervals (CIs). Multiple ^{18}F -FDG PET parameters were logarithmically transformed to meet the assumption of linearity on the logit scale. For these parameters, the relative changes (%) were calculated using the logarithmically transformed parameter values before and after induction chemotherapy.

Second, receiver operating characteristics (ROC) curve analyses (providing area-under-the-curve [AUC] values) were used to assess the potential of the studied ^{18}F -FDG PET parameters to discriminate poor responders from good responders. For the ^{18}F -FDG PET parameter with the highest discriminatory ability (AUC), the sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated for an optimal threshold that was determined by giving equal weight to sensitivity and specificity on the ROC curve.

Third, the Kaplan-Meier method was applied to estimate progression-free and overall survival differences among patients predicted to have a poor versus good response based on the ^{18}F -FDG PET parameter with the highest discriminatory ability. For the survival analysis the log-rank test was used to determine significance. Progression-free and overall survival were calculated from the starting date of induction chemotherapy to the date of disease progression after surgery or the date of death, respectively. In patients who were free of disease progression or alive at last follow-up, the date of last follow-up was used to censor progression-free or overall survival times, respectively. Statistical analysis was performed using SPSS 23.0 (IBM Corp., Armonk [NY], USA) and R 3.1.2 open-source software (<http://www.R-project.org>). A p-value <0.05 was considered statistically significant.

RESULTS

From a total of 132 patients with an esophageal adenocarcinoma who underwent induction chemotherapy and preoperative chemoradiotherapy followed by surgery in the study period, 70 were considered eligible for analysis. Some excluded patients missed at least one of two ¹⁸F-FDG PET scans of interest performed at our institution (n=28); these patients had similar response and survival rates compared to the included cohort. Other excluded patients had a Siewert type 3 gastro-esophageal junction tumor (n=15), a non-FDG avid tumor (n=6), a stent in-situ at the time of scanning (n=1), or underwent an urgent or salvage esophagectomy (n=1 and n=11, respectively).

Among the 70 eligible patients, 27 (39%) had a poor pathologic response (TRG 3-4) to neoadjuvant treatment, whereas 43 (61%) had a good pathologic response (TRG 1-2). Patients with a poor response had a mean age of 60 years and 96% (n=26) of them were male, whereas patients with a good response had a mean age of 59 years and 88% (n=38) of them were male. None of the studied baseline characteristics were significantly related to the pathologic response to neoadjuvant treatment (**Table 1**). More specifically, only small non-significant differences regarding pathologic response for the various induction chemotherapy regimens, radiation therapy characteristics and concurrent chemotherapy regimens were found. However, worse tumor characteristics (i.e. higher clinical T-stage, signet ring cell adenocarcinoma, poor differentiation grade) and co-morbidities (i.e. cardiac co-morbidity, diabetes mellitus, chronic obstructive pulmonary disease, and smoking at diagnosis) were consistently observed more frequently in the poor response group.

No baseline ¹⁸F-FDG PET parameters nor SUV_{max} and SUV_{mean} after induction chemotherapy were related to pathologic poor versus good response (**Table 2**). However, both a larger MTV and a larger TLG after induction chemotherapy were significantly related to a higher chance of a poor pathologic response ($p=0.01$). The relative changes after induction chemotherapy in ¹⁸F-FDG PET intensity parameters (i.e. ΔSUV_{max} and ΔSUV_{mean}) and metabolic tumor volume (i.e. ΔMTV) were also significantly related to pathologic response ($p=0.01$), and their discriminatory ability appeared to be superior compared with single time point measurements (AUC range 0.71-0.72 vs. 0.52-0.69; **Table 2**). The association of the relative change in (the logarithmically transformed) total lesion glycolysis (ΔTLG) with pathologic response was highly significant ($p<0.01$) and this parameter yielded the highest discriminatory ability (AUC 0.74).

Table 1 Baseline characteristics

| Characteristic | Poor response (n=27) | Good response (n=43) | <i>p</i> value |
|---|-------------------------|-------------------------|----------------|
| Male gender | 26 (96.3) | 38 (88.4) | 0.39 |
| Age (years) [†] | 59.9 ± 11.5 | 59.4 ± 10.6 | 0.86 |
| BMI (kg/m ²) [†] | 30.3 ± 5.0 | 30.0 ± 5.0 | 0.79 |
| Cardiac co-morbidity | 7 (25.9) | 7 (16.3) | 0.33 |
| Diabetes mellitus | 7 (25.9) | 8 (18.6) | 0.47 |
| COPD | 3 (11.1) | 1 (2.3) | 0.29 |
| Smoking at diagnosis | 8 (29.6) | 8 (18.6) | 0.29 |
| Karnofsky performance status [†] | 85.6 ± 6.4 | 85.6 ± 6.3 | 0.99 |
| Tumor location | | | 0.70 |
| Distal third of esophagus | 25 (92.6) | 38 (88.4) | |
| Gastro-esophageal junction | 2 (7.4) | 5 (11.6) | |
| EUS-based tumor length (cm) [†] | 6.3 ± 2.8 | 6.1 ± 2.9 | 0.87 |
| Histologic differentiation grade | | | 0.35 |
| Moderate | 12 (44.4) | 24 (55.8) | |
| Poor | 15 (55.6) | 19 (44.2) | |
| Signet ring cell adenocarcinoma | 6 (22.2) | 4 (9.3) | 0.17 |
| Clinical T-stage | | | 0.14 |
| cT2 | 1 (3.7) | 7 (16.3) | |
| cT3 | 26 (96.3) | 36 (83.7) | |
| Clinical N-stage | | | 0.73 |
| cN0 | 7 (26.9) | 10 (23.3) | |
| cN+ | 19 (73.1) | 33 (76.7) | |
| Missing | 1 | - | |
| Induction chemotherapy regimen | | | 0.81 |
| Fluoropyrimidine/oxaliplatin/leucovorin | 14 (51.9) | 24 (55.8) | |
| Fluoropyrimidine/oxaliplatin/docetaxel | 10 (37.0) | 16 (37.2) | |
| Other | 3 (11.1) | 3 (7.0) | |
| Radiation treatment modality | | | 0.79 |
| IMRT | 18 (66.7) | 30 (69.8) | |
| Proton therapy | 9 (33.3) | 13 (30.2) | |
| Total radiation dose | | | 1.00 |
| 45.0 Gy | 1 (3.7) | 2 (4.7) | |
| 50.4 Gy | 26 (96.3) | 41 (95.3) | |
| Concurrent chemotherapy regimen | | | 0.25 |
| Fluoropyrimidine/platinum | 18 (66.7) | 30 (69.8) | |
| Fluoropyrimidine/docetaxel | 3 (11.1) | 9 (20.9) | |
| Other | 6 (22.2) | 4 (9.3) | |

Data are presented as numbers with percentages in parentheses.

[†]: Expressed as mean ± SD.

COPD: chronic obstructive pulmonary disease. EUS: endoscopic ultrasound.

Table 2 Logistic regression and ROC curve analysis of ¹⁸F-FDG PET parameters before and after induction chemotherapy for predicting poor pathologic response to chemoradiotherapy

| Parameter | Poor response (n=27) Median [IQR] | Good response (n=43) Median [IQR] | OR | 95% CI | p value | AUC |
|---|---|---|------|-------------|---------|------|
| ¹⁸F-FDG PET before induction chemotherapy | | | | | | |
| SUV _{max} [†] | 14.2 [8.2, 18.6] | 14.7 [9.7, 20.4] | 0.90 | 0.39 – 2.06 | 0.80 | 0.52 |
| SUV _{mean} [†] | 6.5 [4.7, 9.4] | 6.4 [4.9, 8.9] | 0.76 | 0.28 – 2.08 | 0.60 | 0.53 |
| MTV (mL) [†] | 24.2 [14.9, 46.8] | 26.4 [14.4, 45.1] | 0.96 | 0.53 – 1.73 | 0.90 | 0.52 |
| TLG [†] | 171 [88.9, 299] | 203 [61.1, 454] | 0.93 | 0.61 – 1.43 | 0.75 | 0.52 |
| ¹⁸F-FDG PET after induction chemotherapy | | | | | | |
| SUV _{max} [†] | 7.0 [5.2, 9.2] | 5.0 [3.3, 7.8] | 2.51 | 0.96 – 6.59 | 0.06 | 0.66 |
| SUV _{mean} [†] | 4.3 [3.5, 5.2] | 3.7 [2.6, 4.9] | 2.44 | 0.68 – 8.77 | 0.17 | 0.62 |
| MTV (mL) [†] | 13.1 [7.4, 18.6] | 7.0 [2.5, 12.0] | 2.60 | 1.32 – 5.11 | 0.01* | 0.69 |
| TLG [†] | 48.9 [28.4, 81.0] | 24.5 [8.6, 64.7] | 1.90 | 1.16 – 3.10 | 0.01* | 0.68 |
| Relative difference | | | | | | |
| ΔSUV _{max} (%) | -20.5 [-32.0,-12.5] | -32.4 [-48.8,-24.7] | 1.05 | 1.01 – 1.09 | 0.01* | 0.71 |
| ΔSUV _{mean} (%) | -21.3 [-32.9,-21.3] | -31.4 [-45.5,-19.7] | 1.04 | 1.01 – 1.07 | 0.01* | 0.71 |
| ΔMTV (%) | -13.2 [-37.2, -7.9] | -39.1 [-63.8,-26.1] | 1.04 | 1.01 – 1.06 | 0.01* | 0.72 |
| ΔTLG (%) | -19.5 [-34.1, -9.8] | -34.0 [-52.7,-29.9] | 1.05 | 1.02 – 1.09 | <0.01* | 0.74 |

[†]: Logarithmically transformed for logistic regression analysis to meet the assumption of linearity on the logit scale.

*: Significantly associated with poor versus good pathologic response ($p < 0.05$).

AUC: area under the (receiver operating characteristic [ROC]) curve. IQR: interquartile range.

MTV: metabolic tumor volume. SUV: standardized uptake value. TLG: total lesion glycolysis.

The ideal cut-off value for ΔTLG to distinguish poor pathologic responders from good responders was statistically determined at -26% (i.e. a 26% decrease). Patients with a ΔTLG above (n=25) versus below (n=45) this threshold had a poor pathologic response in 72% versus 20% of cases, respectively. At the threshold of -26%, the ΔTLG yielded a sensitivity of 67% (95% CI: 51-79%), specificity of 84% (95% CI: 74-91%), accuracy of 77% (95% CI: 65-86%), PPV of 72% (95% CI: 55-85%), and NPV of 80% (95% CI: 71-87%) for predicting a poor pathologic response (**Figure 1**). Of note, the threshold for the relative change in the logarithmically transformed TLG values of -26% compared best to a threshold for the relative change in the originally scaled TLG values of -74%. However, this originally scaled ΔTLG yielded a slightly lower predictive performance (AUC 0.71, with sensitivity 70% [95% CI: 54-83%], specificity 74% [95% CI: 64-83%], accuracy 73% [95% CI: 60-83%], PPV 63% [95% CI: 49-75%], and NPV 80% [95% CI: 69-89%]).

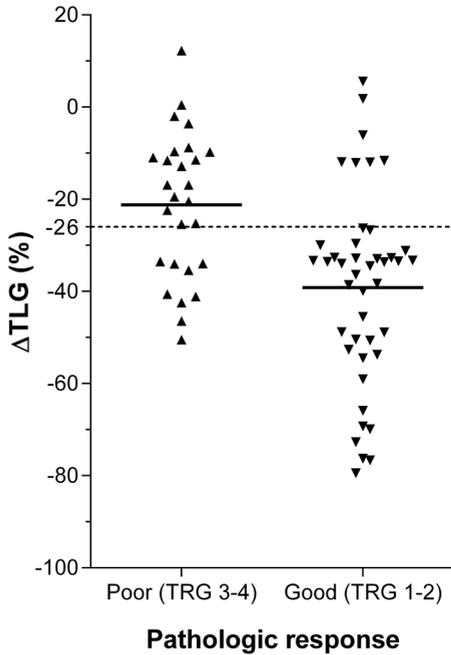


Figure 1 Scatter plot demonstrating the percentage of change in total lesion glycolysis (ΔTLG) after induction chemotherapy before preoperative chemoradiotherapy for esophageal cancer in 27 poor versus 43 good pathologic responders. Horizontal continuous lines represent group means and the dotted line represents the optimal discriminatory cut-off level for ΔTLG of -26%.

Postoperative 30-day and 90-day mortality rates were 1% (1 of 70) and 4% (3 of 70), respectively. These 3 patients (who were part of the predicted good responders group) were excluded from survival analysis. For patients alive at last follow-up, the median follow-up duration was 48 months (range 15 to 99). In the 25 patients with a predicted poor response based on (the logarithmically transformed) ΔTLG the median progression-free survival was 17 months, whereas the median progression-free survival in the 42 patients with a predicted good response was not reached (**Figure 2A**). The progression-free survival was significantly better for the predicted good responders compared to the predicted poor responders based on ΔTLG ($p=0.02$). Although overall survival rates appeared higher in patients with a predicted good response (median, not reached) compared to predicted poor responders (median, 70 months), this difference was not statistically significant ($p=0.18$; **Figure 2B**).

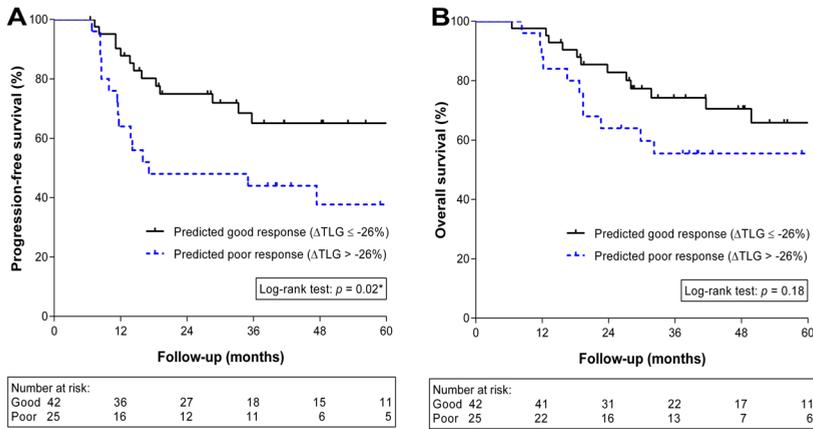


Figure 2 Kaplan-Meier analysis for progression-free survival (A) and overall survival (B) according to predicted good versus poor response by the change in the logarithmically transformed total lesion glycolysis (ΔTLG) after induction chemotherapy before preoperative chemoradiotherapy for esophageal cancer.

DISCUSSION

In this study, the value of ¹⁸F-FDG PET before and after induction chemotherapy for the prediction of response to neoadjuvant treatment was investigated in patients undergoing induction chemotherapy followed by trimodality therapy for esophageal adenocarcinoma. Significant associations were found between treatment-induced changes in studied ¹⁸F-FDG PET parameters and histopathologic tumor regression defined as poor response (TRG 3-4) versus good response (TRG 1-2). A decrease of less than 26% in (the logarithmically transformed) TLG after induction chemotherapy, indicating only a mild reduction in intensity and volume of FDG-uptake of the primary tumor, predicted a poor pathologic response with a specificity of 84% and PPV of 72%. This implies that the baseline (a priori) chance of a poor pathologic response of 39% (i.e. the overall prevalence) almost doubled to 72% (i.e. the PPV) in predicted poor responders. This is particularly interesting when considering modification of the chemotherapy regimen administered concurrently with preoperative CRT after induction chemotherapy (e.g. in patients with burdening toxicity from induction chemotherapy) or even omission of ineffective and toxic preoperative CRT in predicted poor responders. On the other hand, a strong reduction of more than 26% in TLG after induction chemotherapy

predicted a good pathologic response with a sensitivity of 67% and NPV of 80%. This implies that the baseline (a priori) chance of a good pathologic response of 61% (i.e. the overall prevalence) increased to 80% (i.e. the NPV) in predicted good responders. This indicates that ^{18}F -FDG PET before and after induction chemotherapy provides a reasonable basis to encourage good responders to induction chemotherapy to proceed with preoperative chemoradiotherapy.

Several single-arm phase I-II studies^{10-14,19,21-23,25} and two retrospective comparative studies^{15,16} found promising results with the three-step treatment strategy compared to preoperative CRT without induction chemotherapy in terms of treatment response, R0 resection rates and survival rates. However, this potential superiority was not found in a retrospective comparative study¹⁷ and two prospective randomized phase II studies^{27,29}. One study suggested that only patients with stage III and IVa (and not stage II) disease who received induction chemotherapy had a significant survival advantage over preoperative CRT alone¹⁶. The three-step approach has not been evaluated in the context of a phase III trial. Therefore, the use of induction chemotherapy to improve oncologic outcomes remains subject of debate. Nonetheless, the response to induction chemotherapy may serve as a marker for tumor sensitivity indicating whether benefit is to be expected from subsequent CRT or whether different chemotherapeutic agents should be incorporated into the preoperative CRT²⁴⁻²⁶.

13 Since esophageal cancer patients with a poor pathologic response to neoadjuvant treatment do not seem to benefit from this treatment but are exposed to its treatment-related toxicity^{11,13,30,31}, accurately predicting pathologic response before or early during treatment would produce much-needed knowledge to help individualize therapy. To this regard, the predictive value of ^{18}F -FDG PET response has previously been reported in preoperative chemotherapy studies of patients with esophageal adenocarcinoma^{45,46}. In the subsequent MUNICON trial from that group³², ^{18}F -FDG PET-based poor responders early during preoperative chemotherapy were referred for immediate surgery rather than continuation of preoperative chemotherapy, and this discontinuation of ineffective chemotherapy did not adversely affect outcome compared with continuing such therapy³².

The current study demonstrates that ^{18}F -FDG PET before and after induction chemotherapy yields a moderate ability to predict a poor pathologic response to subsequent preoperative CRT. The value of ^{18}F -FDG PET in this setting has been previously described in four smaller cohorts^{20,24,26,47}, one of which had no histopathologic reference as no surgery was performed²⁶. Similar to the current

study, three previous studies with 45, 55, and 46 patients, respectively^{20,24,47}, performed ¹⁸F-FDG PET before and after induction chemotherapy and reported a significant association between early ¹⁸F-FDG PET response and histopathologic tumor regression. Two studies reported the predictive performance of ¹⁸F-FDG PET for predicting a poor pathologic response with sensitivities of 52% and 68%, and specificities of 60% and 52%^{20,47}. The differences with the current study (sensitivity 67%, specificity 84%) may be explained by varying ¹⁸F-FDG PET hardware, scan protocols, and reconstruction algorithms between studies^{20,47} and within one multicenter study⁴⁷, by the different applied thresholds for ¹⁸F-FDG PET response^{20,47}, and by the different treatment regimens used in other studies^{20,47}. One previous study only reported on the value of ¹⁸F-FDG PET before and after induction chemotherapy to predict residual cancer as opposed to a pathologic complete response (i.e. TRG 2-4 vs. 1), and found a sensitivity of 61% and specificity of 89%²⁴. These results led investigators to examine the use of ¹⁸F-FDG PET to direct preoperative therapy in patients with esophageal cancer in the Cancer and Leukemia Group B trial 80803, which was opened in 2011²⁴. Results of that trial, in which the chemotherapy regimen to be used during preoperative CRT will be selected by ¹⁸F-FDG PET response after induction chemotherapy, are currently awaited.

Although ¹⁸F-FDG PET before and after induction chemotherapy appears to have a reasonable discriminatory ability for predicting pathologic response, it remains suboptimal. Studies have been focusing mainly on quantitative parameters, but subjective assessment by clinicians is thought to have some additional potential, as it is felt that on post-treatment scans more focused ¹⁸F-FDG avidity instead of linear uptake may be indicative of a poor response. Unfortunately, other modalities that have been extensively studied for predicting pathologic response – including endoscopic biopsy, endoscopic ultrasonography, and CT – yielded unsatisfactory results^{38,48}. Recently, diffusion-weighted magnetic resonance imaging has been suggested as potentially powerful tool for this purpose⁴⁹, but this tool has not yet been described in the setting of a three-step treatment strategy and requires further validation.

Besides pathologic response, ¹⁸F-FDG PET response (Δ TLG) after induction chemotherapy was also significantly associated with progression-free survival ($p=0.02$) – but not with overall survival ($p=0.18$) – in the current study. This finding is supported by a previous prospective study in which ¹⁸F-FDG PET responders to induction chemotherapy had significantly improved progression-free survival ($p=0.02$), but not overall survival ($p=0.29$)²⁴. In this way, the early

response to induction chemotherapy apparently is an indicator of tumor biology and the likelihood of treatment failure. As such, the early ^{18}F -FDG PET response after induction chemotherapy could aid in patient selection for treatment intensification or modification aiming to reduce the high risk of locoregional and distant recurrences in the poor responders.

Certain limitations apply to this study. First, the study was retrospective by nature. Second, different regimens of induction chemotherapy and preoperative chemoradiotherapy were applied in this study. However, our analysis was strengthened by including the largest sample size on this topic so far, using a prospectively maintained database, and using modern ^{18}F -FDG PET techniques and imaging analysis.

In conclusion, this study demonstrated that ^{18}F -FDG PET seems useful to predict a poor pathologic response early after induction chemotherapy in patients with oesophageal adenocarcinoma undergoing a three-step treatment strategy. As such, the early ^{18}F -FDG PET response after induction chemotherapy has the potential to aid in individualized treatment decision-making in this group of patients. However, the standard use of ^{18}F -FDG PET for this indication cannot yet be recommended, as the findings (e.g. the determined threshold) of the current exploratory study require external validation. Also, a larger sample size is desired as the 95% CIs of the estimated diagnostic performance indices in the current study were relatively wide. Also, additional studies are required to determine and validate whether ^{18}F -FDG PET alone or in combination with other modalities provides sufficient accuracy to justify modification or withdrawal of subsequent CRT prior to surgery.

REFERENCES

1. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
2. Allum WH, Stenning SP, Bancewicz J, et al. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol* 2009;27:5062-7
3. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011;12:681-92
4. Teniere P, Hay JM, Fingerhut A, et al. Postoperative radiation therapy does not increase survival after curative resection for squamous cell carcinoma of the middle and lower esophagus as shown by a multicenter controlled trial. French University Association for Surgical Research. *Surg Gynecol Obstet* 1991;173:123-30
5. Zieren HU, Muller JM, Jacobi CA, et al. Adjuvant postoperative radiation therapy after curative resection of squamous cell carcinoma of the thoracic esophagus: a prospective randomized study. *World J Surg* 1995;19:444-9
6. Pouliquen X, Levard H, Hay JM, et al. 5-Fluorouracil and cisplatin therapy after palliative surgical resection of squamous cell carcinoma of the esophagus. A multicenter randomized trial. French Associations for Surgical Research. *Ann Surg* 1996;223:127-33
7. Ando N, Iizuka T, Kakegawa T, et al. A randomized trial of surgery with and without chemotherapy for localized squamous carcinoma of the thoracic esophagus: the Japan Clinical Oncology Group Study. *J Thorac Cardiovasc Surg* 1997;114:205-9
8. Shapiro J, van Lanschot JJ, Hulshof MC, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol* 2015;16:1090-8
9. Oppedijk V, van der Gaast A, van Lanschot JJ, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. *J Clin Oncol* 2014;32:385-91
10. Ajani JA, Komaki R, Putnam JB, et al. A three-step strategy of induction chemotherapy then chemoradiation followed by surgery in patients with potentially resectable carcinoma of the esophagus or gastroesophageal junction. *Cancer* 2001;92:279-86
11. Bains MS, Stojadinovic A, Minsky B, et al. A phase II trial of preoperative combined-modality therapy for localized esophageal carcinoma: initial results. *J Thorac Cardiovasc Surg* 2002;124:270-7
12. Ilson DH, Bains M, Kelsen DP, et al. Phase I trial of escalating-dose irinotecan given weekly with cisplatin and concurrent radiotherapy in locally advanced esophageal cancer. *J Clin Oncol* 2003;21:2926-32
13. Swisher SG, Ajani JA, Komaki R, et al. Long-term outcome of phase II trial evaluating chemotherapy, chemoradiotherapy, and surgery for locoregionally advanced esophageal cancer. *Int J Radiat Oncol Biol Phys* 2003;57:120-7

14. Ajani JA, Walsh G, Komaki R, et al. Preoperative induction of CPT-11 and cisplatin chemotherapy followed by chemoradiotherapy in patients with locoregional carcinoma of the esophagus or gastroesophageal junction. *Cancer* 2004;100:2347-54
15. Jin J, Liao Z, Zhang Z, et al. Induction chemotherapy improved outcomes of patients with resectable esophageal cancer who received chemoradiotherapy followed by surgery. *Int J Radiat Oncol Biol Phys* 2004;60:427-36
16. Malaisrie SC, Hofstetter WL, Correa AM, et al. The addition of induction chemotherapy to preoperative, concurrent chemoradiotherapy improves tumor response in patients with esophageal adenocarcinoma. *Cancer* 2006;107:967-74
17. Javeri H, Arora R, Correa AM, et al. Influence of induction chemotherapy and class of cytotoxics on pathologic response and survival after preoperative chemoradiation in patients with carcinoma of the esophagus. *Cancer* 2008;113:1302-8
18. Ribí K, Koeberle D, Schuller JC, et al. Is a change in patient-reported dysphagia after induction chemotherapy in locally advanced esophageal cancer a predictive factor for pathological response to neoadjuvant chemoradiation? *Support Care Cancer* 2009;17:1109-16
19. Ruhstaller T, Widmer L, Schuller JC, et al. Multicenter phase II trial of preoperative induction chemotherapy followed by chemoradiation with docetaxel and cisplatin for locally advanced esophageal carcinoma (SAKK 75/02). *Ann Oncol* 2009;20:1522-8
20. Sergeant G, Deroose C, De Hertogh G, et al. Early metabolic response evaluation on PET-CT after a single cycle of chemotherapy in patients with cT3-4N0/+ oesophageal or GE-junction cancer subsequently treated by neoadjuvant chemoradiotherapy. *J Clin Oncol* 2010;28
21. Choong NW, Mauer AM, Haraf DC, et al. Long-term outcome of a phase II study of docetaxel-based multimodality chemoradiotherapy for locally advanced carcinoma of the esophagus or gastroesophageal junction. *Med Oncol* 2011;28 Suppl 1:S152-61
22. De Vita F, Orditura M, Martinelli E, et al. A multicenter phase II study of induction chemotherapy with FOLFOX-4 and cetuximab followed by radiation and cetuximab in locally advanced oesophageal cancer. *Br J Cancer* 2011;104:427-32
23. Eisterer W, De Vries A, Kendler D, et al. Triple induction chemotherapy and chemoradiotherapy for locally advanced esophageal cancer. A phase II study. *Anticancer Res* 2011;31:4407-12
24. Ilson DH, Minsky BD, Ku GY, et al. Phase 2 trial of induction and concurrent chemoradiotherapy with weekly irinotecan and cisplatin followed by surgery for esophageal cancer. *Cancer* 2012;118:2820-7
25. Koo DH, Park SI, Kim YH, et al. Phase II study of use of a single cycle of induction chemotherapy and concurrent chemoradiotherapy containing capecitabine/cisplatin followed by surgery for patients with resectable esophageal squamous cell carcinoma: long-term follow-up data. *Cancer Chemother Pharmacol* 2012;69:655-63
26. Ishihara R, Yamamoto S, Iishi H, et al. Predicting the effects of chemoradiotherapy for squamous cell carcinoma of the esophagus by induction chemotherapy response assessed by positron emission tomography: toward PET-response-guided selection of chemoradiotherapy or esophagectomy. *Int J Clin Oncol* 2012;17:225-32

27. Ajani JA, Xiao L, Roth JA, et al. A phase II randomized trial of induction chemotherapy versus no induction chemotherapy followed by preoperative chemoradiation in patients with esophageal cancer. *Ann Oncol* 2013;24:2844-9
28. Alberts SR, Soori GS, Shi Q, et al. Randomized phase II trial of extended versus standard neoadjuvant therapy for esophageal cancer, NCCTG (Alliance) trial N0849. *J Clin Oncol* 2013;31.
29. Yoon DH, Jang G, Kim JH, et al. Randomized phase 2 trial of S1 and oxaliplatin-based chemoradiotherapy with or without induction chemotherapy for esophageal cancer. *Int J Radiat Oncol Biol Phys* 2015;91:489-96
30. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005;23:2310-7
31. Holscher AH, Bollschweiler E, Bogoevski D, et al. Prognostic impact of neoadjuvant chemoradiation in cT3 oesophageal cancer - A propensity score matched analysis. *Eur J Cancer* 2014;50:2950-7
32. Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet Oncol* 2007;8:797-805
33. van Rossum PS, van Lier AL, Lips IM, et al. Imaging of oesophageal cancer with FDG-PET/CT and MRI. *Clin Radiol* 2015;70:81-95
34. Bruzzi JF, Swisher SG, Truong MT, et al. Detection of interval distant metastases: clinical utility of integrated CT-PET imaging in patients with esophageal carcinoma after neoadjuvant therapy. *Cancer* 2007;109:125-34
35. Stiekema J, Vermeulen D, Vegt E, et al. Detecting interval metastases and response assessment using ¹⁸F-FDG PET/CT after neoadjuvant chemoradiotherapy for esophageal cancer. *Clin Nucl Med* 2014;39:862-7
36. Blom RL, Schreurs WM, Belgers HJ, et al. The value of post-neoadjuvant therapy PET-CT in the detection of interval metastases in esophageal carcinoma. *Eur J Surg Oncol* 2011;37:774-8
37. Elliott JA, O'Farrell NJ, King S, et al. Value of CT-PET after neoadjuvant chemoradiation in the prediction of histological tumor regression, nodal status and survival in oesophageal adenocarcinoma. *Br J Surg* 2014;101:1702-11
38. Westerterp M, van Westreenen HL, Reitsma JB, et al. Esophageal cancer: CT, endoscopic US, and FDG PET for assessment of response to neoadjuvant therapy--systematic review. *Radiology* 2005;236:841-51
39. Wieder HA, Beer AJ, Lordick F, et al. Comparison of changes in tumor metabolic activity and tumor size during chemotherapy of adenocarcinomas of the esophagogastric junction. *J Nucl Med* 2005;46:2029-34
40. Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ* 2003;326:41-4
41. Edge S, Byrd D, Compton C, eds. *AJCC Cancer Staging Manual*. 2010:103-15
42. Chirieac LR, Swisher SG, Ajani JA, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. *Cancer* 2005;103:1347-55

43. Werner-Wasik M, Nelson AD, Choi W, et al. What is the best way to contour lung tumors on PET scans? Multiobserver validation of a gradient-based method using a NSCLC digital PET phantom. *Int J Radiat Oncol Biol Phys* 2012;82:1164-71
44. Roedl JB, Colen RR, Holalkere NS, et al. Adenocarcinomas of the esophagus: response to chemoradiotherapy is associated with decrease of metabolic tumor volume as measured on PET-CT. Comparison to histopathologic and clinical response evaluation. *Radiother Oncol* 2008;89:278-86
45. Weber WA, Ott K, Becker K, et al. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. *J Clin Oncol* 2001;19:3058-65
46. Ott K, Weber WA, Lordick F, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. *J Clin Oncol* 2006;24:4692-8
47. Klaeser B, Nitzsche E, Schuller JC, et al. Limited predictive value of FDG-PET for response assessment in the preoperative treatment of esophageal cancer: results of a prospective multi-center trial (SAKK 75/02). *Onkologie* 2009;32:724-30
48. van Rossum PS, Goense L, Meziani J, et al. Endoscopic biopsy and EUS for the detection of pathologic complete response after neoadjuvant chemoradiotherapy in esophageal cancer: a systematic review and meta-analysis. *Gastrointest Endosc* 2016;83:866-79
49. van Rossum PS, van Lier AL, van Vulpen M, et al. Diffusion-weighted magnetic resonance imaging for the prediction of pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer. *Radiother Oncol* 2015;115:163-70



PART IV

PERIOPERATIVE CARE





Chapter 14

Calcification of arteries supplying the gastric tube: a new risk factor for anastomotic leakage after esophageal surgery

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Radiology 2015;274:124-32

ABSTRACT

PURPOSE

The aim of this study was to evaluate the association between the amount and location of calcification in the supplying arteries of the gastric tube (as determined by a vascular calcification scoring system) and the occurrence of anastomotic leakage after esophagectomy with gastric tube reconstruction in patients with esophageal cancer.

MATERIALS AND METHODS

Institutional review board approval was obtained, and the informed consent requirement was waived for this retrospective study. Consecutive patients undergoing elective esophagectomy for cancer with gastric tube reconstruction and cervical anastomosis between 2003 and 2012 were identified from a prospective database. Then vascular calcification scores were retrospectively assigned by reviewing the routine preoperative computed tomographic (CT) images. In patients with anastomotic leakage, presence and severity of calcifications of the aorta (score 0-2), celiac axis (score 0-2), right post-celiac arteries (common hepatic, gastroduodenal and right gastro-epiploic arteries; score 0-1) and left post-celiac arteries (splenic and left gastro-epiploic arteries; score 0-1) along with patient- and operation-related characteristics were compared to that of patients without leakage using multivariate logistic regression analysis.

RESULTS

Of 246 patients, 58 (24%) experienced anastomotic leakage. No significant differences in patient-related factors were found between patients with and without leakage, except for more chronic use of steroids in the leakage group (7% [4/58] vs. 0% [0/188], $p=0.003$). In univariate analysis, leakage was more common in patients with calcifications of the aorta (27% [28/102] and 35% [13/37] vs. 16% [17/107], $p=0.029$), and of the right post-celiac arteries (55% [6/11] vs. 22% [52/235], $p=0.013$). In multivariate analysis, both minor and major aortic calcifications were associated with leakage; odds ratio [OR] 2.00 (95% confidence interval [CI]: 1.02-3.94) and 2.87 (95% CI: 1.22-6.72), respectively. Also, an independent association with leakage was found for calcifications of the right post-celiac arteries (OR 4.22, 95% CI: 1.24-14.4).

CONCLUSION

Atherosclerotic calcifications of the aorta and right post-celiac arteries supplying the gastric tube are independent risk factors for anastomotic leakage after esophagectomy.

INTRODUCTION

Esophagectomy combined with neoadjuvant chemoradiation therapy is the mainstay of therapy in patients with resectable esophageal cancer¹. Improvements of surgical techniques and perioperative management have led to a steady decrease in postoperative mortality over the years². However, the relatively high incidence (10-30%) of anastomotic leakage after cervical esophagogastrostomy^{1,3,4}, results in an increased risk of stricture formation and higher perioperative mortality rates^{5,6}. Suggested risk factors for developing anastomotic leakage include older age, ischemia of the gastric tube, malnutrition, hypotension, hypoxemia, neoadjuvant therapy, steroid use, smoking, comorbid conditions (e.g. diabetes mellitus, COPD and cardiovascular disease), high body mass index, surgical approach and a low number of esophagectomy procedures performed in a hospital^{2,4,5,7-11}.

Relative ischemia of the gastric tube due to poor tissue perfusion is considered a major cause of anastomotic leakage^{4,12}. During esophagectomy, a major reduction of microvascular blood flow and concomitant compromised tissue oxygenation in the gastric tube has been demonstrated in several studies¹³⁻¹⁵. The most cranial part of the gastric tube is used to create the anastomosis. This part is supplied only by a fine submucosal and mucosal microvascular network¹⁶ and is fed exclusively by the right gastro-epiploic artery after mobilization of the stomach during gastric tube reconstruction (**Figure 1**). Even in stable hemodynamic conditions, the blood flow in this upper part of the gastric tube is decreased compared to the antrum and corpus^{17,18}. One study reported that patients with tissue blood flow at the anastomotic site of less than 10 mL/min/100g all experienced leakage, indicating that blood flow at the anastomotic site may be an important predictive factor¹⁹. Similarly, another study found a vascularization deficit of the reconstruction in 100% of patients with anastomotic leakage, as shown by selective arteriography²⁰.

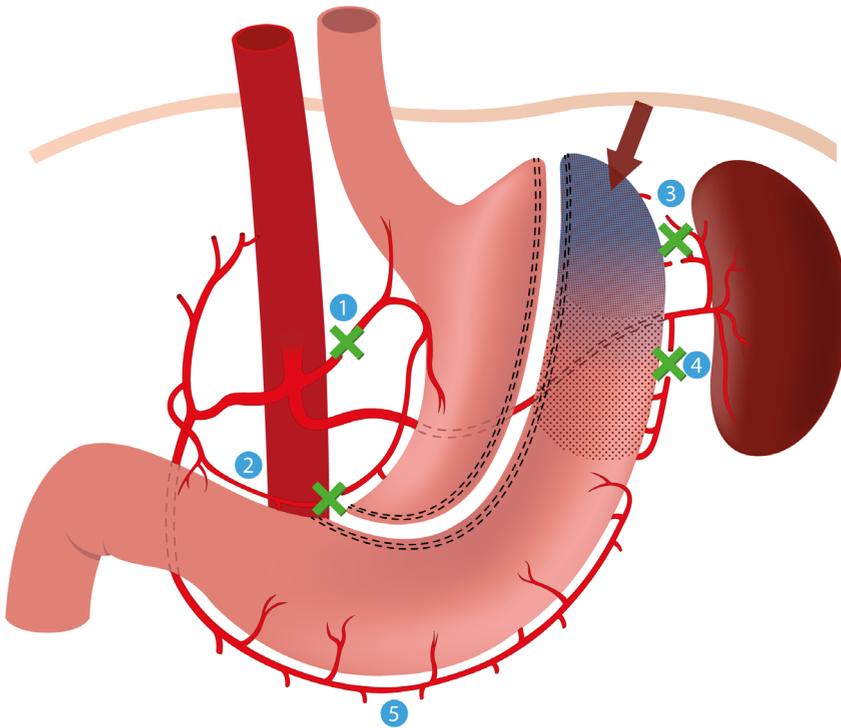


Figure 1 Illustration of the arterial supply of the stomach after constructing the gastric tube for reconstruction in esophageal surgery. During mobilization of the stomach, ligation (*green crosses*) of the left and right gastric artery (**no. 1 and 2**), short gastric arteries (**no. 3**) and left gastro-epiploic artery (**no. 4**) causes the gastric tube to be supplied exclusively by the right gastro-epiploic artery (**no. 5**). This results in a compromised blood flow in particularly the most cranial part of the gastric tube (*red arrow*), which is used to create the cervical anastomosis.

Atherosclerosis is a known cause of ischemia and it has been speculated to compromise the vascular supply of the gastric tube and cervical anastomosis²¹. A recent study reported that vascular calcifications of the aortic wall and supra-aortic arteries, as a measure for atherosclerosis, can be used to predict cardiovascular events²². In this study, we present a similar pragmatic scoring system for the semi-quantitative scoring of vascular calcifications of the supplying arteries of the gastric tube on routine preoperative computed tomographic (CT) images of the chest and abdomen in esophageal cancer patients. The aim of this study was to evaluate the association between the amount and location of calcification in the supplying arteries of the gastric tube (as determined by a vascular calcification scoring system) and the occurrence of anastomotic leakage after esophagectomy with gastric tube reconstruction in patients with esophageal cancer.

MATERIALS AND METHODS

STUDY POPULATION

Institutional review board (IRB) approval was obtained, and the informed consent requirement was waived for this retrospective study. All patients that underwent elective esophagectomy at our tertiary referral center from October 2003 until August 2012 were prospectively collected in a database. Patients with an available preoperative CT of the thorax and abdomen with a slice thickness of 5.0 mm or less were selected for this study. Exclusion criteria were benign disease, premature discontinuation of surgery due to the discovery of T4b or M1 disease during surgery, other reconstruction than gastric tube reconstruction, urgent non-elective surgery, combined laryngeal resection and intrathoracic anastomosis (**Figure 2**).

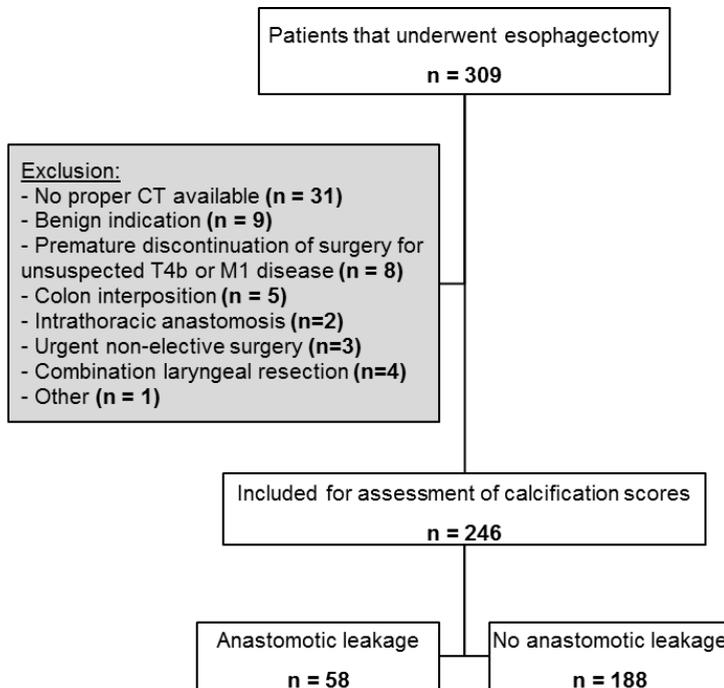


Figure 2 Flowchart of study design.

All patients underwent gastric tube reconstruction with a cervical single-layer hand-sewn anastomosis. A linear stapling device was used for the gastric tube reconstruction and the staple line was manually oversewn in all subjects (Endo GIA™ Stapler, Covidien, Dublin, Ireland). During gastric tube reconstruction

the entire course of the right gastro-epiploic artery was respected. Patient- and operation-related characteristics (i.e. gender, age, body mass index, American Society of Anesthesiologists score, chronic obstructive pulmonary disease, diabetes mellitus, cardiovascular comorbidity, smoking, chronic use of steroids, neoadjuvant treatment, surgical approach, type of anastomosis, duration of operation, year of operation, and supervising surgeon) were collected from a prospective database. In addition, time intervals from CT examination to surgery and from surgery to occurrence of anastomotic leakage were recorded, if applicable.

IMAGE ACQUISITION

All contrast enhanced routine preoperative CT protocols were considered suitable as long as the field of view (FOV) included the full length of the thoracic aorta, celiac axis and common hepatic, gastroduodenal and splenic arteries. Chest and abdominal CT examinations were typically obtained with 16- or 64-section CT scanners from a variety of manufacturers at either referring centers or our own center. Images were typically acquired with 16 x 0.75 mm- or 64 x 0.625 mm-section collimation, a gantry rotation time of 400-750 msec, a tube potential of 120 or 130 kV, an effective tube current ranging from 32 to 215 mAs (mean 122 mAs), and a FOV size of 300 (1%), 320 (2%), 371 (1%), 400 (7%) or 500 mm (89%). An iodinated 90 mL, 300 mg/mL contrast bolus with a saline solution chaser was administered intravenously at 3 or 4 mL/sec in all patients. In the standard protocol of both referring centers and our own center, a region of interest (ROI) was placed in the aortic arch or descending thoracic aorta, and image acquisition was automatically initiated once a selected threshold was reached within this ROI with bolus tracking. Subsequently, chest and abdominal CT images were typically acquired during the arterial phase and portal venous phase respectively.

IMAGE EVALUATION

In patients with more than one CT examination during the preoperative work-up, the findings from the first diagnostic examination were considered, reflecting the moment of clinical decision-making. All preoperative CT examinations were independently reviewed and scored for calcifications by one reader (P.S.N.v.R.). In addition, a randomly sampled subgroup (n=50) was also scored independently by a second reader (L.H.). Both readers were clinical research physicians with one and two years of experience, respectively, in the field of surgical oncology. The readers were trained and supervised by a dedicated radiologist with more than 15 years of experience in gastro-intestinal radiology (M.S.v.L.). Images were analyzed in the

transverse plane. The readers were blinded to the patient- and operation-related characteristics and clinical outcome in terms of anastomotic leakage.

A visual calcification grading system was modified from a previously reported score for grading aortic wall abnormalities in the prediction of cardiovascular events^{22,23}. This grading system was developed specifically for the supplying arteries of the gastric tube. The definitions used for visual grading are provided in **Table 1**, and examples of imaging characteristics are presented in **Figure 3**. The selection of studied vessels was based on anatomical studies that clearly showed that the right gastro-epiploic artery exclusively supplies the gastric tube, and originates from the aorta via the celiac axis, common hepatic artery and gastroduodenal artery^{16,21}.

Table 1 Definitions used to grade calcifications of the supplying arteries of the gastric tube seen on preoperative CT images

| Artery | Score | | |
|--------------------------------|--------|--|--|
| | 0 | 1 | 2 |
| Aorta* | Absent | Minor calcifications ≤9 foci <i>and</i> ≤3 foci extending over ≥3 sections | Major calcifications >9 foci <i>or</i> >3 foci extending over ≥3 sections |
| Celiac axis | Absent | Minor calcifications extending over <3 sections <i>or</i> MCSD of single focus ≤10mm | Major calcifications extending over ≥3 sections <i>and</i> MCSD of single focus >10mm <i>or</i> involving both proximal (aorto- celiac) and distal part (hepato- splenic bifurcation) |
| Right post-celiac arteries† | Absent | ≥1 calcification(s) | -- |
| Left post-celiac arteries‡ | Absent | ≥1 calcification(s) | -- |

Note – Definitions may be considered as guidelines to distinguish absence, minor and major presence of calcifications.

MCSD: maximum cross-sectional diameter.

*: Aorta defined as descending part of thoracic aorta *plus* abdominal part of aorta above celiac level.

†: Right post-celiac arteries defined as common hepatic artery *plus* gastroduodenal artery *plus* right gastro-epiploic artery.

‡: Left post-celiac arteries defined as splenic artery *plus* left gastro-epiploic artery.

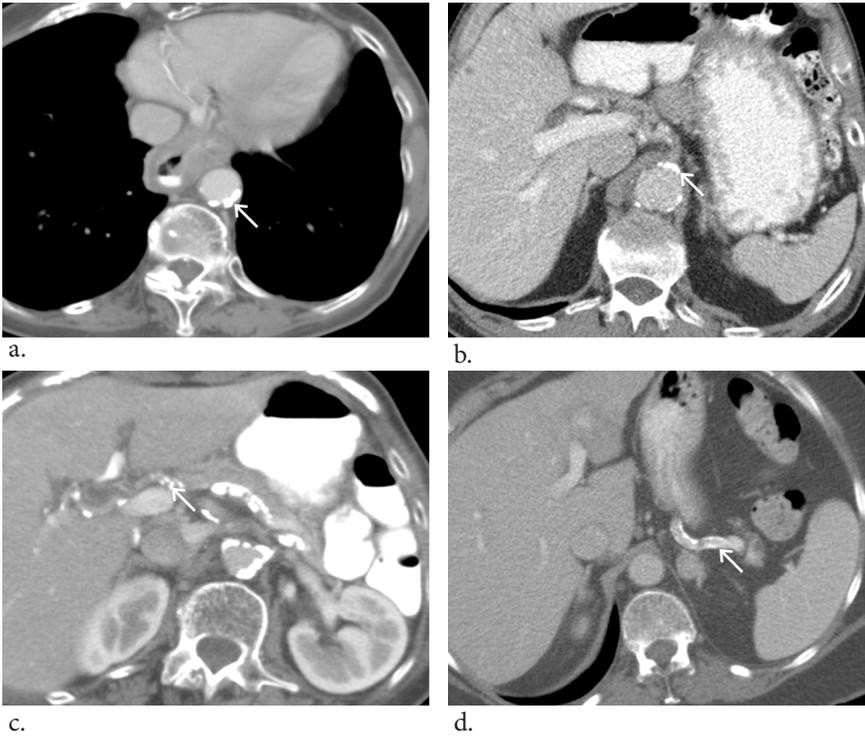


Figure 3 Findings of calcifications on preoperative transverse CT images obtained in four esophageal cancer patients. **(a)** Image shows descending aorta with multiple calcified foci (*white arrow*). An aortic calcification score of 2 was assigned as CT demonstrated 21 foci in the predefined length of the aortic wall with 8 foci extending over ≥ 3 transverse sections. This patient experienced anastomotic leakage on postoperative day 5. **(b)** Image shows calcifications of celiac axis (*white arrow*) that extended over three transverse sections with a maximal cross-sectional diameter of 12 mm. A celiac axis calcification score of 2 was assigned. On the third day after esophagectomy the patient suffered from anastomotic leakage. **(c)** Image shows calcifications of common hepatic artery (i.e. right post-celiac arteries; *white arrow*). A right post-celiac calcification score of 1 was assigned and anastomotic leakage occurred on postoperative day 5 in this patient. **(d)** Image shows calcifications of splenic artery (i.e. left post-celiac arteries; *white arrow*). A calcification score of 1 was assigned to the left post-celiac arteries in this patient who did not experience postoperative anastomotic leakage.

Additionally, calcifications in the splenic and left gastro-epiploic arteries were scored, because a small part of the gastric tube length is suggested to benefit from the left gastro-epiploic arteries¹⁶. Aortic wall calcifications were scored on all transverse images from descending thoracic aorta, starting right after the origination of the left subclavian artery, down to the level of the celiac axis origination (score 0-2). Furthermore, calcifications of the celiac axis (score 0-2), right post-celiac arteries

(common hepatic, gastroduodenal and right gastro-epiploic arteries; score 0-1) and left post-celiac arteries (splenic and left gastro-epiploic arteries; score 0-1) were scored. The right and left post-celiac arteries were scored on a binary scale only because visible vascular calcifications in these smaller vessels were expected to occur relatively infrequent. Scoring more than two categories with small cell counts could easily result in model overfitting with imprecise estimates describing random error rather than a true association in this case.

STATISTICAL ANALYSIS

The primary outcome measure of this study was anastomotic leakage, defined by either extravasation of water-soluble contrast during a contrast swallow study or CT scan, visualization of anastomotic dehiscence or fistulae during endoscopy, or visible loss of saliva through the cervical wound²⁴. Diagnostic tests to identify anastomotic leakage were conducted on indication only; no routine contrast swallow examination was performed²⁵. As clinically apparent cervical leakages generally manifest between 2 and 10 days after esophagectomy and no leakage is expected to occur after long-term observation⁴, the follow-up time of subjects was uniformly truncated to 30 days. A formal check in our prospective database confirmed the absence of anastomotic leakage occurring after 30 days.

The association between clinical characteristics and calcification scores and anastomotic leakage was studied univariately. We used chi-square test for categorical variables or Fisher's exact test for categorical variables with small cell counts, and T-test or Mann-Whitney U test for normally or skewedly distributed continuous variables. We used multivariate logistic regression analysis to study whether calcifications were independently and significantly associated with anastomotic leakage. Variables associated with anastomotic leakage at p-values below 0.25 in univariate analysis were entered into the multivariate model. In a stepwise manner, backward elimination of the least significant variables associated with leakage was performed based on the log likelihood ratio. The likelihood ratio test was used to confirm that the excluded covariates did not significantly change the model fit. Odds ratios (OR) with 95% confidence intervals (95% CI) were estimated. Statistical analysis was performed using SPSS 20.0 (SPSS Inc, Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

Interobserver reproducibility was assessed in a random sample consisting of 50 patients of this study scored by two readers (P.S.N.v.R. and L.H.). Intraobserver reproducibility was assessed in the same sample scored twice by one reader (P.S.N.v.R.) after a 2-month interval between readings. Overall percentages of

agreement were calculated to determine the inter- and intraobserver agreement in grading the scoring model. Inter- and intraobserver reliability was assessed using kappa statistics. We used a weighted-kappa ($w\text{-}\kappa$) for the calcification scores of the aorta (score 0-2) and celiac axis (score 0-2) with linear weighting between successive ordinal categories set at '1'²³. The ($w\text{-}\kappa$) statistic can be interpreted as follows²⁶: a value of 0.81 to 1.00 is considered excellent; 0.61 to 0.80, good; 0.41 to 0.60, moderate; 0.21 to 0.40, fair; and less than 0.20, poor reliability.

RESULTS

From 309 patients who underwent esophagectomy in the study period, 63 patients were excluded, because of unavailability of sufficient quality preoperative CT scan ($n=31$), benign disease ($n=9$), preoperative discontinuation of the operation due to unsuspected T4b or M1 disease ($n=8$), use of colon interposition graft ($n=5$), creation of intrathoracic anastomosis ($n=2$), urgent non-elective resection ($n=3$), and combination with laryngeal resection ($n=4$). One patient experienced a major acute myocardial infarction within three days post-esophagectomy and was excluded from further analysis.

Fifty-eight (24%) of the remaining 246 patients experienced anastomotic leakage after esophagectomy. Median time between CT examination and esophagectomy was 86 days (range 1-174). All but one patient survived the first 30 days after esophagectomy with no loss to follow-up in this period. In addition, censoring was no issue as the one patient that died within the follow-up period of 30 days experienced anastomotic leakage before death. Anastomotic leakage occurred after a median time of 6 days (range 1-26) post-esophagectomy. Patients in the anastomotic leakage group had a mean age of 65 years, and 79% ($n=46/58$) of them were male, whereas patients without leakage had a mean age of 64 years, and 71% ($n=134/188$) were male (**Table 2**). Chronic use of steroids ($n=4$) was rare and all these patients developed anastomotic leakage. Other patient- and treatment-related factors were not significantly associated with the occurrence of anastomotic leakage.

Calcifications of the aorta were highly prevalent; 102 (41%) and 37 (15%) of 246 patients were assigned aortic calcification scores of 1 and 2, respectively (**Table 3**). In univariate analysis, the aortic calcification score was significantly associated with the occurrence of anastomotic leakage (27% [28/102] and 35% [13/37] leakage in groups with minor and major calcifications, respectively, vs. 16% [17/107] in group without calcifications; $p=0.029$). No significant association

Table 2 Baseline characteristics

| Characteristic | Anastomotic leakage (n=58) | No anastomotic leakage (n=188) | p value |
|---|-------------------------------|-----------------------------------|---------|
| Gender | | | 0.227 |
| Male | 46 (26%) | 134 (74%) | |
| Female | 12 (18%) | 54 (82%) | |
| Age (years)[†] | 64.9 ± 9.2 | 63.8 ± 9.2 | 0.398 |
| Body Mass Index (kg/m²)[†] | 25.7 ± 4.3 | 25.7 ± 4.0 | 0.880 |
| ASA score | | | 0.368 |
| 1 | 16 (28%) | 42 (72%) | |
| 2 | 30 (20%) | 119 (80%) | |
| 3 | 12 (32%) | 26 (68%) | |
| 4 | 0 (0%) | 1 (100%) | |
| COPD | | | 0.194 |
| Yes | 11 (32%) | 23 (68%) | |
| No | 47 (22%) | 165 (78%) | |
| Diabetes mellitus | | | 0.669 |
| Yes | 9 (27%) | 25 (73%) | |
| No | 49 (23%) | 163 (77%) | |
| Cardiovascular comorbidity | | | 0.583 |
| Yes | 14 (26%) | 39 (74%) | |
| No | 44 (23%) | 149 (77%) | |
| Smoking | | | 0.325 |
| Yes | 30 (21%) | 111 (79%) | |
| No | 28 (27%) | 77 (73%) | |
| Chronic use of steroids | | | 0.003* |
| Yes | 4 (100%) | 0 (0%) | |
| No | 54 (22%) | 188 (78%) | |
| Neoadjuvant treatment | | | 0.675 |
| No | 29 (26%) | 83 (74%) | |
| Chemotherapy | 25 (22%) | 87 (78%) | |
| Chemoradiotherapy | 4 (18%) | 18 (82%) | |
| Surgical approach | | | 0.443 |
| Laparoscopic transhiatal | 13 (27%) | 35 (73%) | |
| Open transhiatal | 10 (33%) | 20 (67%) | |
| Thoracoscopic | 31 (22%) | 111 (78%) | |
| Thoracoscopic-laparotomic | 1 (8%) | 11 (92%) | |
| Thoracoscopic-laparotomic | 3 (21%) | 11 (79%) | |
| Type of anastomosis | | | 0.435 |
| End-to-end | 3 (33%) | 6 (67%) | |
| End-to-side | 55 (23%) | 182 (77%) | |
| Duration of operation (minutes)[†] | 341 ± 93 | 367 ± 102 | 0.102 |

Table 2 (continued)

| Characteristic | Anastomotic leakage (n=58) | No anastomotic leakage (n=188) | p value |
|----------------------------|-------------------------------|-----------------------------------|---------|
| Year of operation | | | 0.182 |
| 2003-2008 | 25 (29%) | 60 (71%) | |
| 2009-2010 | 15 (17%) | 71 (83%) | |
| 2011-2012 | 18 (24%) | 57 (76%) | |
| Supervising surgeon | | | 0.975 |
| Surgeon 1 | 49 (23%) | 162 (77%) | |
| Surgeon 2 | 4 (29%) | 10 (71%) | |
| Surgeon 3 | 1 (25%) | 3 (75%) | |
| Surgeon 4 | 4 (24%) | 13 (76%) | |

Presented data are numbers of patients with row-based percentages in parentheses.

*: Significant difference between 'anastomotic leakage' and 'no anastomotic leakage' group ($p < 0.05$).

#: Data presented as mean \pm standard deviation.

Table 3 Distribution and univariate comparison of calcification score per trajectory among patients with versus without anastomotic leakage

| Artery | Anastomotic leakage (n=58) | No anastomotic leakage (n=188) | p value |
|-----------------------------------|-------------------------------|-----------------------------------|---------|
| Aorta | | | 0.029* |
| 0 | 17 (16%) | 90 (84%) | |
| 1 | 28 (27%) | 74 (73%) | |
| 2 | 13 (35%) | 24 (65%) | |
| Celiac axis | | | 0.107 |
| 0 | 27 (19%) | 114 (81%) | |
| 1 | 20 (27%) | 54 (73%) | |
| 2 | 11 (35%) | 20 (65%) | |
| Right post-celiac arteries | | | 0.013* |
| 0 | 52 (22%) | 183 (78%) | |
| 1 | 6 (55%) | 5 (45%) | |
| Left post-celiac arteries | | | 0.462 |
| 0 | 42 (22%) | 145 (78%) | |
| 1 | 16 (27%) | 43 (73%) | |

Presented data are numbers of patients with percentages in parentheses and p values determined by chi-square test.

*: Significant difference between 'anastomotic leakage' and 'no anastomotic leakage' group ($p < 0.05$).

was found between celiac axis calcifications, which occurred in 105 (43%) of 246 patients, and anastomotic leakage (27% [20/74] and 35% [11/31] leakage in groups with minor and major calcifications, respectively, vs. 19% [27/141] in the group without calcifications; $p=0.107$). Although calcifications of right post-celiac arteries were uncommonly found ($n=11$ of 246, 4.5%), the incidence of leakage was significantly higher in this group of patients (55% [6/11] vs. 22% [52/235], $p=0.013$). The common hepatic artery showed at least one calcification in all of 11 patients; the gastroduodenal and right gastro-epiploic arteries were additionally (but not exclusively) involved in 5 and 2 of these patients respectively. The presence of left post-celiac arteries calcifications was not significantly associated with a higher incidence of leakage (27% [16/59] vs. 22% [42/187], $p=0.462$). Left post-celiac arteries calcifications included splenic artery involvement in all 59 patients with visible additional involvement of the left gastro-epiploic artery in 3 of these patients only.

The calcification scores of aorta, celiac axis and right post-celiac arteries were entered into the multivariate logistic regression model, along with factors 'gender', 'COPD', and 'year of operation.' 'Chronic use of steroids' was not considered suitable for regression analysis due to the very low prevalence in our sample. 'Duration of operation' was excluded from entering the model because this covariate would not be useful in preoperative risk assessment. After stepwise backward elimination, 'gender', 'COPD', 'year of operation', and calcifications of the celiac axis were eliminated and the vascular calcification scores of aorta and right post-celiac arteries remained independently and significantly associated with a higher risk of anastomotic leakage (**Table 4**). Compared to patients without aortic calcifications, those with an aortic calcification score of 1 and 2 had an increased adjusted risk for leakage (OR 2.00, 95% CI: 1.02-3.94; and OR 2.87, 95% CI: 1.22-6.72, respectively). Similarly, a significant association with leakage was found for major calcifications of the right post-celiac arteries (OR 4.22, 95% CI: 1.24-14.4).

The 50 randomly selected patients for determining observer agreements appeared representative for the whole study group with a mean age of 64.1 (± 8.4), and male gender in 74% of cases (37 of 50). Anastomotic leakage occurred in 11 of 50 (22%) patients. The aorta calcification score showed excellent inter- and intraobserver overall agreement (94% [47/50] and 94% [47/50], respectively) and excellent inter- and intraobserver reliability with $w\text{-}\kappa$ values of 0.93 (95% CI: 0.84-1.00) and 0.93 (95% CI: 0.84-1.00), respectively. Also, excellent inter- and intraobserver overall agreement was found in scoring celiac axis calcifications (88% [44/50] and 90% [45/50], respectively) with excellent inter- and intraobserver reliability ($w\text{-}\kappa$ of

Table 4 Results of multivariate logistic regression analysis with stepwise backward elimination

| Variable | | OR (95% CI) | p value |
|-----------------------------------|---------|---------------------------|---------|
| Aorta | 1 vs. 0 | 2.00 (1.02-3.94) | 0.044* |
| | 2 vs. 0 | 2.87 (1.22-6.72) | 0.015* |
| Celiac axis | 1 vs. 0 | <i>Not in final model</i> | - |
| | 2 vs. 0 | <i>Not in final model</i> | - |
| Right post-celiac arteries | 1 vs. 0 | 4.22 (1.24-14.4) | 0.021* |
| Left post-celiac arteries | 1 vs. 0 | <i>Not in final model</i> | - |

Adjustment variables included gender, COPD, and year of operation. *: Marked parameters are each independently associated with anastomotic leakage. For example: an odds ratio of 4.22 shows that the presence of calcifications in the right post-celiac arteries (score 1 vs. 0) leads to a 322% increase in the odds of experiencing anastomotic leakage.

0.81 [95% CI: 0.67-0.95] and 0.84 [95% CI: 0.72-0.97], respectively). Calcifications in the right post-celiac arteries showed excellent inter- and intraobserver overall agreement (94% [47/50] and 98% [49/50], respectively) with good inter- and intraobserver reliability (κ of 0.64 [95% CI: 0.27-1.00] and 0.79 [95% CI: 0.39-1.00], respectively). Calcifications in the left post-celiac arteries showed excellent inter- and intraobserver overall agreement (84% [42/50] and 88% [44/50], respectively) with moderate to good inter- and intraobserver reliability (κ of 0.59 [95% CI: 0.33-0.84] and 0.69 [95% CI: 0.46-0.92], respectively).

DISCUSSION

Calcifications of the arterial supply of the gastric tube, detected on routine preoperative CT images, are associated with the occurrence of cervical anastomotic leakage after esophagectomy for cancer. Preoperative calcifications of the aorta (score 1-2 vs. 0), and right post-celiac arteries (score 1 vs. 0) were independently associated with postoperative anastomotic leakage. A visual grading system with excellent inter- and intraobserver reproducibility was developed.

The finding that no standard patient- or operation-related factors (except for chronic use of steroids) were significantly associated with anastomotic leakage in this reasonably large series of 246 patients, underlines the current inability to accurately predict anastomotic leakage. In this context, it must be noted that

the aetiology of anastomotic leakage is multifactorial and is not solely based on calcifications. More risk factors need to be identified in order to allow for individualized prediction. The calcification scoring method, involving the use of image characteristics detected on routine scanning, can be used as an important factor in future prediction models in order to identify patients at high risk for leakage.

The calcification grading system in this study was largely based on a previously described and validated visual grading system for scoring aortic abnormalities seen on routine diagnostic CT images, which was shown to be useful in the prediction of cardiovascular events^{22,23}. Besides calcifications, scores for irregularity, plaques and elongation of the aortic wall were analyzed in these studies, but the addition of these parameters did not lead to substantial improvement of the prediction model. A prediction model based solely on calcifications was demonstrated to be most appropriate for clinical use with good to excellent inter- and intraobserver reproducibility^{22,23}. Similar to these findings, the scoring model in our study also showed good to excellent inter- and intraobserver reproducibility ($w\text{-}\kappa$ ranging from 0.64 to 0.93). The model is based on simple definitions and can be used in standard diagnostic CT protocols. In contrast, other used calcium-scoring techniques that require special semi-automatic calcium-scoring software or special CT protocols have limited reproducibility and substantial practical difficulties^{27,28}.

The final model resulting from multivariate analysis contains a plausible patho-physiologic rationale, since the right gastro-epiploic artery, originating from this trajectory, mainly supplies the gastric tube and anastomosis^{16,21}. The finding that the calcification score in the left post-celiac arteries (i.e. splenic and left gastro-epiploic arteries) did not significantly differ in patients with anastomotic leakage from those without such leakage adds further to this hypothesis, since these arteries barely contribute to the blood supply of the gastric tube.

Ischemia as an underlying mechanism for anastomotic leakage is likely to be moderated by a combination of both generalized vascular disease (marked by aortic calcifications) and compromised local perfusion (marked by right post-celiac arteries calcifications). Furthermore, anastomotic leakage has been related to congestion due to insufficient venous drainage at the anastomotic site, the method of construction of the anastomosis, width of the gastric tube, mechanical tension, and poor nutritional status^{3,4,12}. With regard to these suggested causes, different attempts to optimize the conditions of the anastomosis have been reported. The proposed calcification scoring system of this paper can help in selecting those patients that might benefit from one of these interventions in the future.

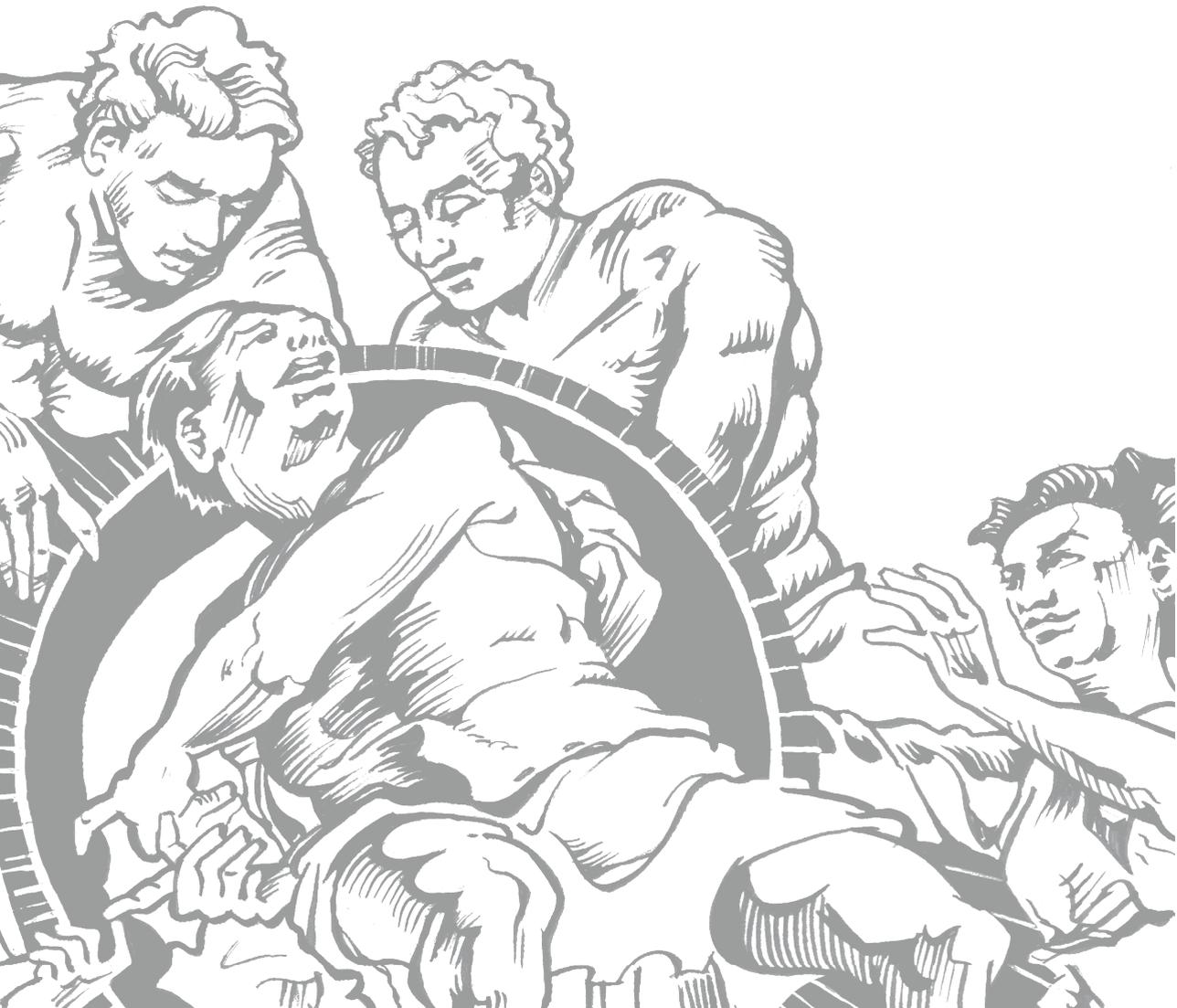
The strength that lies in the simple and straightforward assessment of calcifications in our model might be considered as a potential limitation of this study. Typical chunky calcifications were not differentiated from long thin calcifications. Also, variant vascular anomalies of the gastric and hepatic arteries, and celiac axis were not assessed separately. Finally, calcifications in the arteries are at most a surrogate for atherosclerosis and impaired perfusion and there might be more specific ways to determine the extent of vascular disease and local perfusion, such as using dedicated CT-angiography of the abdomen or laser Doppler flowmetry.

Our study demonstrated that vascular calcifications of the arteries that supply the gastric tube, defined by a visual grading system with good to excellent inter- and intraobserver reproducibility, are independently associated with anastomotic leakage of the esophagogastrostomy. Future research should aim to include this new parameter in the development of a risk prediction model for anastomotic leakage.

REFERENCES

1. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
2. Lerut T, Coosemans W, Decker G, et al. Anastomotic complications after esophagectomy. *Dig Surg* 2002;19:92-8
3. Walther B, Johansson J, Johnsson F, et al. Cervical or thoracic anastomosis after esophageal resection and gastric tube reconstruction: a prospective randomized trial comparing sutured neck anastomosis with stapled intrathoracic anastomosis. *Ann Surg* 2003;238:803-12; discussion 812-4
4. Urschel JD. Esophagogastrostomy anastomotic leaks complicating esophagectomy: a review. *Am J Surg* 1995;169:634-40
5. Atkins BZ, Shah AS, Hutcheson KA, et al. Reducing hospital morbidity and mortality following esophagectomy. *Ann Thorac Surg* 2004;78:1170-6
6. Alanezi K, Urschel JD. Mortality secondary to esophageal anastomotic leak. *Ann Thorac Cardiovasc Surg* 2004;10:71-5
7. Briel JW, Tamhankar AP, Hagen JA, et al. Prevalence and risk factors for ischemia, leak, and stricture of esophageal anastomosis: gastric pull-up versus colon interposition. *J Am Coll Surg* 2004;198:536-41; discussion 541-2
8. Charnley RM, Paterson-Brown S. Surgeon volumes in oesophagogastric and hepatopancreatobiliary resectional surgery. *Br J Surg* 2011;98:891-3
9. Zhang SS, Yang H, Luo KJ, et al. The impact of body mass index on complication and survival in resected oesophageal cancer: a clinical-based cohort and meta-analysis. *Br J Cancer* 2013;109:2894-2903
10. Kassis ES, Kosinski AS, Ross P, Jr, et al. Predictors of anastomotic leak after esophagectomy: an analysis of the society of thoracic surgeons general thoracic database. *Ann Thorac Surg* 2013;96:1919-26
11. Markar SR, Arya S, Karthikesalingam A, et al. Technical factors that affect anastomotic integrity following esophagectomy: systematic review and meta-analysis. *Ann Surg Oncol* 2013;20:4274-81
12. Dewar L, Gelfand G, Finley RJ, et al. Factors affecting cervical anastomotic leak and stricture formation following esophagogastrectomy and gastric tube interposition. *Am J Surg* 1992;163:484-9
13. Jacobi CA, Zieren HU, Muller JM, et al. Anastomotic tissue oxygen tension during esophagectomy in patients with esophageal carcinoma. *Eur Surg Res* 1996;28:26-31
14. Jacobi CA, Zieren HU, Zieren J, et al. Is tissue oxygen tension during esophagectomy a predictor of esophagogastric anastomotic healing? *J Surg Res* 1998;74:161-4
15. Schroder W, Stippel D, Gutschow C, et al. Postoperative recovery of microcirculation after gastric tube formation. *Langenbecks Arch Surg* 2004;389:267-71
16. Liebermann-Meffert DM, Meier R, Siewert JR. Vascular anatomy of the gastric tube used for esophageal reconstruction. *Ann Thorac Surg* 1992;54:1110-5
17. Klijn E, Niehof S, de Jonge J, et al. The effect of perfusion pressure on gastric tissue blood flow in an experimental gastric tube model. *Anesth Analg* 2010;110:541-6
18. Buise M, van Bommel J, Jahn A, et al. Intravenous nitroglycerin does not preserve gastric microcirculation during gastric tube reconstruction: a randomized controlled trial. *Crit Care* 2006;10:R131

19. Ikeda Y, Niimi M, Kan S, et al. Clinical significance of tissue blood flow during esophagectomy by laser Doppler flowmetry. *J Thorac Cardiovasc Surg* 2001;122:1101-6
20. Khoury-Helou A, Nonent M, Vandenbroucke F, et al. Vascular deficit is the major cause of fistula in esophageal surgery. *Ann Chir* 2001;126:857-62
21. Ndoye JM, Dia A, Ndiaye A, et al. Arteriography of three models of gastric oesophagoplasty: the whole stomach, a wide gastric tube and a narrow gastric tube. *Surg Radiol Anat* 2006;28:429-37
22. Gondrie MJ, Mali WP, Jacobs PC, et al. Cardiovascular disease: prediction with ancillary aortic findings on chest CT scans in routine practice. *Radiology* 2010;257:549-59
23. Jacobs PC, Prokop M, Oen AL, et al. Semi-quantitative assessment of cardiovascular disease markers in multislice computed tomography of the chest: interobserver and intraobserver agreements. *J Comput Assist Tomogr* 2010;34:279-84
24. Nederlof N, Tilanus HW, Tran TC, et al. End-to-end versus end-to-side esophago-gastrostomy after esophageal cancer resection: a prospective randomized study. *Ann Surg* 2011;254:226-33
25. Boone J, Rinkes IB, van Leeuwen M, et al. Diagnostic value of routine aqueous contrast swallow examination after oesophagectomy for detecting leakage of the cervical oesophagogastric anastomosis. *ANZ J Surg* 2008;78:784-90
26. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159-74
27. Komen N, Klitsie P, Dijk JW, et al. Calcium score: a new risk factor for colorectal anastomotic leakage. *Am J Surg* 2011;201:759-65
28. Komen N, Klitsie P, Hermans JJ, et al. Calcium scoring in unenhanced and enhanced CT data of the aorta-iliacal arteries: impact of image acquisition, reconstruction, and analysis parameter settings. *Acta Radiol* 2011;52:943-50



Chapter 15

Aortic calcification increases the risk of anastomotic leakage after Ivor-Lewis esophagectomy

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ABSTRACT

BACKGROUND

Anastomotic leakage is associated with increased morbidity and mortality after esophagectomy. Calcification of the arteries supplying the gastric tube has been identified as risk factor for leakage of the cervical anastomosis, but its potential contribution to the risk of intrathoracic anastomotic leakage has not been elucidated. The purpose of this study was to evaluate the relationship between calcification and the occurrence of leakage of the intrathoracic anastomosis after Ivor-Lewis esophagectomy.

MATERIALS AND METHODS

Consecutive patients who underwent minimally invasive esophagectomy for cancer at two institutes were analyzed. Diagnostic computed tomography images were used to detect calcification of the arteries supplying the gastric tube (e.g. aorta, celiac axis). Multivariable logistic regression analysis was used to determine the relationship between vascular calcification and anastomotic leakage.

RESULTS

Of 167 included patients, 40 (24%) experienced anastomotic leakage. In univariable analysis, leakage was most frequently observed in patients with calcification of the aorta (major calcification; 37% leakage [16 of 43], and minor calcification; 32% [18 of 56] versus absence of calcification; 9% [6 of 70], $p < 0.001$). Calcification of other studied arteries was not significantly associated with leakage. Minor and major aortic calcifications remained significantly associated with leakage in multivariable analysis (odds ratio [OR] 5.4, 95% confidence interval [CI]:1.7–16.5, and OR 7.0, 95% CI:1.9–26.4; respectively).

CONCLUSIONS

Atherosclerotic calcification of the aorta is an independent risk factor for leakage of the intrathoracic anastomosis after Ivor-Lewis esophagectomy for cancer. The calcification scoring system may aid in patient selection and lead to earlier diagnosis of this potentially fatal complication.

INTRODUCTION

Surgical resection of the esophagus combined with neoadjuvant chemoradiation or perioperative chemotherapy is the cornerstone of treatment with curative intent for patients with resectable non-metastatic esophageal cancer¹⁻³. Anastomotic leakage is a frequently encountered complication after esophagectomy that is associated with increased postoperative morbidity, length of hospital stay and mortality⁴⁻⁷. Furthermore, anastomotic leakage has been shown to negatively affect long-term cancer specific-survival after esophagectomy⁸. Despite advances in surgical treatment and improvement in perioperative care, incidence rates of up to 24-30% have been reported for anastomotic leakage after esophagectomy^{3,9}.

Identifying risk factors for anastomotic leakage after esophagectomy could aid in early recognition and subsequently limit the impact of this complication. Currently it is difficult to accurately predict anastomotic leakage based on standard patient or treatment-related characteristics only. Tissue ischemia and a compromised perfusion of the gastric tube are considered the main causes of insufficient anastomotic healing^{4,10}. As an important contributor to tissue ischemia, atherosclerosis is associated with a detrimental effect on anastomotic healing¹¹. In a recently published study, atherosclerotic calcification of the arteries supplying the gastric tube as determined by routine diagnostic computed tomography (CT) scans was identified as independent risk factor for anastomotic leakage of the cervical anastomosis after esophagectomy¹².

The potential contribution of atherosclerotic calcification to the risk of anastomotic leakage after esophagectomy with an intrathoracic anastomosis has not been elucidated. The shorter length of the gastric tube in case of an intrathoracic anastomosis may cause relatively less ischemia compared to a cervical anastomosis⁵. Accordingly, the aim of this study was to evaluate the relationship between atherosclerotic calcification of the arteries supplying the gastric tube (as determined by scoring calcifications on CT) and the occurrence of leakage of the intrathoracic anastomosis after Ivor-Lewis esophagectomy for cancer.

MATERIALS AND METHODS

STUDY POPULATION

The institutional review board approved this retrospective study and the requirement to obtain informed consent was waived. All consecutive patients who underwent an elective, minimally invasive Ivor-Lewis esophagectomy for cancer in the Catharina Hospital, Eindhoven, and the Ziekenhuisgroep Twente,

Almelo, between April 2012 and March 2015 were selected from prospectively collected institutional databases. Within these databases, patients with an available preoperative thoraco-abdominal contrast-enhanced CT scan were included. All patients underwent a total minimally invasive esophagectomy with gastric tube reconstruction using an intracorporal anastomosis. The intrathoracic anastomosis was created using a side-to-side linear stapling technique or end-to-side hand-sewn technique at the level of the carina. Patients who underwent preoperative vascular conditioning (e.g. stenting of the celiac artery) or a reconstruction other than a gastric tube were excluded from this study. Patient and treatment-related characteristics from the remaining eligible patients were extracted from the prospectively acquired databases. Parameters of interest included gender, age, body mass index (BMI), American Society of Anesthesiologists (ASA) score, chronic obstructive pulmonary disease (COPD), coronary artery disease and other cardiac co-morbidity, hypertension, peripheral vascular disease, diabetes mellitus, smoking status at diagnosis, neoadjuvant treatment and anastomotic technique.

IMAGE ACQUISITION AND EVALUATION

Thoraco-abdominal CT images were acquired using commercially available 16- or 64-section CT scanners at our own or referring centers. All contrast-enhanced routine CT protocols were considered suitable if the field-of-view at least included the total thoracic aorta, celiac axis, right postceliac arteries (i.e. common hepatic, gastroduodenal, and right gastroepiploic arteries) and left postceliac arteries (splenic and left gastroepiploic arteries). Images were acquired with a slice thickness of 2 mm (5% of patients), 2.5 mm (12% of patients), 3.0 mm (47% of patients) or 5 mm (36% of patients). In case more than one CT scan was available, the first diagnostic scan conducted during the diagnostic work-up was used. In all patients an iodinated contrast bolus was administered intravenously. The CT images were acquired during either the arterial phase or the portal venous phase.

The CT images were retrospectively reviewed and scored for location and amount of calcification by one reader (L.G.). The reader was trained to use a previously described simple vascular scoring system for calcifications of the arteries of the gastric tube¹² by the authors that proposed the system using a training set of 25 randomly selected patients who were not part of the study sample. This scoring system has been shown to yield good to excellent inter- and intraobserver reproducibility¹². The reader was blinded to patient and treatment-related characteristics and surgical outcome.

Calcification of the thoracic aorta was scored on transverse CT images from the origin of the left subclavian artery, down to the origin of the celiac axis (score 0-2). An aortic calcification score of 1 was assigned in case of nine or fewer calcified foci and three or fewer calcified foci extending over three or more contiguous axial images. A score of 2 was assigned in case more than nine calcified foci or more than three calcified foci extending over three or more contiguous axial images were observed. Also, calcification of the celiac axis was scored (score 0-2). A score of 1 was assigned when calcifications extended over fewer than three contiguous axial images or a single calcified focus was smaller than or equal to 10 mm (long axis). In case of larger calcifications or involvement of both the proximal (aortoceliac) and distal (hepatosplenic bifurcation) parts of the celiac axis, a score of 2 was assigned. Scores of 0, 1 and 2 were considered as absence, minor or major presence of calcification, respectively. The right postceliac arteries and left postceliac arteries were scored according to the absence or presence of calcification (score 0-1). The threshold of 3 or more contiguous axial images was initially proposed for CT-scans with 5 mm slices. In case of thinner slices the grading system was adjusted accordingly. Examples of image characteristics are presented in **Figure 1**.

STATISTICAL ANALYSIS

The primary outcome measure of this study was anastomotic leakage defined as either clinical signs of leakage from a thoracic drain, radiologic signs of leakage including contrast leakage or fluid and air levels surrounding the anastomosis, or signs of anastomotic dehiscence during endoscopy or re-operation. In case anastomotic leakage was clinically suspected, a CT scan or endoscopy was performed; no routine diagnostic tests were performed¹³.

The association of patient and treatment-related characteristics and calcification scores with anastomotic leakage was studied univariably. Categorical parameters were compared using the Chi-square test or Fisher's exact test in case of small cell count. The Student's T-test and Mann-Whitney U test were used to compare groups with and without anastomotic leakage for parametric and non-parametric continuous parameters, respectively. Subsequently, variables with $p \leq 0.25$ in univariable analysis were entered in a multivariable logistic regression model to evaluate whether these factors were independently associated with the occurrence of anastomotic leakage. Odds ratios (ORs) with 95% confidence intervals (CIs) were provided. Statistical analysis was performed using SPSS 20.0 (IBM Corp. Armonk, NY, USA). A p -value of <0.05 was considered statistically significant.



Figure 1 Examples of calcification on preoperative CT images in patients with esophageal cancer. **A)** Image shows the descending aorta with plaques and calcified foci (*arrow*), a calcification score of 2 was assigned. **B)** Image shows calcification of the celiac axis (*arrow*), a calcification score of 2 was assigned. **C)** Image shows calcification of the common hepatic artery (*arrow*), yielding a right postceliac artery calcification score of 1. **D)** Image shows calcified foci in the splenic artery (*arrow*), yielding a left postceliac artery score of 1.

RESULTS

In the study period, a total of 170 patients underwent a total minimally invasive esophagectomy with gastric tube reconstruction and intrathoracic anastomosis (Ivor-Lewis). Of these patients, three were excluded because no gastric tube formation could be performed during surgery ($n=1$) or preoperative vascular conditioning was performed ($n=2$). Forty (24%) of the remaining 167 patients experienced anastomotic leakage, occurring after a median time of 5 days (range 1-14) after esophagectomy. Of these, 10 patients (25%) showed some signs of tissue ischemia or necrosis of the gastric conduit during postoperative endoscopy. Treatment of anastomotic leakage consisted of antibiotics and nil-by-mouth in 4

of 40 patients (10%), endoscopic re-intervention (stent placement or mediastinal drainage) in 18 patients (45%), and surgical re-intervention in 18 patients (45%). Baseline patient and treatment-related characteristics are presented in **Table 1**. None of these characteristics were significantly associated with the occurrence of anastomotic leakage in univariable analysis. However, patients with anastomotic leakage had a slightly higher age compared to patients without anastomotic leakage (mean: 66.5 versus 63.5 years, respectively; $p=0.053$).

Table 1 Patient and treatment-related characteristics in relation to anastomotic leakage

| Characteristic | No anastomotic leakage (n=127) | Anastomotic leakage (n=40) | <i>p</i> value |
|--|-----------------------------------|-------------------------------|----------------|
| Male gender | 105 (82.7) | 34 (85.0) | 0.732 |
| Age (years)* | 63.5 ± 8.8 | 66.5 ± 9.2 | 0.053 |
| BMI (kg/m²)* | 26.3 ± 4.4 | 26.8 ± 5.9 | 0.893 |
| ASA score | | | 0.548 |
| I | 9 (7.1) | 4 (10.0) | |
| II | 86 (67.7) | 29 (72.5) | |
| III | 32 (25.2) | 7 (17.5) | |
| COPD | 20 (15.7) | 7 (17.5) | 0.793 |
| Coronary artery disease[†] | 14 (11.0) | 8 (20.0) | 0.143 |
| Other cardiac co-morbidity* | 12 (9.4) | 4 (10.0) | 0.564 |
| Hypertension[‡] | 40 (31.5) | 13 (32.5) | 0.443 |
| Peripheral vascular disease | 9 (7.1) | 2 (2.0) | 0.643 |
| Diabetes mellitus | 22 (17.3) | 6 (15.0) | 0.732 |
| Renal insufficiency¶ | 7 (5.5) | 2 (5.0) | 1.000 |
| Smoker at diagnosis | 24 (18.9) | 8 (20.0) | 0.520 |
| Neoadjuvant therapy | | | 0.776 |
| No therapy | 10 (7.9) | 4 (10.0) | |
| Chemotherapy | 110 (86.6) | 35 (87.5) | |
| Chemoradiotherapy | 7 (5.5) | 1 (2.5) | |
| Anastomotic technique | | | 0.940 |
| Side-to-side stapling | 96 (75.6) | 30 (75.0) | |
| End-to-side hand-sewn | 31 (24.4) | 10 (25.0) | |

*: Data are depicted as mean ± standard deviation.

†: Requiring percutaneous coronary intervention or coronary artery bypass graft.

*: A record of historical treatment of any cardiac disorder at a cardiology department (other than coronary artery disease).

‡: Requiring pharmacologic therapy.

||: Requiring vascular reconstruction, bypass surgery or percutaneous intervention to the extremities (excluding vein stripping) or documented aortic aneurysm with or without repair.

¶: Based on a glomerular filtration rate of <60 mL/min/1.73 m².

The overall prevalence of calcification of the studied arteries including the thoracic aorta, celiac axis and left postceliac arteries was high (i.e. 59%, 43% and 25%, respectively). In contrast, calcification of the right postceliac arteries was found in only 5 (3%) of 167 patients. A comparison of calcification per trajectory for patients with versus without anastomotic leakage is shown in **Table 2**. In univariable analysis, the presence of aortic calcification was significantly associated with a higher risk of anastomotic leakage (32% leakage [18 of 56] and 37% leakage [16 of 43] in groups with minor and major calcification, respectively, versus 9% leakage [6 of 70] in the group without calcification, $p < 0.001$). Calcification of the celiac axis was not significantly associated with anastomotic leakage (18% leakage [7 of 39] and 33% leakage [11 of 33] in groups with minor and major calcification, respectively, versus 23% leakage [22 of 95] in the group without calcification, $p = 0.496$). Although the risk of anastomotic leakage in patients with calcification of the right and left postceliac arteries appeared higher compared to patients without these calcifications, the risk differences were not statistically significant (40% leakage [2 of 5] versus 24% leakage [38 of 162]; $p = 0.393$, and 32% leakage [13 of 41] versus 21% [27 of 126]; $p = 0.180$, respectively).

Table 2 Distribution of calcification scores per trajectory and the proportion of patients with anastomotic leakage

| Artery | n (%) | Anastomotic leakage (% of row) | p value |
|----------------------------------|------------|-----------------------------------|---------|
| Thoracic aorta | | | <0.001 |
| 0 | 68 (40.7) | 6 (8.8) | |
| 1 | 56 (33.5) | 18 (32.1) | |
| 2 | 43 (25.7) | 16 (37.2) | |
| Celiac axis | | | 0.496 |
| 0 | 95 (56.9) | 22 (23.2) | |
| 1 | 39 (23.4) | 7 (17.9) | |
| 2 | 33 (19.8) | 11 (33.3) | |
| Right postceliac arteries | | | 0.393 |
| 0 | 162 (97.0) | 38 (23.5) | |
| 1 | 5 (3.0) | 2 (40.0) | |
| Left postceliac arteries | | | 0.180 |
| 0 | 126 (75.0) | 27 (21.4) | |
| 1 | 42 (25.0) | 13 (31.7) | |

Data represent numbers of patients with percentages in parentheses.

Age and presence of coronary artery disease along with the calcification scores of the aorta and left postceliac arteries were selected for multivariable logistic regression analysis (**Table 3**). Minor (score 1) and major (score 2) aortic calcification remained significantly and independently associated with an increased risk of anastomotic leakage (adjusted OR 5.35, 95% CI: 1.73–16.55 and adjusted OR 7.01, CI: 1.96–26.44, respectively). Age, presence of cardiac comorbidity and calcification of the left post celiac arteries were not independently associated with anastomotic leakage in multivariable analysis.

Table 3 Results of multivariable logistic regression analysis in assessing risk of developing anastomotic leakage

| Variable | Outcome | | |
|---------------------------------|------------|--------------|---------|
| | Odds ratio | 95% CI | p value |
| Thoracic aorta | | | |
| 1 vs. 0 | 5.35 | 1.73 - 16.55 | 0.004 |
| 2 vs. 0 | 7.01 | 1.86 - 26.44 | 0.004 |
| Left postceliac arteries | | | |
| 1 vs. 0 | 0.92 | 0.38 - 2.16 | 0.855 |
| Age | 0.99 | 0.94 - 1.04 | 0.669 |
| Coronary artery disease | 1.55 | 0.56 - 4.33 | 0.402 |

CI: confidence interval. OR: odds ratio.

DISCUSSION

Accurate risk assessment of anastomotic leakage after esophagectomy could aid in the selection of patients who may benefit from preoperative preventative strategies and postoperative decision-making. Unfortunately, we are currently not able to accurately predict anastomotic leakage after esophagectomy using standard patient or treatment-related characteristics. This study demonstrates that the presence and severity of calcification of the thoracic aorta, as determined on routine preoperative CT images, are independently associated with the risk of leakage of the intrathoracic anastomosis after esophagectomy for cancer. The calcification scoring method deserves attention and validation as a risk factor in future prediction models to identify patients at high risk for leakage.

This study used a previously described system for grading calcification of the arteries of the gastric tube, which has been shown to yield good to excellent inter- and intra-observer reproducibility¹². In turn, this calcification grading system was based on a validated visual grading system used to score vascular calcification on routine diagnostic CT images for the prediction of cardiovascular events^{14,15}. Our observed association between aortic calcification and leakage of the intrathoracic anastomosis corresponds with the results of a previous study that identified calcification of the aorta and right postceliac arteries as independent risk factor for leakage of the cervical anastomosis after esophagectomy¹². Similarly, another study identified calcification of the iliac arteries as risk factor for anastomotic leakage after colorectal surgery¹⁶. Therefore, the current study adds to the increasing body of evidence on the association between atherosclerotic calcification and leakage of gastro-intestinal anastomoses.

Tissue ischemia, potentially resulting in anastomotic leakage, is thought to be moderated by both compromised local perfusion and generalized vascular disease (indicated by aortic calcification)^{11,12,17,18}. During mobilization of the stomach, the left and right gastric artery, short gastric arteries, and left gastroepiploic artery are ligated, causing the blood supply of the gastric tube to depend exclusively on the right gastroepiploic artery¹⁹. This procedure results in a compromised blood flow in the most cranial part of the gastric tube, which is used to create the anastomosis. Our finding that aortic calcification rather than calcification of the smaller vessels (i.e. celiac axis and postceliac arteries) significantly increased the risk of anastomotic leakage, suggests that generalized vascular disease may be more indicative for the risk of anastomotic leakage than local vascular disease of the arteries supplying the gastric tube. Vascular calcification has been associated with many typical cardiovascular risk factors that are also associated with anastomotic leakage, such as age, diabetes, peripheral vascular disease and renal dysfunction⁶. In the current study, none of these cardiovascular co-morbidities were significantly associated with anastomotic leakage. Therefore, aortic calcification may help to identify high-risk patients who have not yet been diagnosed with these typical risk factors.

Enhancement of blood flow to the gastric tube has been suggested as possible approach to improve tissue oxygenation and anastomotic healing^{20,21}. Gastric ischemic preconditioning aims to preoperatively improve blood flow to the gastric tube by laparoscopic ligation or arterial embolization of the left gastric artery prior to surgery^{22,23}. Furthermore, recent experimental studies reported on novel surgical revascularization procedures that could improve blood flow at the anastomotic

site, for example by increasing the length of the arterial arcade by leaving the collaterals of the left gastro-epiploic artery in situ (ligating it at the splenic hilus)²⁴, by transient bloodletting of the short gastric vein²⁵, or by microvascular additional 'supercharging' anastomoses of graft vessels to recipient vessels for microvascular blood flow augmentation at the level of the gastric tube²⁶. In current clinical practice there is no strong evidence to implement ischemic conditioning and surgical revascularization procedures, which may be due to the inability to adequately identify the patients who may actually benefit from this invasive intervention²⁷. The aortic calcification scoring system could aid in the selection of patients who are at high risk of anastomotic leakage, to further assess the potential benefit of these preventative interventions in clinical studies. This is supported by our finding that the absence of aortic calcification seems to have a relatively high negative predictive value for anastomotic leakage, since the observed risk of anastomotic leakage in this group was only 9%.

Recognition of the increased risk (of up to 38%) for developing anastomotic leakage in patients with major calcification of the thoracic aorta may have important implications. When confronted with this finding preoperatively, the physical condition of the patients to tolerate a leakage requires special attention. Also, postoperatively these patients should be monitored intensively for indications of clinical deterioration. Furthermore, these patient may benefit from drain amylase assessment²⁸ and early gastric tube assessment with endoscopy in the first week after surgery before mediastinal spread or ischemia-associated sepsis become clinically manifest. Endoscopy after esophagectomy has proven to be an accurate method to diagnose anastomotic leakage and provide information on the condition of the gastric tube^{29,30}. Selecting patients for endoscopy based on a predisposed risk for anastomotic leakage could prevent an unnecessary and invasive endoscopy for a substantial proportion of patients. Therefore, a routine comment on the thoracic aortic calcium burden in the radiology report of the diagnostic thoraco-abdominal CT scan in all patients evaluated for esophageal cancer could in aid pre- and postoperative decision-making.

Postoperative anastomotic leakage was relatively common in the current series, occurring in 24% of the patients. Although this appears higher than some other studies, our definition of anastomotic leakage is rather unrestrictive including any sign of clinical or radiologic evidence of leakage. As such, the leakage rate in this study appears to be comparable to the leakage rates of 22% to 30% that were reported in the recent multicenter randomized controlled CROSS-trial³.

A few limitations apply to this study. First, this study was confined to a population that underwent elective minimally invasive Ivor-Lewis esophagectomy. Outcomes might be different in populations that undergo other surgical approaches. Second, no prospective data is yet available to prove additional clinical benefit of the proposed calcification score in terms of morbidity reduction. Third, a visual grading system may not be the most accurate method to assess atherosclerotic calcifications, and there may be more distinct methods to analyze the extensiveness of vascular disease and local perfusion. However, the visual grading system used in the current study is easy to use, can be applied on routine diagnostic CT scans, and has been shown to yield good to excellent inter- and intra-observer reproducibility¹².

In conclusion, this study demonstrated the value of assessing atherosclerotic calcification of the thoracic aorta on routine preoperative CT images to identify patients at high risk of intrathoracic anastomotic leakage after Ivor-Lewis esophagectomy. The applied calcification scoring system may aid in patient selection for interventions that optimize the condition of the anastomosis and lead to earlier diagnosis of this potentially fatal complication.

REFERENCES

1. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20
2. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: An updated meta-analysis. *Lancet Oncol* 2011;12:681-92
3. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
4. Urschel JD. Esophagogastrostomy anastomotic leaks complicating esophagectomy: A review. *Am J Surg* 1995;169:634-40
5. Kassis ES, Kosinski AS, Ross P, et al. Predictors of anastomotic leak after esophagectomy: An analysis of the society of thoracic surgeons general thoracic database. *Ann Thorac Surg* 2013;96:1919-26
6. Iannettoni MD, Whyte RI, Orringer MB. Catastrophic complications of the cervical esophagogastric anastomosis. *J Thorac Cardiovasc Surg* 1995;110:1493-500; discussion 1500-1
7. Alanezi K, Urschel JD. Mortality secondary to esophageal anastomotic leak. *Ann Thorac Cardiovasc Surg* 2004;10:71-5
8. Lagarde SM, de Boer JD, ten Kate FJ, et al. Postoperative complications after esophagectomy for adenocarcinoma of the esophagus are related to timing of death due to recurrence. *Ann Surg* 2008;247:71-6
9. Kim RH, Takabe K. Methods of esophagogastric anastomoses following esophagectomy for cancer: A systematic review. *J Surg Oncol* 2010;101:527-33
10. Dewar L, Gelfand G, Finley RJ, et al. Factors affecting cervical anastomotic leak and stricture formation following esophagogastric resection and gastric tube interposition. *Am J Surg* 1992;163:484-9
11. Pham TH, Perry KA, Enestvedt CK, et al. Decreased conduit perfusion measured by spectroscopy is associated with anastomotic complications. *Ann Thorac Surg* 2011;91:380-5
12. van Rossum PS, Haverkamp L, Verkooijen HM, et al. Calcification of arteries supplying the gastric tube: A new risk factor for anastomotic leakage after esophageal surgery. *Radiology* 2015;274:124-32
13. Boone J, Rinkes IB, van Leeuwen M, et al. Diagnostic value of routine aqueous contrast swallow examination after oesophagectomy for detecting leakage of the cervical oesophagogastric anastomosis. *ANZ J Surg* 2008;78:784-90
14. Gondrie MJ, Mali WP, Jacobs PC, et al. Cardiovascular disease: Prediction with ancillary aortic findings on chest CT scans in routine practice. *Radiology* 2010;257:549-59
15. Jacobi CA, Zieren HU, Zieren J, et al. Is tissue oxygen tension during esophagectomy a predictor of esophagogastric anastomotic healing? *J Surg Res* 1998;74:161-4
16. Komen N, Klitsie P, Dijk JW, et al. Calcium score: A new risk factor for colorectal anastomotic leakage. *Am J Surg* 2011;201:759-65
17. Zehetner J, DeMeester SR, Alicuben ET, et al. Intraoperative assessment of perfusion of the gastric graft and correlation with anastomotic leaks after esophagectomy. *Ann Surg* 2015;262:74-8

18. Campbell C, Reames MK, Robinson M, et al. Conduit vascular evaluation is associated with reduction in anastomotic leak after esophagectomy. *J Gastrointest Surg* 2015;19:806-12
19. Liebermann-Meffert DM, Meier R, Siewert JR. Vascular anatomy of the gastric tube used for esophageal reconstruction. *Ann Thorac Surg* 1992;54:1110-5
20. Reavis KM, Chang EY, Hunter JG, et al. Utilization of the delay phenomenon improves blood flow and reduces collagen deposition in esophagogastric anastomoses. *Ann Surg* 2005;241:736-45; discussion 745-7
21. Urschel JD, Antkowiak JG, Delacure MD, et al. Ischemic conditioning (delay phenomenon) improves esophagogastric anastomotic wound healing in the rat. *J Surg Oncol* 1997;66:254-6
22. Yetasook AK, Leung D, Howington JA, et al. Laparoscopic ischemic conditioning of the stomach prior to esophagectomy. *Dis Esophagus* 2013;26:479-86
23. Diana M, Hubner M, Vuilleumier H, et al. Redistribution of gastric blood flow by embolization of gastric arteries before esophagectomy. *Ann Thorac Surg* 2011;91:1546-51
24. Buunen M, Rooijens PP, Smaal HJ, et al. Vascular anatomy of the stomach related to gastric tube construction. *Dis Esophagus* 2008;21:272-4
25. Kono K, Sugai H, Omata H, et al. Transient bloodletting of the short gastric vein in the reconstructed gastric tube improves gastric microcirculation during esophagectomy. *World J Surg* 2007;31:780-4; discussion 785-6
26. Sekido M, Yamamoto Y, Minakawa H, et al. Use of the "supercharge" technique in esophageal and pharyngeal reconstruction to augment microvascular blood flow. *Surgery* 2003;134:420-4
27. Markar SR, Arya S, Karthikesalingam A, et al. Technical factors that affect anastomotic integrity following esophagectomy: Systematic review and meta-analysis. *Ann Surg Oncol* 2013;20:4274-81
28. Berkelmans GH, Kouwenhoven EA, Smeets BJ, et al. Diagnostic value of drain amylase for detecting intrathoracic leakage after esophagectomy. *World J Gastroenterol* 2015;21:9118-25
29. Maish MS, DeMeester SR, Choustoulakis E, et al. The safety and usefulness of endoscopy for evaluation of the graft and anastomosis early after esophagectomy and reconstruction. *Surg Endosc* 2005;19:1093-102
30. Page RD, Asmat A, McShane J, et al. Routine endoscopy to detect anastomotic leakage after esophagectomy. *Ann Thorac Surg* 2013;95:292-8



Chapter 16

Ischemic conditioning of the stomach in the prevention of esophagogastric anastomotic leakage after esophagectomy

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Annals of Thoracic Surgery 2016;101:1614-23

ABSTRACT

Esophagectomy with esophagogastric anastomosis is a major procedure, and its most feared complication is anastomotic leakage. Ischemic conditioning of the stomach is a method used with the aim of reducing the risk of leakage. It consists of partial gastric devascularization through embolization or laparoscopy followed by esophagectomy and anastomosis at a second stage, thus providing the time for the gastric conduit to adapt to the acute ischemia at the time of its formation. This review analyzes the information from all currently available experimental and clinical studies with the purpose of assessing the current role of the technique and to provide future recommendations.

INTRODUCTION

Esophagectomy plays a key role in the curative treatment of esophageal cancer¹. The procedure encompasses the subtotal resection of the esophagus and its replacement most commonly by a gastric conduit which is anastomosed to the proximal residual esophagus. Esophagectomy is a major surgical procedure with specific rates of morbidity and mortality^{2,3}. Its most feared complication is anastomotic leakage. Leakages convey a remarkable impact on the postoperative course of the patients as they are associated with increased mortality, length of stay, and stricture formation²⁻⁴. Overall, major postoperative complications exert a long-lasting negative effect on the oncologic outcome as well as on the quality of life in patients who undergo esophagectomy for cancer⁵. Leakage rates after esophageal anastomoses are higher compared to anastomoses involving other parts of the gastrointestinal tract⁶. Older series report high esophagogastric leakage incidence reaching up to the one third of the cases^{7,8}. Despite improvements and modifications in the creation of the gastric conduit and in the technique of the anastomosis, reported leakage rates of modern series still remain high⁹⁻¹³.

Although the cause of anastomotic leakage after esophagogastric anastomosis is thought to be multi-factorial, there is evidence that the underlying relative ischemia at the site of anastomosis of the newly formed gastric conduit plays a major role^{11,14,15}. Various techniques and modalities that potentially increase the blood perfusion of the gastric conduit or of both components of the esophagogastric anastomosis have been assessed with the goal to reduce the anastomotic leakage rate¹⁶. The main focus has been on the preoperative partial gastric devascularization known as “ischemic conditioning of the stomach” and the subsequent delayed esophagogastric anastomosis with the purpose to allow time for microcirculation improvement¹⁷.

The purpose of this review is to evaluate the experimental and clinical studies regarding the use of ischemic conditioning of the stomach for the prevention of anastomotic leakage following esophagectomy and esophagogastric anastomosis. Particularly, this review aims to assess and discuss the current role of the technique considering the results of a recent meta-analysis¹⁷ and to propose recommendations for potential future development.

MATERIALS AND METHODS

Two of the authors conducted independently the literature investigation for the period between 1960 and April 2015, and the assessment of the eligibility of the reports for the scope of this review. A PubMed, Embase and Cochrane database search was performed identifying all articles related to the application of ischemic conditioning of the stomach in animals, and in patients undergoing esophagectomy and esophagogastric anastomosis. Medical subject headings that were used to identify such articles were combinations of “esophagectomy”, “esophageal cancer”, “anastomotic leakage”, “prevention”, “IC”, and synonyms. Abstracts obtained from these searches were evaluated. The references of articles and reviews found in the literature search were also examined to find additional related papers. Eligible articles were then considered as five separate groups such as experimental research, clinical studies performing ischemic conditioning with preoperative arterial embolization (PAE) or with laparoscopic arterial ligation, reviews and meta-analysis, and clinical studies with the intent to provide insight in the pathophysiology of the method.

RESULTS

LITERATURE RESULTS

Using the primary search terms 21 publications concerning ischemic conditioning of the stomach were yielded. Cross-reference investigation increased the number of pertinent reports to 38 in total. There were 11 studies in animals¹⁸⁻²⁸, whereas from the 16 clinical studies, ischemic conditioning was achieved with PAE in five²⁹⁻³³, and using laparoscopy in the remaining eleven^{9,10,34-42}. A recent meta-analysis¹⁷ evaluated the results of the twelve clinical comparative studies^{10,29-33,36,40,42}. In addition, six reviews^{8,43-46} and two short communications dealt with the subject^{47,48}. Two experimental reports in humans investigated the effects of the technique at bio- or micro-molecular level^{49,50}.

MECHANISM OF ISCHEMIC CONDITIONING OF THE STOMACH

IC of the stomach aims to preoperatively redistribute the gastric blood supply and thereby ameliorate the tissue oxygenation at the site of the esophagogastric anastomosis with the purpose of reducing postoperative leakage rates. It is based on the occlusion of most or all of the arteries of the stomach with the exception of the right gastro-epiploic artery, days or weeks before the completion of the esophagogastric anastomosis. The aim of the technique is to provide adequate

time to the stomach to adapt to the ischemic conditions caused by the abrupt disruption of its normal vascular supply that occurs during its mobilization for the creation of the gastric conduit. It is believed that the vascularity and thus the blood flow of the greater curvature is increased over time in the pre-conditioned stomach as a response to tissue ischemia and hypoxia compared to the conduit that is anastomosed shortly after its creation^{29,49}.

Preoperative ischemic conditioning of the stomach is performed using either percutaneous embolization or laparoscopic ligation of the arteries. Preoperative arterial embolization (PAE) is performed as an in-hospital procedure³⁰. The femoral artery is catheterized using the Seldinger technique and vascular anatomy is appreciated through digitally subtracted angiographic series of the celiac trunk and of the superior mesenteric artery. The left gastric artery is embolized with coils as a standard procedure. Additionally, occlusion of the splenic artery at its root, of the origin of the short gastric arteries, and of the right gastric artery have been described²⁹⁻³³. Position of coils and the efficacy of embolization are verified by angiography at the end of the procedure. The laparoscopic arterial ligation is performed using a 5-abdominal trocar approach, identically as for minimally invasive esophagectomy¹⁶. The abdominal cavity is inspected in order to verify resectability. Biopsies are taken as required. If resectable, the gastrohepatic ligament is divided and the left gastric vessels are exposed and ligated at their root. Also, the short-gastrics can be divided. Optionally the surgeon can place a feeding jejunostomy.

ANIMAL STUDIES

Various animal models have been used for the assessment of the changes that supervene to the gastric remnant and subsequent esophagogastric anastomosis after partial gastric devascularization. The procedures used in animal studies were laparoscopy or laparotomy with ligation of the left gastric artery in all cases, and in addition the short gastric and/or the right gastric vessels were divided in some cases¹⁸⁻²⁸. The procedure proved to be feasible and safe in all studies. Relevant details of the animal studies are depicted in **Table 1**.

Table 1 Animal studies evaluating ischemic gastric conditioning

| Author, year | Animal | Study design | n | Area of measurement | Technique | Time interval | Effect of gastric devascularization on BF/ Main results of ischemic conditioning |
|--------------------|---------|------------------------|----|---------------------|---|--------------------------|---|
| Urschel 1995 | Rat | Descriptive | 20 | Gastric fundus | LDE, LP with LGL, control | 7, 14 days | Sudden drop of BF/ Perfusion increases with time from ligation (81% at 14 days compared to baseline) |
| Urschel 1997 | Rat | Comparative | 34 | Proximal stomach | LDE, LP with LGL, control | 3 weeks | Sudden drop of BF/ At 3 weeks blood perfusion returned to normal, fewer anastomotic leaks, higher anastomotic wound breaking strength |
| Urschel 1997 | Rat | Comparative | 45 | Gastric body | LP with LGL, re-LP with gastrotomy and suturing, control | 14 days | Less gastrotomy suturing dehiscence, anastomotic burst unaffected |
| Alfabet 2003 | Rat | Descriptive | 24 | Proximal stomach | LDE, LP with LGL, control | 3, 7, 10, 14 days | Sudden drop of BF/ Perfusion increases over time from ligation (reaches 96% at 14 days) |
| Leme 2004 | Rat | Comparative | 23 | Proximal stomach | LDE, LS with LGL/SGL, control | 7, 14 days | Sudden drop of BF/ Perfusion increases over time from ligation (reaches initial levels at 14 days) |
| Reavis 2005 | Opossum | Comparative | 37 | Gastric fundus | LDE, LP with LGL/SGL/ RGL, re-LP with EA, control, histology | 28 days | Sudden drop of BF/ Perfusion 3 times better at re-laparotomy, increased vasodilation and angiogenesis, less anastomotic collagen deposition, less ischemic injury, less muscularis atrophy) |
| Cuenca-Abente 2008 | Pig | Descriptive | 8 | Gastric fundus | LDE, LS with LGL/SGL and partial gastric transection, control | 3 weeks | Sudden drop of BF/ Increased vascularity and improved blood flow at control |
| Lamas 2008 | Rat | Randomized comparative | 42 | Gastric fundus | LP with LGL, control, histology, biochemical analysis | 1, 3, 6, 10, 15, 21 days | Neovascularization and complete histologic recovery at 15 days (improvement over time) |

Table 1 (continued)

| Author, year | Animal | Study design | n | Area of measurement | Technique | Time interval | Effect of gastric devascularization on BF/ Main results of ischemic conditioning |
|-----------------|-------------|------------------------|----|-----------------------------|---|----------------|---|
| Mittermair 2008 | Rat | Comparative | 20 | Great and lesser curvatures | Fluorescence microscopy, LP with LGL | 28, 56 days | Sudden drop of BF/ Gastric microperfusion significantly showed continuous improvement over time |
| Beck 2010 | Mongrel dog | Comparative | 17 | Proximal gastric | Fluorescent microspheres, LS with SGL/LGL- vs SGL- vs no-artery ligation, re-operation with THE/CA, control | 3 weeks | Sudden and severe drop of BF/ Ligation of LG+SG more effective than SG alone or no preconditioning |
| Perry 2013 | Oposum | Randomized comparative | 24 | Anastomotic site | LP with LGL/SGL/RGL, re-LP with EA, control | 7, 30, 90 days | Significant neovascularization at 30 days. Degree of inflammation at anastomosis, muscularis preservation, and levels of collagen deposition improved with longer conditioning period |

Note. 'Time interval' indicates time from devascularization to re-operation(s) or control. BF: blood flow. EA: esophagectomy and anastomosis. LDF: laser Doppler flowmetry. LGL: left gastric artery ligation. LP: laparotomy. LS: laparoscopy. RGL: right gastric artery ligation. SGL: short gastric arteries ligation. THE: transhiatal esophagectomy.

Measurements in animals showed that gastric perfusion drops substantially immediately after vessel ligation, with a subsequent continuous increase over time approaching the initial levels after 2 to 3 weeks^{18-20,24-26} or even more latently in one report²⁷. Additional benefit in the conduit blood flow was shown when the short gastric arteries were ligated in addition to the left gastric artery in one comparative study²⁸. Peak neovascularization and complete histologic recovery occurred at 15 days after ischemia whereas muscularis propria preservation and decreased inflammation and collagen deposition at the healing anastomosis were more significant at 30 days as compared to 7 days following the procedure²⁰⁻²³. Finally, there is evidence that ischemically conditioned rats had lower rates of gastrotomy suturing dehiscence and fewer anastomotic leakages after esophagogastric anastomosis compared to unconditioned controls^{25,26}. The latter procedures were performed at 2 or 3 weeks after gastric partial devascularisation.

CLINICAL STUDIES

Ischemic conditioning of the stomach using preoperative arterial embolization

Attempts to prevent anastomotic leakage after esophagogastric anastomosis in humans with preoperative ischemic conditioning of the stomach using coil embolization were initiated in Japan in the 1990s^{29,31,32}. This technique is performed through femoral artery access, arteriography of the celiac tripod, and embolization of most of the feeding arteries of the stomach sparing the right gastro-epiploic artery. The left gastric artery was embolized with coils in all studies²⁹⁻³³. Other vessels that were occluded in various combinations were the proximal or distal part of the splenic artery, the short gastric arteries, and the right gastric artery.

All clinical studies using PAE were non-randomized and showed that it is a feasible and safe procedure²⁹⁻³³. Relevant details are depicted in **Table 2**. On average, the time interval from PAE to esophagogastric anastomosis was approximately 2 weeks, with even shorter intervals in a substantial number of patients. Studies that measured the perfusion of the stomach at the time of the esophagogastric anastomosis showed that PAE resulted in less reduction of the blood flow at the anastomotic site of the gastric conduit compared to non-preconditioned patients^{29,31,32,37}. Also, lower rates of anastomotic leakage in patients with PAE compared to controls were reported²⁹⁻³³. Hospital stay for the procedure was 1 to 2 days on average^{29,31,33}. Complications after the procedure were minor and were all treated conservatively. They included abdominal pain, nausea or vomiting. Few cases of splenic infarction and distal pancreatitis were noted, which were attributed to embolization of the distal part of the splenic artery instead of its root.

Table 2 Clinical studies using preoperative arterial embolization (PAE)

| Author, year | n | Study design | Technique | Time interval | Anastomosis | Effect of embolization to BF after gastric tube formation | Leakage (%) PAE vs. non-PAE | Leakage severity | Other complications |
|----------------------------|-------------|---------------------------|--|----------------------|----------------|---|-----------------------------|---|---|
| Akiyama 1996 ^{*†} | 24 | Retro, comparative | LGE/SE/RGE beyond 2 nd or 3 rd branch, LDF | NR | NR | Less BF drop with PAEs (23% vs 65%) / More PAE cases maintained >50% of tissue BF (88% vs 8%) | NR | NR | NR |
| Akijama 1998 [†] | 71 (PAE 51) | Retro, comparative | LGE/SE/RGE beyond 2 nd or 3 rd branch, LDF | >1 week is suggested | CE 33%, IT 28% | Improved BF with PAE (67% vs 33%) | 2% vs 8% | NR | Severe abd pain (6%) [‡] , 1 splenic necrosis [‡] , 1 distal pancreatitis ^{‡,ab} |
| Isomura 1999 ^{*†} | 37 | Retro, comparative | LGE/RGE/SE | NR | CE 72%, IT 67% | Less drop in BF with PAE (27.5% vs 68.9%) | NR | NR | NR |
| Diana 2011 | 38 (PAE 19) | Mainly retro, comparative | LGE/SGE/SE (2 patients required 2 nd procedure) | 17±5 days | NR | NR | 11% vs. 21% | 100% mild (PAE) vs 37.5% mild (non-PAE) | Similar complication rates, 1 partial splenic necrosis ^b |
| Farran 2011 | 39 | Retro, descriptive | LGE/RGE/SE | 14-21 days | CE 100% | NR | 3% | NR | 2.6% distal pancreatitis ^b , 9% splenic infarction ^b |

Note: 'Time interval' indicates time from PAE to esophagectomy. †: same institution. *: abstract only. ‡: SE embolized beyond its root. ^b: treated conservatively. BF: blood flow. CE: cervical. IT: intrathoracic. LGE: left gastric artery embolization. NR: not reported. Retro: retrospective. RGE: right gastric artery embolization. SA: splenic artery. SE: splenic artery embolization.

Ischemic conditioning of the stomach using laparoscopy

The methodology of laparoscopic ischemic conditioning varies among the published series. Studies have ranged between performing ligation of the left gastric artery alone, to the total mobilization of the stomach including the cardia with ligation of all the gastric arteries (sparing the right gastro-epiploic artery) and creation of the gastric conduit, and clearance of lymphatic stations at the celiac tripod, the hepatic and the splenic arteries^{9,10,34-42}. All studies showed that laparoscopic preoperative conditioning of the stomach is feasible and safe, with low to nil conversion rates^{9,34-41}. It is noticeable that partial devascularization of the stomach has been performed rather as an additional procedure in the context of staging laparoscopy, or jejunal fistula formation^{9,10,34,35,38,39,42}. Also, it appears that the time interval between ischemic conditioning and esophagogastric anastomosis has been determined empirically, or according to institutional resources, as it varied widely from 2 days to several weeks. Relevant details from the studies evaluating laparoscopic ischemic conditioning are depicted in **Table 3**.

Six studies showed decreased leakage rates in patients undergoing ischemic conditioning (0 – 13.4%) compared to those without conditioning (8.5 – 26%), whereas these rates were increased in one study^{10,36-40,42}. Of note, the latter series employed a mean interval of 6 days between the two procedures³⁸. Also, reduced leakage severity rates were reported in the preconditioned patients resulting in decreased need for re-intervention via thoracotomy^{10,38-40}. None of the above-mentioned investigations was randomized. Accordingly, non-comparative series concluded that all leakages were minor and treated successfully conservatively or endoscopically using a stent^{9,41}.

The investigators of one study pointed out the impact of timing between preconditioning and esophagogastric anastomosis⁴². They showed that it is premature to proceed to the anastomosis at a short time interval since that results in significantly higher leakage rates compared to longer intervals. In particular, all seven patients who underwent esophagectomy and anastomosis at five days after laparoscopic ischemic conditioning developed ischemic conduit failure and leakage, whereas the corresponding rate for a two-week time interval was 5.7% out of 35 cases. In four of the early cases, ischemia of the tip of the gastric tube was detected already at the time of the main surgery, and this ischemic part was resected before anastomosis. Another study reported two circumscribed necroses of the upper part of the fundus after gastric tube formation at the second operation in a total of 83 patients⁴¹. In that study also, the ischemic area was resected after the gastric pull-up and subsequent anastomosis was performed, resulting in minor leakage in one of these patients only without major sequelae.

Table 3 Clinical studies using laparoscopic ischemic conditioning (LIC)

| Author, year | n (LIC) | Study design | Technique | Time interval | Leakage (%) LIC vs non-LIC | Leakage severity | Other complications / Other conclusions |
|--------------------|-----------|-----------------------------|-------------------------------|----------------------------|----------------------------|--|---|
| Nguyen 2006† | 9 | Retro, descriptive | STL, LGL, jej-T | 12 ± 10 d | 0 | NA | NA |
| Hölscher 2007‡ | 83 | Retro, descriptive | GM, LGL, OE, IT | 4.3 d (range 3-7) | 6 | All leakages were minor (stented) | Major postoperative complications 13.3%. Death 0% at 90 days. |
| Berrisford 2009§ | 77 (22) | Prosp database, comparative | STL, LGL 3-stage tMIE, CA | 2 wks (median 15.5 d) | 9.5 vs 20 | Reduced leakage severity (1/2 vs 4/11) | NA |
| Schröder 2010‡ | 419 (238) | Retro, comparative | GM, LGL, OE, IT | 4-5 d | 7.6 vs 9.4 | Reduced early leakage % (44.4 vs 64.7), reduced leakage severity % (less thoracotomies after LIC 16.7 vs 58.8) | LIC reduced: septic complications, leakage-related mortality % (22.2 vs 35.3), mortality % (2.9 vs 6.1) |
| Perry 2010 | 32 (7) | Prosp database, comparative | STL, LGL/SGL, jej-T, tMIE, CA | 1 wk (n=5), 12 wks (n=2) | 0 vs 16 | NA | Strictures: 14% after LIC vs 12% in controls |
| Veera-mootoo 2010§ | 97 (42) | Prosp database, comparative | STL, LGL, 3-stage tMIE, CA | 2 wks (35 pts) 5 d (7 pts) | 11.9 vs 20 | Reduced leakage severity % (4.8 vs 12.7) | Timing of operation after LIC had a definite impact on the conduit failure rate |
| Nguyen 2012† | 152 (81) | Retro, comparative | STL, LGL±SGL, tMIE, IT | 2 - 75 d (mean 6±5.4) | 11.1 vs 8.5 | Reduced need for surgical treatment of leakage (1/81 vs 4/71 were re-operated) | Strictures: 29.6% after LIC vs 25.3% in controls |

Table 3 (continued)

| Author, year | n (LIC) | Study design | Technique | Time interval | Leakage (%) LIC vs non-LIC | Leakage severity | Other complications / Other conclusions |
|--------------------------------|----------|-----------------------------|-----------------------------------|-------------------------|----------------------------|---|---|
| Wajed 2012 ^s | 131 (67) | Prosp database, comparative | STL, LG, 3-stage tMIE, CA | 2 wks | 13.4 vs 18.8 | Reduced leakage severity % (3 vs 12.5) | NA |
| Veera-mootoo 2012 ^s | 16 (8) | RCT | DFM, STL, LGL, 3-stage tMIE, CA | 2 wks | NA | NA | LIC does not improve perfusion at the conduit tip |
| Zahedi 2012 ^{*†} | 63 (23) | Retro, comparative | STL, CNL, LGL/ SGL, jej-T, OE, IT | 6.6 ± 1.5 d (range 3-9) | 13 vs 26 | NA | Less strictures after LIC (8% vs 32%) |
| Yetasook 2013 [*] | 24 | Retro, descriptive | STL, CNL, LGL/ SGL, jej-T, OE, IT | 4-10 d | NA | All leakages (3) were minor (2 stented, 1 observed) | NA |

Note. 'Time interval' indicates time from LIC to esophagectomy. †: same institution. ‡: same institution. §: same institution. CA: anastomosis at cervical level. CNL: celiac nodes dissection. d: days. DFM: Doppler flowmetry. GM: gastric mobilization. IT: intra-thoracic anastomosis. jej-T: jejunostomy tube. LGL: left gastric artery ligation. NA: not applicable. OE: open esophagectomy. pts: patients. RCT: randomized controlled trial. Retro: retrospective. SGL: short gastric arteries ligation. STL: staging laparoscopy. tMIE: totally minimally invasive esophagectomy. wk(s): week(s).

Meta-analysis of the clinical studies of ischemic conditioning of the stomach

A recent meta-analysis evaluated conclusively the effect of ischemic conditioning of the stomach on the rates of postoperative leakage from the esophagogastric anastomosis¹⁷. Accordingly, 1,215 patients were collected from 12 studies that compared anastomotic leakage rates after embolization or laparoscopic ischemic conditioning with a control group. The incidence of anastomotic leakage was lower in the preconditioned patients (8.8% vs 14.1%, $p=0.10$), however this pooled comparison did not reach statistical significance. Subgroup analysis was based on five studies with 245 patients undergoing PAE, and seven reports with 970 patients that underwent ischemic conditioning with laparoscopic ligation. The reduced leakage rates in the embolization and ligation subgroups for preconditioned patients vs controls were 3.9% vs 12.1% ($p=0.12$) and 10.4% vs 14.5% ($p=0.23$), respectively.

This meta-analysis has therefore demonstrated a non-significant reduction in the incidence of anastomotic leakage following esophagectomy through the use of ischemic conditioning, which seemed more prominent in the patients who underwent arterial embolization. The authors concluded that there is no strong evidence base to advocate a clinical benefit from using ischemic conditioning prior to esophagectomy and esophagogastric anastomosis and that caution should be exercised in the widespread adoption of this technique.

DISCUSSION

APPRAISAL OF THE LITERATURE RESULTS

This review summarizes the reports that deal with the ischemic conditioning of the stomach and its potential benefits in reducing leakage rates and severity after esophagectomy and esophagogastric anastomosis. Blood flow measurements and histologic analysis in experimental studies support that ischemic conditioning increases the perfusion of the gastric tube if a time interval of at least two to three weeks is used. The clinical studies showed that ischemic conditioning reduces the drop of the blood flow at the construction of the gastric tube. There were promising postoperative results in terms of anastomotic leakage prevention and reduction of leakage severity after PAE or laparoscopic gastric ischemic conditioning. Accordingly, the use of this method is followed by reduced percentages of anastomotic leakage of the esophagogastric anastomosis - particularly in the embolization group-, however the comprehensive and subgroup pooled analyses did not attain statistical significance. This finding precludes the widespread adoption

of the technique for the prevention of anastomotic leakage after esophagogastric anastomosis. Nevertheless, the methodology employed in the clinical studies showed great variation which was not discussed in the meta-analysis described above¹⁷. In-depth assessment of the methodology is crucial as it shows that there are additional issues to consider for the conclusive evaluation of the role of the technique.

The correct timing between partial gastric devascularization and esophagogastric anastomosis is yet considered unclear⁴⁷. Nevertheless, data from experimental and clinical studies suggest that the effect of ischemic conditioning increases with time and a minimum time interval of two weeks is necessary for an adequate conditioning of the gastric conduit. So far, most clinical reports that evaluated the effectiveness of the technique in the reduction of anastomotic leakage did not implement rigid and precise protocols with a standardized interval. Anastomosis was performed early after gastric partial devascularization in a part of the patients, which may have deprived the results from showing a potential additional benefit from the technique^{38,40,42}. A short time interval between ischemic conditioning and esophagectomy with esophagogastric anastomosis particularly occurred in patients of the laparoscopic arterial ligation studies, in which the ligation procedure was coupled to laparoscopic staging or jejunal fistula formation. This may have resulted in potential bias and it may also partly explain the relatively better results achieved with PAE as opposed to laparoscopic ligation.

One clinical study so far has evaluated and defined the timing between the two procedures as a risk factor for postoperative leakage⁴². As few patients have been studied this essential variable cannot be part of a pooled sub-group analysis. However, this investigation suggests that there is a high risk of gastric conduit ischemia during or after the main operation when this is performed within 5 days from ischemic conditioning as opposed to a 15-day interval⁴². Although data are weak, performing the main procedure at two-weeks after laparoscopic ischemic conditioning should be preferred to earlier intervals. If performed early there is risk of conduit ischemia and, moreover, the benefit of ischemic conditioning is minimized. The same report described a subjective increase in the difficulty of the abdominal dissection overall in the ligation group related to scarring around the lesser curve of the stomach⁴². This, however, was not reflected in an increased operating time or blood loss compared to the cases without ligation further suggesting that, despite of adhesion formation, relatively delayed esophagectomy after laparoscopic conditioning is feasible and does not risk the integrity of the right gastro-epiploic vessels. A longer than a two-week interval to esophagectomy and anastomosis may be implemented in patients with PAE as, in that case, tissue scarring is not the issue.

Another subject of note is that the available studies investigated the effect of gastric partial devascularization to all candidates for esophagectomy while no attempt was made to identify a cohort with enhanced benefit from the technique. Accordingly, cautious interpretation of the meta-analysis²² may suggest that ischemic conditioning of the stomach for the prevention of anastomotic leakages is not suitable at least for unselected patients undergoing esophagectomy. Only one study selected seven patients with poor cardiopulmonary status for ischemic conditioning with the aim to reduce postoperative leakage³⁶. Although it remains yet hypothetical, careful selection of patients with higher risk for anastomotic leakage could increase the relative benefit and contribute to better results after gastric ischemic conditioning.

The identification of universal preoperative predictors of leakage after esophagogastric anastomosis has been difficult so far due to the lack of widely accepted definitions and to the consequent heterogeneity of reporting^{51,52}. Nevertheless, a large study on over 7500 esophagectomies showed that non-technical factors that predict anastomotic leakage were congestive heart failure, hypertension, and renal insufficiency². Another study suggested a risk score based on the presence, number, and extent of calcifications in the aorta and the right post-celiac arteries as determined on diagnostic computed tomography (CT) scanning⁵³. Raised scores in the corresponding vessels were associated with increased odds of anastomotic leakage of 2 and 4.2 times respectively⁵³. It is notable that the predictors suggested in the reports mentioned above are either predisposing factors or consequences of local and diffuse arterial disease which possibly constitute the major underlying cause of anastomotic leakage after esophagogastric anastomosis, namely ischemia.

The adoption of predictors for anastomotic leakage after esophagectomy and esophagogastric anastomosis may contribute in the better selection of patients for gastric ischemic conditioning. The use of congestive heart failure and renal insufficiency as accrual parameters in a randomized trial would result to an insufficient cohort as these factors were coded in less than 3% of cases². Accordingly, the difference in leakage rates between patients with hypertension (12%) and without hypertension (9%) is small². As a result, the investigation of the effect of ischemic conditioning only in hypertensive patients is not feasible as it would require large numbers of cases to confirm any benefit from the procedure. Contrarily, aortic calcifications - that have also been related to anastomotic leakage - are common to esophagectomy patients (30%)⁵³ and could serve as inclusion criterium for ischemic conditioning trials.

Another recommendation for future evaluation of gastric ischemic conditioning would be standardization of anesthesia and surgical techniques in all patients with the aim to achieve universally homogeneous perioperative factors that potentially affect the hemostasis of the gastric tube. To this regard, it should be acknowledged that thoracic sympathectomy is not a standard practice during esophagectomy, and it should be avoided in all cases as it may affect the blood supply to the fundus⁵⁴. Moreover, there have been concerns from experimental studies that the use of vasopressors may locally impair fundic perfusion in settings of acute hemorrhagic hypovolemia⁵⁵. Acute blood loss during esophagectomy, corrected solely by the use of norepinephrine, requires further investigation to evaluate its clinical significance⁵⁵. Therefore, future investigations in patients with ischemic conditioning should address acute perioperative hypovolemia rather than the administration of fluids. On the contrary, the use of vasopressors under normovolemic conditions has no adverse effect on gastric microvascular flow⁵⁶.

Application of ischemic conditioning of the stomach could also be considered in patients with an intraoperative verification of poor vascular status of the future gastric anastomotic site. The use of fluorescence imaging with indocyanine green can visualize the vascularity and perfusion of the stomach during both laparotomy and laparoscopy¹⁵. Ischemic conditioning is unnecessary in patients with good perfusion of the upper stomach after its mobilization and arterial ligation, and before the transection of the gastric tube. In contrast, if poor vascular status is notified during the operation, the procedure could be terminated at this point and the gastric tube transection, esophagectomy and esophagogastric anastomosis could be performed secondarily after two weeks. Additionally, an experimental report suggested that the blood supply of the fundus of the gastric conduit depends on the ratio of the length of the gastro-epiploic vascular arcade and the length of the greater curvature⁵⁷. However, this finding has not been implemented yet in clinical settings as an intraoperative determinant of the fundic perfusion and deserves further attention.

It is worth noting that the stomach is structured with a wide net of intramural vessels which is more prominent in the lesser curvature⁵⁸. Preservation of this intramural vascular network at the side of the lesser curvature - which could be achieved by whole stomach interposition - could theoretically maximize the effect of ischemic conditioning. One institution^{9,37} used the Collard whole stomach interposition technique⁵⁹ for esophagectomy in preconditioned patients, in which the lesser curvature is denuded rather than ligated. Postoperative leakages were only minor with an approximate rate of 12.5%^{9,37}. Only minor leakages with a

low rate of 6% have been reported also after removal of the lesser curve during esophagectomy in patients with ischemic conditioning⁴¹. Due to the limited evidence and lack of direct comparative studies, the influence of preservation versus removal of the lesser curvature during esophagectomy on the impact of gastric ischemic conditioning remains to be elucidated.

Finally, the impact of ischemic conditioning of the stomach on the severity of the leakages and on the postoperative complications has not been studied thoroughly. Although published data showed less severe leakages and a reduced need for re-interventions in preconditioned patients, pertinent pooled information is currently lacking. As esophagectomy constitutes a major operation followed by severe complications and a protracted length of stay, a comprehensive investigation of the potential benefit of gastric partial devascularization to the postoperative course is warranted. Of interest, esophagectomy followed by delayed esophagogastrostomy has the same physiologic principles with preoperative ischemic conditioning of the stomach. Anastomosis is delayed for 3 months after esophagectomy with the aim of improved vascularity in the gastric remnant⁶⁰. Nihil anastomotic leakage has been reported using this method in high-risk patients, however two major procedures are performed with the presence of a cervical esophagostomy in the mean interval⁶⁰.

FUTURE RECOMMENDATIONS

This review shows that widespread practice of ischemic conditioning of the stomach for the prevention of anastomotic leakage is currently not justified. Further clinical research with the implementation of improved methodology is warranted for the evaluation of this modality. An important potential goal of the investigation should be the identification of those patients who may have actual benefit from the technique in terms of postoperative leakage and leakage severity. A prospective randomized study should employ rigid protocols of two weeks interval between laparoscopic ischemic conditioning of the stomach and esophagectomy with esophagogastric anastomosis. A longer interval may be used for patients with PAE as this method does not produce tissue scarring. Suggested timing for embolization in patients scheduled for neo-adjuvant chemoradiation can be after this therapy and the re-staging investigations in order to avoid the inclusion of potential drop-off cases from surgery. The technique should be employed only in patients with a higher than the average risk for postoperative leakage in order to achieve targeted benefit. For example, the effect of ischemic conditioning could be assessed only in patients with aortic calcification as determined on the routine diagnostic CT scan,

or in cases where intraoperative measurements show poor perfusion of the gastric fundus after arterial ligation.

The left gastric artery is the standard target vessel of ischemic conditioning, whereas the right gastroepiploic should always be spared. In the case of PAE, selective occlusion of the right gastric and of the short gastric arteries should be considered. On the contrary, embolization of the splenic artery, particularly at its distant part, does not appear necessary and should not be performed in order to avoid splenic infarction and pancreatitis. Additionally, occlusion of this vessel during conditioning could jeopardize the spleen after esophagectomy, as the short gastric vessels are then ligated.

In conclusion, further research with improved methodology and careful evaluation of the ischemic conditioning of the stomach is necessary for the determination of the exact role of the technique in the prevention of anastomotic leakage after esophagogastric anastomosis.

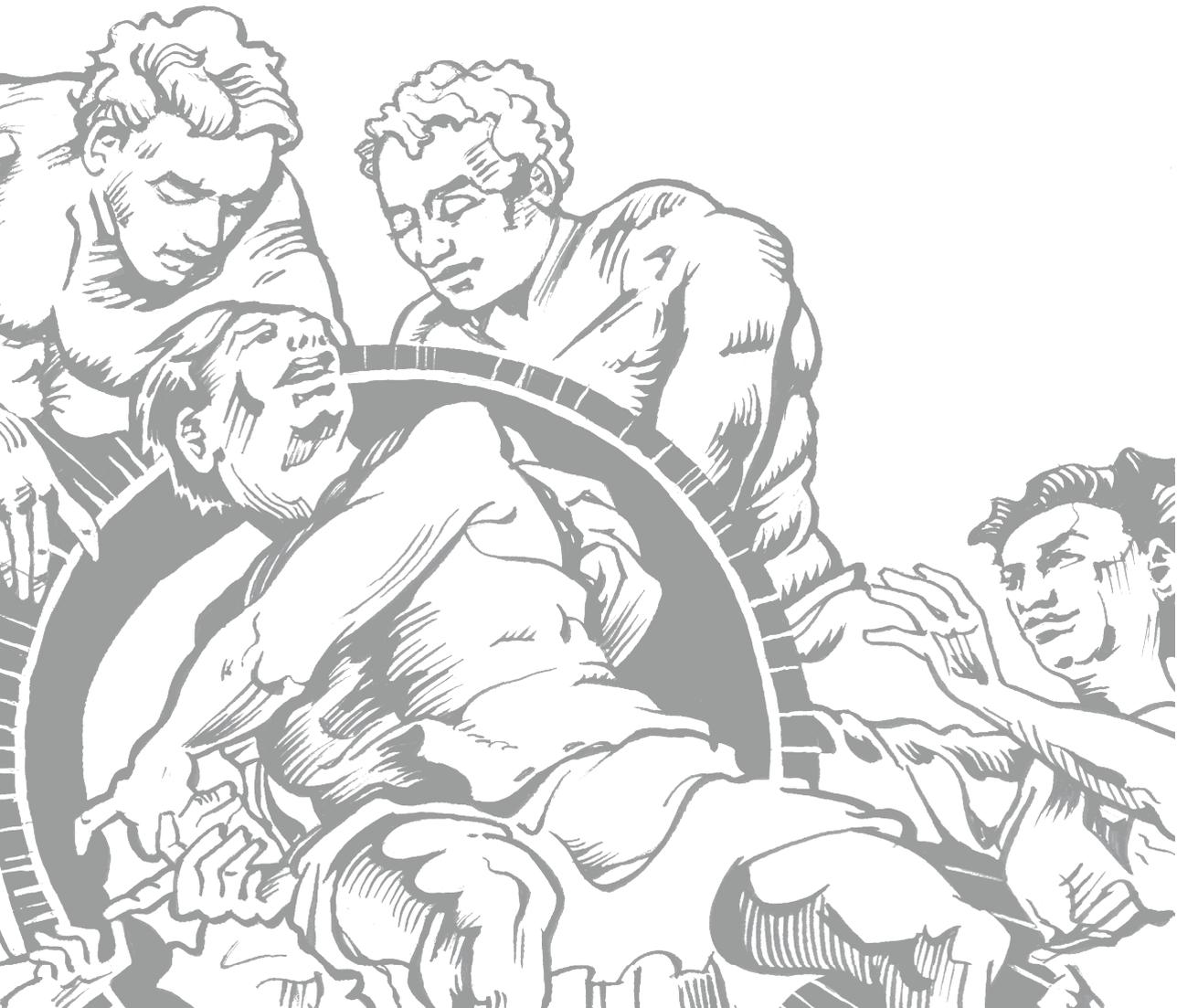
REFERENCES

1. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
2. Kassis ES, Kosinski AS, Ross P Jr, et al. Predictors of anastomotic leak after esophagectomy: an analysis of the society of thoracic surgeons general thoracic database. *Ann Thorac Surg* 2013;96:1919-26
3. Schweigert M, Solymosi N, Dubecz A, et al. One decade of experience with endoscopic stenting for intrathoracic anastomotic leakage after esophagectomy: brilliant breakthrough or flash in the pan? *Am Surg* 2014;80:736-45
4. Schuchert MJ, Abbas G, Nason KS, et al. Impact of anastomotic leak on outcomes after transhiatal esophagectomy. *Surgery* 2010;148:831-40
5. Derogar M, Orsini N, Sadr-Azodi O, et al. Influence of major postoperative complications on health-related quality of life among long-term survivors of esophageal cancer surgery. *J Clin Oncol* 2012;30:1615-9
6. Morse BC, Simpson JP, Jones YR, et al. Determination of independent predictive factors for anastomotic leak: analysis of 682 intestinal anastomoses. *Am J Surg* 2013;206:950-6
7. Sugimachi K, Yaita A, Ueo H, et al. A safer and more reliable operative technique for esophageal reconstruction using a gastric tube. *Am J Surg* 1980;140:471-4
8. Urschel JD. Esophagogastrostomy anastomotic leaks complicating esophagectomy: a review. *Am J Surg* 1995;169:634-40
9. Yetasook AK, Leung D, Howington JA, et al. Laparoscopic ischemic conditioning of the stomach prior to esophagectomy. *Dis Esophagus* 2013;26:479-86
10. Wajed SA, Veeramootoo D, Shore AC. Video. Surgical optimisation of the gastric conduit for minimally invasive oesophagectomy. *Surg Endosc* 2012;26:271-6
11. Zehetner J, DeMeester SR, Alicuben ET, et al. Intraoperative assessment of perfusion of the gastric graft and correlation with anastomotic leaks after esophagectomy. *Ann Surg* 2014;260:1030-3
12. Park SY, Kim DJ, Yu WS, Jung HS. Robot-assisted thoracoscopic esophagectomy with extensive mediastinal lymphadenectomy: experience with 114 consecutive patients with intrathoracic esophageal cancer. *Dis Esophagus* 2016;29:326-32
13. Alldinger I, Sisic L, Hochreiter M, et al. Outcome, complications, and mortality of an intrathoracic anastomosis in esophageal cancer in patients without a preoperative selection with a risk score. *Langenbecks Arch Surg* 2015;400:9-18
14. Ikeda Y, Niimi M, Kan S, et al. Clinical significance of tissue blood flow during esophagectomy by laser Doppler flowmetry. *J Thorac Cardiovasc Surg* 2001;122:1101-6
15. Zehetner J, DeMeester SR, Alicuben ET, et al. Intraoperative assessment of perfusion of the gastric graft and correlation with anastomotic leaks after esophagectomy. *Ann Surg* 2015;262:74-8
16. Yuan Y, Duranceau A, Ferraro P, et al. Vascular conditioning of the stomach before esophageal reconstruction by gastric interposition. *Dis Esophagus* 2012;25:740-9

17. Markar SR, Arya S, Karthikesalingam A, et al. Technical factors that affect anastomotic integrity following esophagectomy: systematic review and meta-analysis. *Ann Surg Oncol* 2013;20:4274-81
18. Alfabet C, Montero EF, Paes Leme LF, et al. Progressive gastric perfusion in rats: role of ischemic conditioning. *Microsurgery* 2003;23:513-6
19. Leme LF, Montero EF, Del Grande JC, et al. Videolaparoscopic model for the gastric ischemic conditioning in rats. *Acta Cir Bras* 2004;19:565-70
20. Reavis KM, Chang EY, Hunter JG, et al. Utilization of the delay phenomenon improves blood flow and reduces collagen deposition in esophagogastric anastomoses. *Ann Surg* 2005;241:736-47
21. Lamas S, Azuara D, de Oca J, et al. Time course of necrosis/apoptosis and neovascularization during experimental gastric conditioning. *Dis Esophagus* 2008;21:370-6
22. Cuenca-Abente F, Assalia A, del Genio G, et al. Laparoscopic partial gastric transection and devascularization in order to enhance its flow. *Ann Surg Innov Res* 2008;2:3
23. Perry KA, Banarjee A, Liu J, et al. Gastric ischemic conditioning increases neovascularization and reduces inflammation and fibrosis during gastroesophageal anastomotic healing. *Surg Endosc* 2013;27:753-60
24. Urschel JD. Ischemic conditioning of the rat stomach: implications for esophageal replacement with stomach. *J Cardiovasc Surg (Torino)* 1995;36:191-3
25. Urschel JD, Takita H, Antkowiak JG. The effect of ischemic conditioning on gastric wound healing in the rat: implications for esophageal replacement with stomach. *J Cardiovasc Surg (Torino)* 1997;38:535-8
26. Urschel JD, Antkowiak JG, Delacure MD, et al. Ischemic conditioning (delay phenomenon) improves esophagogastric anastomotic wound healing in the rat. *J Surg Oncol* 1997;66:254-6
27. Mittermair C, Klaus A, Scheidl S, et al. Functional capillary density in ischemic conditioning: implications for esophageal resection with the gastric conduit. *Am J Surg* 2008;196:88-92
28. Beck SM, Malay MB, Gagné DJ, et al. Experimental model of laparoscopic gastric ischemic preconditioning prior to transhiatal esophagectomy. *Surg Endosc* 2011;25:2470-7
29. Akiyama S, Ito S, Sekiguchi H, et al. Preoperative embolization of gastric arteries for esophageal cancer. *Surgery* 1996;120:542-6
30. Diana M, Hübner M, Vuilleumier H, et al. Redistribution of gastric blood flow by embolization of gastric arteries before esophagectomy. *Ann Thorac Surg* 2011;91:1546-51
31. Akiyama S, Kodera Y, Sekiguchi H, et al. Preoperative embolization therapy for esophageal operation. *J Surg Oncol* 1998; 69:219-23
32. Isomura T, Itoh S, Endo T, et al. Efficacy of gastric blood supply redistribution by transarterial embolization: preoperative procedure to prevent postoperative anastomotic leaks following esophagoplasty for esophageal carcinoma. *Cardiovasc Intervent Radiol* 1999;22:119-23
33. Farran L, Miro M, Alba E, et al. Preoperative gastric conditioning in cervical gastropasty. *Dis Esophagus* 2011;24:205-10
34. Nguyen NT, Longoria M, Sabio A, et al. Preoperative laparoscopic ligation of the left gastric vessels in preparation for esophagectomy. *Ann Thorac Surg* 2006;81:2318-20

35. Veeramootoo D, Shore AC, Wajed SA. Randomized controlled trial of laparoscopic gastric ischemic conditioning prior to minimally invasive esophagectomy, the LOGIC trial. *Surg Endosc* 2012;26:1822-9
36. Perry KA, Enestvedt CK, Pham TH, et al. Esophageal replacement following gastric devascularization is safe, feasible, and may decrease anastomotic complications. *J Gastrointest Surg* 2010;14:1069-73
37. Zahedi M, Ganai S, Yetasook A, et al. Laparoscopic ischemic conditioning as a modality to reduce gastric conduit morbidity following esophagectomy. Poster presented at the 53rd Annual Meeting of the Society for Surgery of the Alimentary Tract, May 18-22, 2012, San Diego Convention Center, San Diego, California.
38. Nguyen NT, Nguyen XM, Reavis KM, et al. Minimally invasive esophagectomy with and without gastric ischemic conditioning. *Surg Endosc* 2012;26:1637-41
39. Berrisford RG, Veeramootoo D, Parameswaran R, et al. Laparoscopic ischaemic conditioning of the stomach may reduce gastric-conduit morbidity following total minimally invasive oesophagectomy. *Eur J Cardiothorac Surg* 2009;36:888-93
40. Schröder W, Hölscher AH, Bludau M, et al. Ivor-Lewis esophagectomy with and without laparoscopic conditioning of the gastric conduit. *World J Surg* 2010;34:738-43
41. Hölscher AH, Schneider PM, Gutschow C, et al. Laparoscopic ischemic conditioning of the stomach for esophageal replacement. *Ann Surg* 2007;245:241-6
42. Veeramootoo D, Shore AC, Shields B, et al. Ischemic conditioning shows a time-dependent influence on the fate of the gastric conduit after minimally invasive esophagectomy. *Surg Endosc* 2010;24:1126-31
43. Urschel JD. Ischemic conditioning of the stomach may reduce the incidence of esophagogastric anastomotic leaks complicating esophagectomy: a hypothesis. *Dis Esophagus* 1997;10:217-9
44. Urschel JD. Esophagogastric anastomotic leaks: the importance of gastric ischemia and therapeutic applications of gastric conditioning. *J Invest Surg* 1998;11:245-50
45. Urschel JD. Gastric conditioning. *Recent Results Cancer Res* 2000;155:135-44
46. Varela E, Reavis KM, Hinojosa MW, et al. Laparoscopic gastric ischemic conditioning prior to esophagogastrectomy: technique and review. *Surg Innov* 2008;15:132-5
47. Demeester SR. Invited commentary. *Ann Thorac Surg* 2010;90:1126-7
48. Parameswaran R, Berrisford R, Wajed S. Re: Laparoscopic ischemic conditioning of the stomach for esophageal replacement. *Ann Surg* 2008;247:398-9
49. Bludau M, Hölscher AH, Vallböhmer D, et al. Ischemic conditioning of the gastric conduit prior to esophagectomy improves mucosal oxygen saturation. *Ann Thorac Surg* 2010;90:1121-6
50. Bludau M, Hölscher AH, Vallböhmer D, et al. Vascular endothelial growth factor expression following ischemic conditioning of the gastric conduit. *Dis Esophagus* 2013;26:847-52
51. Cassivi SD. Leaks, strictures, and necrosis: a review of anastomotic complications following esophagectomy. *Semin Thorac Cardiovasc Surg* 2004;16:124-32
52. Blencowe NS, Strong S, McNair AG, et al. Reporting of short-term clinical outcomes after esophagectomy: a systematic review. *Ann Surg* 2012;255:658-66

53. van Rossum PS, Haverkamp L, Verkooijen HM, et al. Calcifications of the arteries supplying the gastric tube: a new risk factor for anastomotic leakage in esophageal surgery. *Radiology* 2015;274:124-32
54. Ishigami K, Murakami T, Oka M. Neurovascular manipulation for safer surgery of thoracic esophageal cancer. In: Siewert JR, Hoelscher AH, eds. *Diseases of the Esophagus*. Springer-Verlag, Berlin, Germany, 1988:437-442
55. Theodorou D, Drimousis PG, Larentzakis A, et al. The effects of vasopressors on perfusion of gastric graft after esophagectomy. An experimental study. *J Gastrointest Surg* 2008;12:1497-501
56. Van Bommel J, De Jonge J, Buise MP, et al. The effects of intravenous nitroglycerine and norepinephrine on gastric microvascular perfusion in an experimental model of gastric tube reconstruction. *Surgery* 2010;148:71-7
57. Mori T. An experimental study on the hemodynamics of the gastric tube for esophageal reconstruction. *Nippon Geka Hokan* 1991;60:250-63
58. Kudo T, Abo S, Itabashi T. Prognosis of esophageal substitute in tissue variability and anastomotic leakage. In: Siewert JR, Hoelscher AH, eds. *Diseases of the Esophagus*. Springer-Verlag, Berlin, Germany, 1988:522-5
59. Collard JM, Tinton N, Malaise J, et al. Esophageal replacement: gastric tube or whole stomach? *Ann Thorac Surg* 1995;60:261-7
60. Oezcelik A, Banki F, DeMeester S, et al. Delayed esophagogastrostomy: a safe strategy for management of patients with ischemic gastric conduit at time of esophagectomy. *J Am Coll Surg* 2009;208:1030-4



Chapter 17

Intraoperative and postoperative risk factors for anastomotic leakage and pneumonia after esophagectomy for cancer

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Diseases of the Esophagus 2016

ABSTRACT

BACKGROUND

Morbidity and mortality after esophagectomy are often related to anastomotic leakage or pneumonia. This study aimed to assess the relationship of intraoperative and postoperative vital parameters with anastomotic leakage and pneumonia after esophagectomy.

MATERIALS AND METHODS

Consecutive patients who underwent transthoracic esophagectomy with cervical anastomosis for esophageal cancer from January 2012 to December 2013 were analyzed. Univariable and multivariable logistic regression analyses were used to determine potential associations of hemodynamic and respiratory parameters with anastomotic leakage or pneumonia.

RESULTS

From a total of 82 included patients, 19 (23%) developed anastomotic leakage and 31 (38%) experienced pneumonia. The single independent factor associated with an increased risk of anastomotic leakage in multivariable analysis included a lower minimum intraoperative pH (odds ratio [OR] 0.85, 95% confidence interval [CI] 0.77–0.94). An increased risk of pneumonia was associated with a lower mean arterial pressure (MAP) in the first 12 hours after surgery (OR 0.93, 95% CI 0.86–0.99) and a higher maximum intraoperative pH (OR 1.14, 95% CI 1.02–1.27).

CONCLUSION

A lower minimum intraoperative pH (below 7.25) is associated with an increased risk of anastomotic leakage after esophagectomy, whereas a lower postoperative average MAP (below 83 mmHg) and a higher intraoperative pH (above 7.34) increase the risk of postoperative pneumonia. These parameters indicate the importance of setting strict perioperative goals to be protected intensively.

INTRODUCTION

Surgical resection of the esophagus with en-bloc lymphadenectomy is the cornerstone of curative treatment for patients with esophageal cancer¹⁻³. Anastomotic leakage and pneumonia are the most frequently encountered complications after esophagectomy^{4,5}. Both complications are associated with increased postoperative morbidity, length of hospital stay and mortality⁶⁻¹⁰. Furthermore, both anastomotic leakage and pneumonia have been shown to negatively affect long-term cancer-specific survival after esophagectomy^{11,12}. Despite improvement in surgical techniques and perioperative management, incidence rates of up to 24-30% and 27-46% have been reported for anastomotic leakage and pulmonary complications, respectively^{4,5,13}.

Several factors, such as neoadjuvant chemoradiotherapy, anatomic site of the anastomosis, diabetes mellitus, body mass index (BMI), age, congestive heart failure, hypertension, renal insufficiency and smoking have been reported to contribute to the risk of anastomotic leakage or pneumonia after esophagectomy^{5,7,9,14}. A reduction in tissue perfusion and subsequent oxygenation of the gastric tube is considered to be one of the main causes of insufficient anastomotic healing^{6,14}. Therefore, the maintenance of vascular blood flow and adequate tissue oxygenation in the intraoperative and postoperative period are likely of importance^{15,16}. Also, pulmonary complications may be related to intraoperative hypoxemia and hypotension, which trigger the release of pro-inflammatory mediators and activation of leucocytes¹⁷. Perioperative hypotension, decreased oxygen content and other hemodynamic and respiratory factors are modifiable and may therefore provide potential opportunities for anastomotic and pulmonary protection intraoperatively and during the early postoperative phase at the intensive care unit (ICU).

In general, however, the influence of specific modifiable intraoperative and postoperative management factors on the occurrence of anastomotic leakage and pneumonia has not yet been elucidated. Also, some of these management factors may potentially be useful for early identification of patients who carry a high risk of developing these complications. Therefore, the aim of this post-hoc analysis was to evaluate associations of intraoperative and postoperative management factors on the occurrence of anastomotic leakage and pneumonia after transthoracic esophagectomy in patients with esophageal cancer.

MATERIALS AND METHODS

STUDY POPULATION

Institutional review board approval was obtained and the requirement for written informed consent was waived for this study. All patients who underwent elective esophagectomy at our tertiary referral center from January 2012 to December 2013 were included. Data on patient and treatment-related characteristics were extracted from a prospectively acquired surgical database. Intraoperative management data were collected from continuously recorded digital intraoperative measurements, whereas postoperative ICU management data were extracted from a prospectively collected ICU database.

ANESTHETIC PROCEDURE

Before surgery all patients received an epidural catheter to provide adequate intraoperative and postoperative analgesia. Pre-procedural medication consisted of prophylactic antibiotics (cefazolin 2,000 mg, metronidazole 500 mg) and intravenous injection of 10 mg/kg methylprednisolone 30 minutes prior to incision¹⁸. Anesthesia was performed using intravenously administered propofol, sufentanil and a muscle relaxant. Endotracheal intubation was performed with a left-sided double-lumen tube to enable desufflation of the right lung during the thoracic phase of the procedure. During single-lung ventilation, a pressure-controlled ventilation strategy was used with a maximum pressure of 27 cm H₂O and maximum tidal volume of 6 ml/kg. During double-lung ventilation, tidal volumes were set at 6-8 ml/kg with the aim to maintain end-tidal CO₂ between 40 and 45 mmHg.

SURGICAL PROCEDURE

To limit the influence of different surgical procedures on the results, only patients who underwent transthoracic resection with extended two-field lymphadenectomy were included. Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy was the standard procedure for patients with esophageal cancer of all stages in our institute¹⁹. Exclusion criteria were benign disease and combined laryngeal resection. For the construction of the gastric tube a linear stapling device was used and the staple line was manually oversewn (Endo GIA™ Stapler, Covidien, Dublin, Ireland). All anastomoses were performed in the neck, using a single-layer hand-sewn end-to-side esophagogastrostomy. All surgical procedures were carried out by two experienced upper gastro-intestinal surgeons (JPR and RvH).

After the surgical procedure, patients were transferred to the ICU while maintaining sedation and intubation. Extubation was encouraged when patients were considered cardiorespiratory stable (median time to extubation was 6 hours [interquartile range (IQR): 1-10]). Following extubation, patients remained in the ICU until safe transfer to the surgical ward was deemed appropriate.

VARIABLES AND RISK FACTORS

Baseline parameters of interest included age, gender, BMI, American Society of Anesthesiologists (ASA) score, chronic obstructive pulmonary disease (COPD), diabetes mellitus, cardiovascular comorbidity, history of smoking and neoadjuvant treatment. The retrieved intraoperative and postoperative management factors consisted of hemodynamic characteristics, respiratory characteristics, fluid management, laboratory findings and temperature. Data on postoperative management was restricted to the first 24 hours of ICU admission after surgery. A detailed description of studied factors is provided in **Table 1**.

Both clinical and radiologic anastomotic leakage was scored within 30 days after surgery. Clinical leakage was defined as visualization of anastomotic dehiscence or fistulae during endoscopy, visible loss of saliva through the cervical wound, or sepsis caused by mediastinal or intrathoracic manifestations confirmed by CT scan. Radiologic leakage was defined as extravasation of water-soluble contrast during a barium swallow study or CT scan. Postoperative pneumonia was defined according to the definition of the Utrecht Pneumonia Score (UPS)²⁰. In this clinical scoring system points are assigned based on leukocyte count, temperature and radiography findings. Pneumonia is defined as a score of minimally 2 points, with at least 1 point for pulmonary radiography (i.e. findings of either diffused or well-circumscribed infiltrate).

STATISTICAL ANALYSIS

Multiple imputation of missing values was performed to deal with missing values for intraoperative and postoperative management factors, using 20 imputed datasets²¹. The association of patient and treatment-related factors with anastomotic leakage and pneumonia was studied univariably. Categorical parameters were compared using the Chi-square test or Fisher's exact test in case of small cell counts. The Student's T-test and Mann-Whitney U test were used to compare groups with and without anastomotic leakage and with or without pneumonia for parametric and non-parametric continuous parameters, respectively. In order to analyze whether the different intraoperative and postoperative management factors influenced the

risk of anastomotic leakage and pneumonia, univariable logistic regression models were constructed providing odds ratios (ORs) with 95% confidence intervals (CIs). Logarithmic transformations were applied for several parameters to achieve improved linearity on the log odds scale. Also, for several parameters the values were multiplied by 100 to facilitate an easier interpretation of the OR estimates.

Subsequently, parameters with a $p \leq 0.10$ in univariable analysis were entered in a multivariable logistic regression model to evaluate whether these factors were independently associated with the occurrence of anastomotic leakage or pneumonia. High correlations between some parameters were expected (e.g. $p\text{CO}_2$ and pH), resulting in the statistical problem of (multi)collinearity. Therefore, from highly correlated pairs of parameters (i.e. Spearman rank correlation coefficient $r \geq 0.6$) only the one parameter with the lowest p -value in univariable analysis was pre-selected for the multivariable model. For parameters that remained independently and significantly related to anastomotic leakage or pneumonia, receiver operating characteristic (ROC) curve analyses were performed to determine ideal cut-off values by giving equal weight to sensitivity and specificity. Statistical analysis was performed using SPSS 20.0 (IBM Corp. Armonk, NY, USA). A p -value of <0.05 was considered statistically significant.

RESULTS

In the study period a total of 106 patients underwent esophagectomy with gastric tube reconstruction. Of these patients, 24 were excluded because of a transhiatal resection ($n=15$), benign disease ($n=4$), insufficient recording of postoperative data ($n=3$) at the ICU, or a combination with laryngeal resection ($n=2$). In 19 (23%) of the remaining 82 patients anastomotic leakage occurred, whereas 31 patients (38%) experienced postoperative pneumonia. Anastomotic leakage occurred after a median time of 8 days (range 3-17) after esophagectomy, whereas pneumonia was diagnosed after a median of 5 days (range 2-18). Missing values were encountered for 15 variables, but the percentage of missing values per variable was limited (median 6%, range 1% to 9%). The imputed variables are addressed in **Table 1**.

The median length of hospital stay was prolonged in patients with anastomotic leakage compared to patients without anastomotic leakage (median [IQR]: 27 days [21-33] versus 13 days [11-18], respectively; $p<0.001$). Also, in patients with pneumonia the length of hospital stay was increased compared to patients without pneumonia (median [IQR]: 19 days [13-35] versus 13 days [10-18], respectively; $p<0.001$). In-hospital mortality occurred in 3 (3.7%) of 82 patients, of which 2

Table 1 Studied intraoperative and postoperative management factors

| Intraoperative factors | Postoperative factors (first 24 hours) |
|---|---|
| Hemodynamic factors | |
| Duration of surgery (minutes) | First postoperative systolic RR [†] |
| Blood loss (mL) | First postoperative diastolic RR [†] |
| Minimum hemoglobin measured | Average MAP at different time points* † |
| Number of blood transfusions | Total duration MAP <60 (minutes) |
| Inotrope requirement (yes or no) | Total duration systolic RR < 90 (minutes) |
| Maximum inotrope dose in (mg/h) | Inotrope requirement (yes or no) |
| Time in minutes of inotrope admission | Maximum inotrope dose in (mg/h) |
| Minimum measured MAP | Total duration inotrope requirement (minutes) |
| Time in minutes that systolic RR was <90 | Inotrope requirement at different time points* |
| Time in minutes that MAP was <60 | Urine production (mL) at different time points**† |
| Diuresis <30cc/h (yes or no) | First measured postoperative hemoglobin |
| Maximum measured heart rate | Fluid balance (mL) 0-6, 0-12, 0-18 hours after surgery† |
| Minimum measured heart rate | Diuresis <30cc/h (yes or no) |
| Average heart rate | |
| Total fluid infusion (mL) | |
| Average diuresis (mL/h) | |
| Respiratory factors | |
| Duration one-lung ventilation (minutes) | Mean respiratory rate |
| Average saturation | Average saturation |
| Minimum FiO ₂ | pO ₂ /FiO ₂ ratio |
| Maximum FiO ₂ | Time to extubation (minutes)† |
| Average FiO ₂ | First ABG pH |
| Maximum pH in ABG [†] | First ABG pCO ₂ |
| Minimum pH ABG † | First ABG pO ₂ |
| pH <7.36 (yes/no)† | First ABG bicarbonate |
| Maximum ABG pCO ₂ [†] | First ABG base excess |
| Minimum ABG pCO ₂ [†] | |
| Maximum ABG pO ₂ [†] | |
| Minimum ABG pO ₂ [†] | |
| Maximum ABG bicarbonate [†] | |
| Minimum ABG bicarbonate [†] | |
| Average PEEP | |
| Mean tidal volumes | |
| Other factors | |
| Average temperature measured | First postoperative temperature measured |
| Minimum temperature measured | Maximum temperature measured |
| Maximum temperature measured | |

*: Different time points: 0-6, 7-12, 13-18,19-24, 0-12, 13-24 and 0-24 hours after surgery. RR: blood pressure. MAP: mean arterial pressure. ABG: arterial blood gas. mL: milliliter. h: hour.

†: Imputed variables.

suffered from both pneumonia and anastomotic leakage. Simultaneous occurrence of anastomotic leakage and pneumonia within the same individual was found in 7 of 82 patients (8.5%). No significant difference in incidence of pneumonia among patients with or without anastomotic leakage was found (37% versus 38%, respectively; $p=0.572$).

Patient and treatment-related characteristics and their univariable association with anastomotic leakage and pneumonia are demonstrated in **Table 2**. COPD was relatively rare ($n=4$), but significantly related to a higher risk of anastomotic leakage ($p=0.037$). Other studied patient and treatment-related factors were not significantly associated with the occurrence of either anastomotic leakage or pneumonia.

Table 2 Patient and treatment-related characteristics in relation to postoperative complications

| Characteristic | No anastomotic leakage (n=63) | Anastomotic leakage (n=19) | <i>p</i> value | No pneumonia (n=51) | Pneumonia (n=31) | <i>p</i> value |
|----------------------------|-------------------------------|----------------------------|----------------|---------------------|------------------|----------------|
| Male gender | 50 (79.4) | 14 (73.7) | 0.752 | 39 (76.5) | 25 (80.6) | 0.658 |
| Age (years)* | 63.0 ± 9.0 | 63.9 ± 6.8 | 0.813 | 63.6 ± 8.4 | 62.5 ± 8.8 | 0.569 |
| BMI (kg/m ²)* | 25.1 ± 3.3 | 25.4 ± 5.3 | 0.987 | 25.3 ± 3.9 | 24.9 ± 3.5 | 0.382 |
| ASA score | | | 0.505 | | | 0.147 |
| I | 17 (27.0) | 3 (15.8) | | 9 (17.6) | 11 (35.5) | |
| II | 34 (54.0) | 13 (68.4) | | 33 (64.7) | 14 (45.2) | |
| III | 12 (19.0) | 3 (15.8) | | 9 (17.6) | 6 (19.4) | |
| COPD | 1 (1.6) | 3 (15.8) | 0.037 | 1 (2.0) | 3 (9.7) | 0.116 |
| FEV ₁ predicted | 102.7 ± 16.1 | 99.7 ± 22.0 | 0.286 | 103.5 ± 17.4 | 99.6 ± 17.8 | 0.840 |
| Cardiac co-morbidity | 20 (31.7) | 5 (26.3) | 0.652 | 12 (23.5) | 13 (41.9) | 0.079 |
| Vascular co-morbidity | 24 (38.7) | 8 (41.1) | 0.791 | 19 (38.0) | 13 (41.9) | 0.725 |
| Diabetes mellitus | 6 (9.5) | 3 (15.8) | 0.426 | 3 (5.9) | 6 (19.4) | 0.076 |
| Smoking at diagnosis | 15 (23.8) | 1 (5.3) | 0.101 | 8 (15.7) | 8 (25.8) | 0.262 |
| Neoadjuvant therapy | | | 0.314 | | | 0.225 |
| No therapy | 8 (12.7) | 1 (5.3) | | 4 (7.8) | 5 (16.1) | |
| Chemotherapy | 12 (19.0) | 5 (26.3) | | 13 (25.5) | 4 (12.9) | |
| Chemoradiotherapy | 43 (68.3) | 13 (68.4) | | 34 (66.7) | 22 (71.0) | |

Data presented as numbers of patients with percentages in parentheses. *Data presented as mean ± standard deviation. Cardiac co-morbidity: history of myocardial infarction, heart failure, cardiac arrhythmia, or (treated) coronary artery disease. Vascular co-morbidity: history of hypertension or peripheral artery disease.

ANASTOMOTIC LEAKAGE

Intraoperative and postoperative management factors that showed a potential association with anastomotic leakage in univariable analysis ($p \leq 0.10$) are presented in **Table 3**. In univariable analyses studying intraoperative factors a lower minimum pH, lower maximum pH, higher pCO_2 , and higher minimum pCO_2 in the arterial blood gas (ABG) were significantly associated with an increased risk of anastomotic leakage. Postoperatively on the ICU, a higher pCO_2 in the first postoperative ABG after esophagectomy was significantly associated with an increased risk of anastomotic leakage. No other intraoperative and postoperative management factors were significantly associated with anastomotic leakage (Supplementary Tables 1-3, online). Specifically, no differences between patients with and without anastomotic leakage were noted for the mean arterial pressure (MAP) and duration of inotrope requirement (in the form of noradrenaline).

Table 3 Univariable analyses of intraoperative and postoperative management factors potentially associated with anastomotic leakage ($p \leq 0.10$)

| Parameter | No anastomotic leakage | Anastomotic leakage | OR | 95% CI | p value |
|-------------------------------------|------------------------|---------------------|-------|---------------|--------------|
| Intraoperative | | | | | |
| Maximum pH in ABG* | 7.36 [7.32-7.39] | 7.33 [7.27-7.36] | 0.880 | 0.789 - 0.980 | 0.020 |
| Minimum pH in ABG* | 7.30 [7.27-7.35] | 7.22 [7.15-7.30] | 0.847 | 0.767 - 0.934 | 0.001 |
| Maximum pCO_2 in ABG | 52.0 [46.0-56.0] | 65.0 [50.0-76.0] | 1.091 | 1.032 - 1.125 | 0.002 |
| Minimum pCO_2 in ABG | 43.0 [39.3-46.0] | 46.0 [40.0-53.0] | 1.112 | 1.024 - 1.206 | 0.011 |
| Postoperative | | | | | |
| pH in first postoperative ABG* | 7.38 [7.35-7.41] | 7.35 [7.33-7.38] | 0.907 | 0.818 - 1.006 | 0.063 |
| pCO_2 in first postoperative ABG* | 41.0 [36.0-46.0] | 44.0 [38.0-52.0] | 1.100 | 1.006 - 1.203 | 0.036 |

Data presented as median with interquartile range [IQR] between brackets. *Note.* Only factors showing a potential association ($p \leq 0.10$) with the outcome are presented. ABG: arterial blood gas. CI: confidence interval. OR: Odds ratio. *Parameter multiplied by 100 to facilitate interpretation of the OR.

In multivariable analysis, a lower intraoperative minimum pH remained independently associated with a higher risk of anastomotic leakage (OR 0.85 [per 0.01 increase in pH], 95% CI 0.77–0.94, $p=0.003$; **Table 4**). Using ROC analysis the minimum pH below which the risk of anastomotic leakage increased significantly was statistically determined at 7.25 (**Table 6**). Patients with a pH below versus above this threshold had a chance of 51% versus 12% to develop anastomotic leakage, respectively (**Table 6, Figure 1**). The first postoperative pCO_2 did not retain its significant association with anastomotic leakage when adjusted for intraoperative minimum pH.

Table 4 Results of multivariable logistic regression analysis

| Parameter | Outcome | | |
|---|---------|---------------|----------------|
| | OR | 95% CI | <i>p</i> value |
| Anastomotic leakage | | | |
| Intraoperative minimum pH in ABG* | 0.848 | 0.766 - 0.939 | 0.001 |
| pCO ₂ in first postoperative ABG | 1.091 | 0.989 - 1.204 | 0.083 |
| Pneumonia | | | |
| Postoperative MAP 0-12h | 0.927 | 0.864 - 0.995 | 0.035 |
| Intraoperative maximum pH in ABG* | 1.136 | 1.017 - 1.269 | 0.024 |
| Postoperative diuresis <30 mL/h | 1.931 | 0.584 - 6.384 | 0.281 |
| Intraoperative blood loss (mL) [†] | 1.000 | 0.999 - 1.000 | 0.362 |

ABG: arterial blood gas. CI: confidence interval. OR: odds ratio. MAP: mean arterial pressure. mL: milliliter. [†]Log-transformed parameter. *Parameter multiplied by 100 to facilitate interpretation of the OR.

Table 5 Univariable analyses of intraoperative and postoperative management factors potentially associated with pneumonia (*p* ≤ 0.10)

| Parameter | No pneumonia | Pneumonia | OR | 95% CI | <i>p</i> value |
|---------------------------------|------------------|------------------|-------|---------------|----------------|
| Intraoperative | | | | | |
| Blood loss (mL) [†] | 360 [200-580] | 460 [340-810] | 1.672 | 0.939 - 2.977 | 0.081 |
| Maximum pH in ABG* | 7.34 (7.30-7.37) | 7.37 (7.34-7.40) | 1.152 | 1.034 - 1.283 | 0.010 |
| Minimum pCO ₂ in ABG | 45.0 (42.0-49.0) | 39.0 (39.0-45.0) | 0.919 | 0.845 - 1.000 | 0.050 |
| Postoperative | | | | | |
| Average MAP 0-6h | 79.1 (75.0-86.7) | 77.4 (71.7-80.3) | 0.941 | 0.889 - 0.997 | 0.039 |
| Average MAP 7-12h | 78.4 (71.5-92.1) | 74.5 (68.7-81.1) | 0.936 | 0.887 - 0.986 | 0.013 |
| Average MAP 13-18h | 83.2 (74.2-95.2) | 80.0 (71.8-82.8) | 0.961 | 0.924 - 1.000 | 0.050 |
| Average MAP 13-24h | 81.4 (72.3-97.2) | 82.7 (72.6-88-2) | 0.966 | 0.927 - 1.006 | 0.092 |
| Average MAP 0-12h | 77.5 (73.6-87.8) | 75.8 (72.8-78.5) | 0.917 | 0.858 - 0.980 | 0.011 |
| Average MAP 0-24h | 79.3 (75.7-90.6) | 77.8 (70.9-81.8) | 0.938 | 0.888 - 0.992 | 0.025 |
| Diuresis <30 mL/h (yes/no) | 30 (58.8%) | 25 (80.1%) | 3.215 | 1.070 - 9.660 | 0.037 |

ABG: arterial blood gas. CI: confidence interval, h: hour. MAP: mean arterial pressure. OR: odds ratio. [†]Log-transformed parameter. *Parameter multiplied by 100 to facilitate interpretation of the OR.

PNEUMONIA

Parameters that showed a potential association with the development of pneumonia in univariable analysis (*p* ≤ 0.10) are presented in **Table 5**. In univariable analysis, patients with postoperative pneumonia had a significantly higher maximum pH and lower minimum pCO₂ in the intraoperative ABG measurements. Postoperative

ICU management factors associated with pneumonia included a lower average MAP in the first 6, 12 and 24 hours after surgery and a urine production of less than 30 mL during at least one hour in the first 24 hours after surgery. No other intraoperative and postoperative management factors were significantly associated with pneumonia (Supplementary Tables 1-3, online).

The maximum intraoperative pH, intraoperative blood loss, average MAP between 0 to 12 hours postoperatively and postoperative urine production of <30 mL during at least one hour in the first 24 hours were selected for multivariable analysis (Table 4). Higher maximum intraoperative pH (OR 1.14 [per 0.01 increase in pH], 95% CI 1.02–1.27, $p=0.024$) and lower average MAP (OR 0.93, 95% CI 0.86–0.99, $p=0.035$) in the first 12 hours after esophagectomy on the ICU remained independently associated with pneumonia.

Using ROC analysis, the maximum intraoperative pH above which the risk of pneumonia increased significantly was statistically determined at 7.34. Patients with a maximum intraoperative pH above versus below this threshold had a chance of 52% versus 23% to develop pneumonia, respectively (Table 6, Figure 1). The average postoperative MAP (0-12 hours) below which the risk of pneumonia increased significantly was identified at 83 mmHg. Patients with an average postoperative MAP (0-12 hours) below versus above this threshold had a chance of 49% versus 9% to develop pneumonia after esophagectomy, respectively (Table 6, Figure 1). Postoperative urine production of <30 mL during at least 1 hour in the first 24 hours and intraoperative blood loss did not retain their significant association with pneumonia when adjusted for the maximum intraoperative pH and average MAP in the first 12 hours after esophagectomy.

Table 6 Diagnostic performance of vital parameters resulting from multivariable analysis for predicting the postoperative complications

| Parameter | Outcome | | | | |
|----------------------------------|---------------|-------|-------|--------|--------|
| | Ideal cut-off | SE(%) | SP(%) | PPV(%) | NPV(%) |
| Anastomotic leakage | | | | | |
| Intraoperative minimum pH in ABG | 7.25 | 63.9 | 81.4 | 51.0 | 88.1 |
| Pneumonia | | | | | |
| Average MAP 0-12h | 83.21 | 93.5 | 41.1 | 49.1 | 91.3 |
| Intraoperative maximum pH in ABG | 7.34 | 70.0 | 59.9 | 51.5 | 76.7 |

MAP: mean arterial pressure. ABG: arterial blood gas. SE: sensitivity. SP: specificity. PPV: positive predictive value. NPV: negative predictive value.

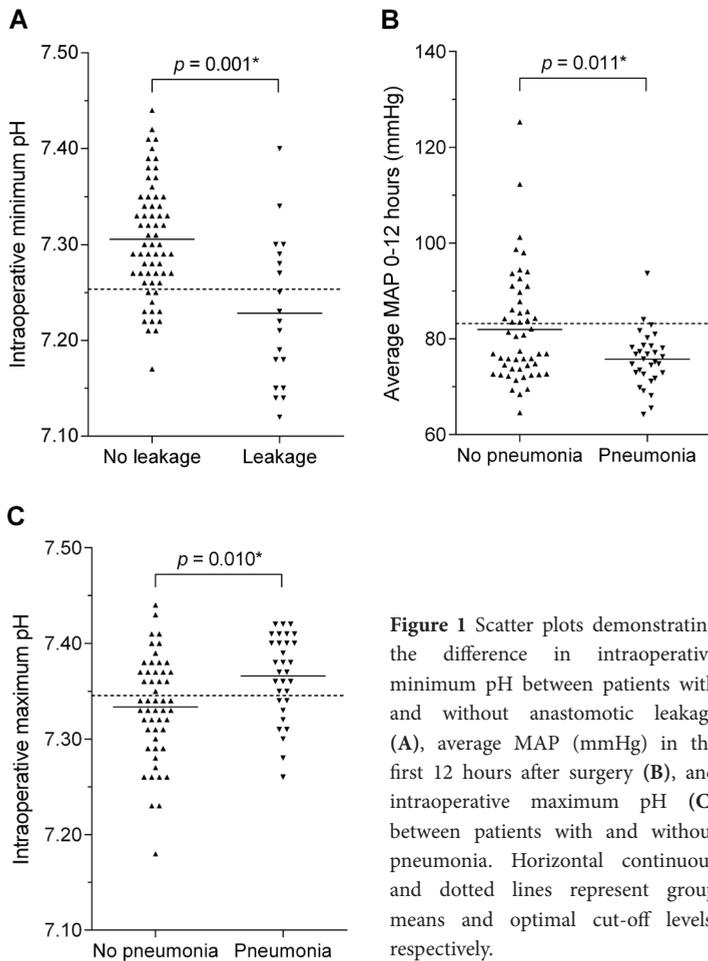


Figure 1 Scatter plots demonstrating the difference in intraoperative minimum pH between patients with and without anastomotic leakage (A), average MAP (mmHg) in the first 12 hours after surgery (B), and intraoperative maximum pH (C) between patients with and without pneumonia. Horizontal continuous and dotted lines represent group means and optimal cut-off levels, respectively.

DISCUSSION

Recognition of the influence of intraoperative and postoperative management factors on the occurrence of the two most frequently encountered complications after esophagectomy for cancer could contribute to the improvement of intraoperative and postoperative decision-making and development of preventative therapeutic approaches. However, so far these influences have not yet been analyzed in detail. In this study extensive measurements of hemodynamic and respiratory factors during and early after esophagectomy were performed to investigate the association of these factors with postoperative anastomotic leakage and pneumonia. A lower

minimum intraoperative pH (below 7.25) was found to be significantly associated with anastomotic leakage, whereas a higher intraoperative pH (above 7.34) and a lower average MAP (below 83 mmHg) in the first 12 hours after esophagectomy were significantly and independently related to pneumonia. These findings can be used to set and protect specific perioperative cardiorespiratory goals that may lead to reduced postoperative complications.

Previous studies have identified blood loss during surgery²², hypotensive events²², insufficient oxygen delivery²³ and the need for inotropic support²⁴ as perioperative risk factors for anastomotic leakage after esophagectomy. In the current study no differences between patients with and without for anastomotic leakage with regard to perioperative MAP measurements, intraoperative blood loss and the need for inotropic support between patients with and without for anastomotic leakage were observed. However, a lower minimum intraoperative pH was identified as independent risk factor for anastomotic leakage. The intraoperative pH may be an indicator of surgical stress and the patient's physical reserve, since a low pH can frequently be attributed to hypovolemia and tissue hypoperfusion²⁵. Tissue hypoperfusion is often associated with hypotension and hypoxemia. Hypoxemia and poor tissue perfusion have previously been considered as major causes of anastomotic leakage^{6,14,23}. The current study rather suggests that intraoperative pH measurement may serve as a better predictor for the occurrence of anastomotic leakage compared to parameters related to blood pressure and blood loss.

Our study demonstrated that a lower average MAP in the first 12 hours after surgery was independently associated with a higher risk of pneumonia. This observation corresponds with the results of a previous study that found an association between hypotension and respiratory complications after esophagectomy¹⁷. Perioperative hypotension has been linked to the release of pro-inflammatory mediators and activation of circulating neutrophils^{17,26}. This inflammatory response can cause lung injury by damaging the endothelial and epithelial cells, which predicted the occurrence of pulmonary complications in another study²⁷. The development of lung injury caused by the described chain of events may contribute to the development of postoperative pneumonia. In addition, a higher pH in the intraoperative ABG was found to be associated with an increased risk of developing pneumonia. The higher pH in these patients was accompanied by lower pCO₂ values in these patients, which may suggest ventilation-induced hypocapnia. This might in turn be a consequence of relatively high ventilation frequency or high tidal volumes applied during intraoperative ventilation which can cause ventilation-induced lung injury^{28,29}. However, we were not able to substantiate this hypothesis since

both higher intraoperative tidal volumes, higher positive end-expiratory pressure (PEEP) and higher ventilation frequencies were not associated with pneumonia (Supplementary Table 2, online). Other factors that have been associated with postoperative pulmonary complications in previous studies include increased infusion of crystalloid and colloids, the use of inotropics and the impairment of pO_2/FiO_2 ^{17,26,27}. These associations could not be confirmed by the current study, but we reasonably assume that at least to some extent these parameters are related to blood pressure and ABG measurements that did appear influential in this study.

Understanding the mechanism associated with the development of anastomotic leakage and pneumonia is of importance, since this may lead to prevention and earlier diagnosis of these potentially fatal complications. In the current series, the parameters associated with anastomotic leakage and pneumonia were likely related to a state of cardiorespiratory instability. It remains unclear whether the association is causal, or if the parameters merely represent a compromised physiologic state associated with an increased risk of anastomotic leakage and pneumonia. Therefore, further investigations are indicated to evaluate the effect of hemodynamic and respiratory interventions, during and after esophagectomy on the postoperative course.

Postoperative anastomotic leakage was relatively common in the current series, occurring in 22% of the patients. Although this appears higher than some other studies, our definition of anastomotic leakage is rather unrestrictive including basically any sign of clinical or radiologic evidence of leakage. Furthermore, the leakage rate in this study appears to be comparable to the leakage rates of 22% and 30% that were reported in the recent multicenter randomized controlled CROSS-trial⁴.

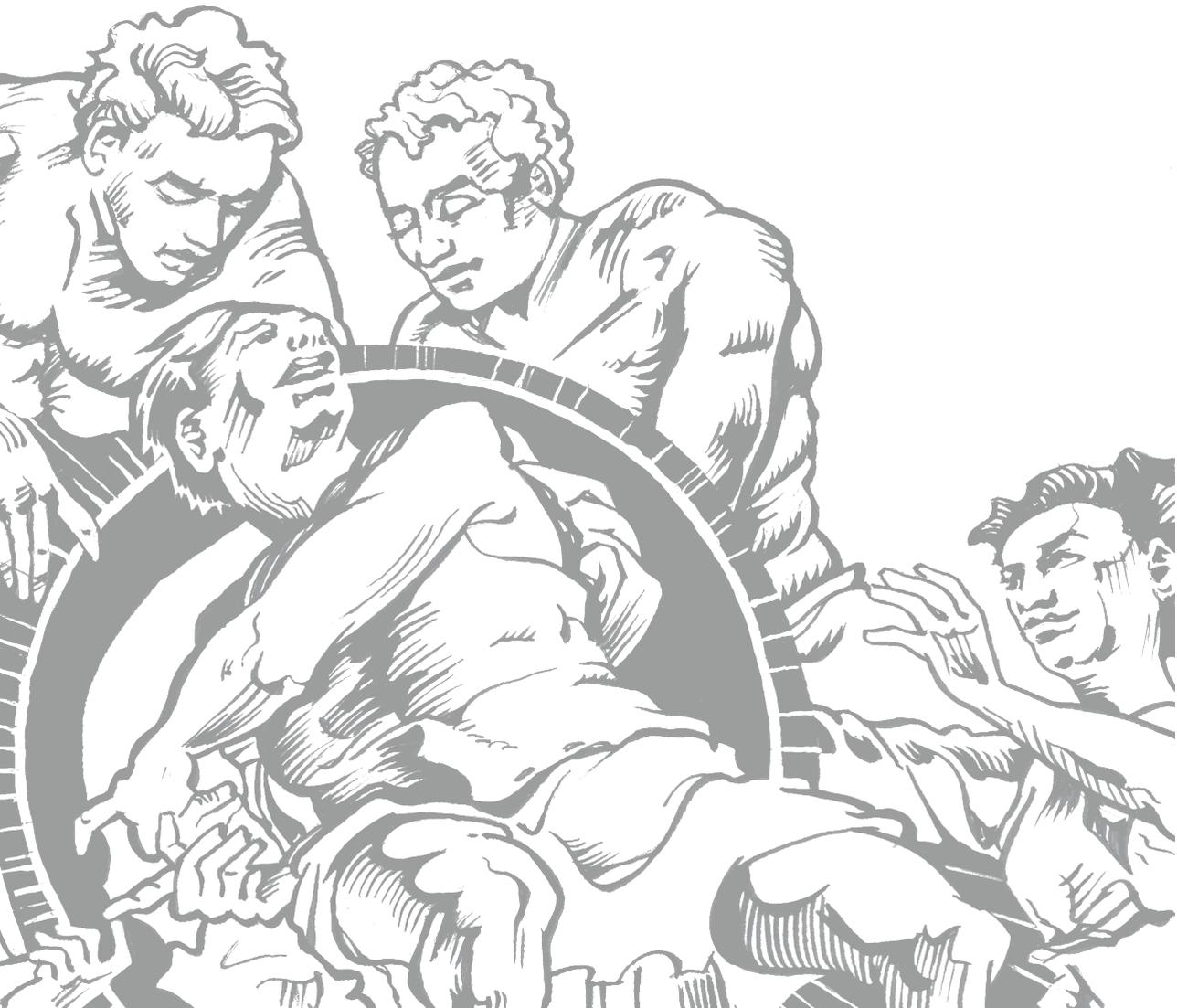
Certain limitations apply to this study. First, the study was single centered and included a relatively small sample size. Second, this is a hypothesis-generating observational study, and therefore the identified associations with anastomotic leakage and pneumonia cannot provide inference of causality. Given the exploratory nature of the study we did not adjust for multiple testing, and therefore false-positive findings cannot be excluded.

In conclusion, this study provides an elaborative means of investigating the possible association of intraoperative and postoperative management factors with anastomotic leakage and pneumonia in patients undergoing esophagectomy for cancer. Intraoperative lower minimum arterial pH (below 7.25) was associated with the development of anastomotic leakage. A lower postoperative average mean arterial pressure (below 83 mmHg) and a higher maximum intraoperative pH (above 7.34) were associated with the development of postoperative pneumonia. These findings may lead to protocols that set goals to provide for better perioperative cardiorespiratory management reducing postoperative complications. Further investigations are indicated to evaluate the effect of hemodynamic and respiratory interventions during and after esophagectomy on the occurrence of anastomotic leakage and pneumonia.

REFERENCES

1. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003;349:2241-52
2. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. *Lancet* 2013;381:400-12
3. Cheedella NK, Suzuki A, Xiao L, et al. Association between clinical complete response and pathological complete response after preoperative chemoradiation in patients with gastroesophageal cancer: Analysis in a large cohort. *Ann Oncol* 2013;24:1262-6
4. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
5. Ferguson MK, Durkin AE. Preoperative prediction of the risk of pulmonary complications after esophagectomy for cancer. *J Thorac Cardiovasc Surg* 2002;123:661-9
6. Urschel JD. Esophagogastrotomy anastomotic leaks complicating esophagectomy: A review. *Am J Surg* 1995;169:634-40
7. Kassis ES, Kosinski AS, Ross P, et al. Predictors of anastomotic leak after esophagectomy: An analysis of the society of thoracic surgeons general thoracic database. *Ann Thorac Surg* 2013;96:1919-26
8. Iannettoni MD, Whyte RI, Orringer MB. Catastrophic complications of the cervical esophagogastric anastomosis. *J Thorac Cardiovasc Surg* 1995;110:1493-500; discussion 1500-1
9. Avendano CE, Flume PA, Silvestri GA, et al. Pulmonary complications after esophagectomy. *Ann Thorac Surg* 2002;73:922-6
10. Alanezi K, Urschel JD. Mortality secondary to esophageal anastomotic leak. *Ann Thorac Cardiovasc Surg* 2004;10:71-5
11. Booka E, Takeuchi H, Nishi T, et al. The impact of postoperative complications on survivals after esophagectomy for esophageal cancer. *Medicine (Baltimore)* 2015;94:e1369
12. Markar S, Gronnier C, Duhamel A, et al. The impact of severe anastomotic leak on long-term survival and cancer recurrence after surgical resection for esophageal malignancy. *Ann Surg* 2015;262:972-80
13. Kim RH, Takabe K. Methods of esophago-gastric anastomoses following esophagectomy for cancer: A systematic review. *J Surg Oncol* 2010;101:527-33
14. Dewar L, Gelfand G, Finley RJ, et al. Factors affecting cervical anastomotic leak and stricture formation following esophago-gastrectomy and gastric tube interposition. *Am J Surg* 1992;163:484-9
15. Ikeda Y, Niimi M, Kan S, et al. Clinical significance of tissue blood flow during esophagectomy by laser doppler flowmetry. *J Thorac Cardiovasc Surg* 2001;122:1101-6
16. Jacobi CA, Zieren HU, Zieren J, et al. Is tissue oxygen tension during esophagectomy a predictor of esophagogastric anastomotic healing? *J Surg Res* 1998;74:161-4
17. Tandon S, Batchelor A, Bullock R, et al. Peri-operative risk factors for acute lung injury after elective oesophagectomy. *Br J Anaesth* 2001;86:633-8
18. Weijs TJ, Dieleman JM, Ruurda JB, et al. The effect of perioperative administration of glucocorticoids on pulmonary complications after transthoracic oesophagectomy: A systematic review and meta-analysis. *Eur J Anaesthesiol* 2014;31:685-94

19. van der Sluis PC, Ruurda JP, Verhage RJ, et al. Oncologic long-term results of robot-assisted minimally invasive thoraco-laparoscopic esophagectomy with two-field lymphadenectomy for esophageal cancer. *Ann Surg Oncol* 2015;22 Suppl 3:1350-6
20. van der Sluis PC, Verhage RJ, van der Horst S, et al. A new clinical scoring system to define pneumonia following esophagectomy for cancer. *Dig Surg* 2014;31:108-16
21. van der Heijden GJ, Donders AR, Stijnen T, et al. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: A clinical example. *J Clin Epidemiol* 2006;59:1102-9
22. Michelet P, D'Journo XB, Roch A, et al. Perioperative risk factors for anastomotic leakage after esophagectomy: Influence of thoracic epidural analgesia. *Chest* 2005;128:3461-6
23. Kusano C, Baba M, Takao S, et al. Oxygen delivery as a factor in the development of fatal postoperative complications after oesophagectomy. *Br J Surg* 1997;84:252-7
24. Zakrison T, Nascimento BA, Tremblay LN, et al. Perioperative vasopressors are associated with an increased risk of gastrointestinal anastomotic leakage. *World J Surg* 2007;31:1627-34
25. Waters JH, Miller LR, Clack S, et al. Cause of metabolic acidosis in prolonged surgery. *Crit Care Med* 1999;27:2142-6
26. Paul DJ, Jamieson GG, Watson DI, et al. Perioperative risk analysis for acute respiratory distress syndrome after elective oesophagectomy. *ANZ J Surg* 2011;81:700-6
27. D'Journo XB, Michelet P, Marin V, et al. An early inflammatory response to oesophagectomy predicts the occurrence of pulmonary complications. *Eur J Cardiothorac Surg* 2010;37:1144-51
28. Grant MC, Yang D, Stone A, et al. A meta-analysis of intraoperative ventilation strategies to prevent pulmonary complications: Is low tidal volume alone sufficient to protect healthy lungs? *Ann Surg* 2016;263:881-7
29. Whitehead T, Slutsky AS. The pulmonary physician in critical care: Ventilator induced lung injury. *Thorax* 2002;57:635-42



Chapter 18

Neoadjuvant radiation to the gastric fundus increases the risk of anastomotic leakage after transthoracic esophagectomy for esophageal cancer

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Annals of Thoracic Surgery 2016 [In press]

ABSTRACT

BACKGROUND

Concerns have been raised regarding the toxicity of neoadjuvant chemoradiotherapy (nCRT) for esophageal cancer that could contribute to an increased risk of postoperative complications. The aim of this study was to determine the influence of the neoadjuvant radiation dose to the gastric fundus on the risk of postoperative anastomotic leakage in patients with esophageal cancer undergoing nCRT followed by transthoracic esophagectomy.

MATERIAL AND METHODS

Between January 2012 and July 2015, 97 consecutive patients with esophageal cancer who underwent nCRT followed by transthoracic esophagectomy were included in this single-center cohort study. The gastric fundus was retrospectively contoured on the pre-treatment planning CT. Within this contour, dose-volume histogram parameters were calculated and logistic regression analysis was used to determine their influence on the risk of postoperative anastomotic leakage.

RESULTS

In 25 (26%) of 97 patients anastomotic leakage occurred. The mean radiation dose to the gastric fundus was significantly higher in patients with versus without leakage (median 35.6 Gy versus 24.9 Gy, respectively; $p=0.047$). A mean dose above versus below 31.4 Gy was associated with leakage rates of 43% versus 15%, respectively. Also, in patients with anastomotic leakage the minimum radiation dose, V25, V30, and V35 to the gastric fundus were significantly higher. Adjusted for tumor location, clinical T-stage, and radiation modality, the mean radiation dose to the gastric fundus remained significantly and independently associated with an increased risk of anastomotic leakage (adjusted odds ratio 1.05 per 1 Gy increase, 95% confidence interval: 1.002-1.10; $p=0.043$).

CONCLUSION

Efforts should be made to minimize the radiation dose to the gastric fundus when planning nCRT for esophageal cancer, since higher dose levels to the gastric fundus are associated with an increased risk of anastomotic leakage after subsequent transthoracic esophagectomy and cervical anastomosis.

INTRODUCTION

Esophageal cancer is the sixth leading cause of cancer-related mortality and continues to affect more than 450,000 people worldwide¹. Esophagectomy is the cornerstone of curative treatment for esophageal cancer and the long-term survival benefit of neoadjuvant chemoradiotherapy (nCRT) is well established²⁻⁴. Over the past decades, a steady decrease in postoperative mortality has been achieved by improvements of surgical techniques and perioperative management⁵. However, anastomotic leakage of the esophagogastrostomy remains one of the major complications negatively impacting surgical and oncologic outcomes^{5,6}. Reported incidence rates of anastomotic leakage after esophagectomy range between 6% and 41%^{3,7-11}.

Concerns have been raised regarding the toxicity of nCRT that could contribute to an increased risk of postoperative complications. Several non-randomized studies reported an increase in surgical morbidity in patients that underwent nCRT¹²⁻¹⁵. Postoperative pulmonary complications have convincingly been related to neoadjuvant radiation dose to the lungs¹⁶⁻¹⁸. However, the influence of neoadjuvant radiation on postoperative anastomotic leakage has been less extensively studied. In this respect, radiation dose to the gastric fundus is of interest as this part of the stomach is used for the esophagogastric anastomosis.

The available evidence on the potential association between neoadjuvant radiation dose to the gastric fundus and the risk of anastomotic leakage after esophagectomy is equivocal^{19,20}. Therefore, currently it remains unclear whether efforts should be made to limit the dose to the gastric fundus when planning neoadjuvant radiation treatment for esophageal cancer. The aim of the present study was to determine the influence of neoadjuvant radiation dose to the gastric fundus on the risk of anastomotic leakage in a large homogeneous cohort of patients with esophageal cancer undergoing nCRT followed by transthoracic esophagectomy and cervical anastomosis.

MATERIAL AND METHODS

STUDY POPULATION

This study was approved by our institutional review board, and the informed consent requirement was waived. From a prospectively acquired database, consecutive patients with esophageal or gastro-esophageal junction (GEJ) cancer were identified who underwent nCRT followed by transthoracic esophagectomy between January 2012 and July 2015 at our tertiary referral center. All patients

had biopsy-proven resectable carcinoma with no evidence of distant metastases. Patients who underwent transhiatal esophagectomy, salvage esophagectomy or non-elective surgery and patients in whom no gastric conduit reconstruction was performed were excluded. The diagnostic work-up consisted of endoscopy with biopsy, endoscopic ultrasound (EUS), ultrasonography of the neck, and either standalone computed tomography (CT) or integrated ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET)/CT scanning for clinical staging.

TREATMENT PROTOCOL

The nCRT regimen consisted of a total radiation dose of 41.4 Gy in 23 fractions of 1.8 Gy in 5 weeks combined with weekly intravenous administration of carboplatin (area under the curve of 2 mg/mL per minute) and paclitaxel (50 mg/m² body-surface area)³. Some patients (with a clinical T4b tumor) received a total radiation dose of 50.4 Gy in 28 fractions of 1.8 Gy in 6 weeks. The gross tumor volume (GTV) was defined by the primary tumor and any suspicious regional lymph nodes as determined by all available information (physical examination, endoscopy, EUS, CT, and ^{18}F -FDG PET if available). The clinical target volume (CTV) included the GTV plus a cranial and caudal margin of 3 cm; in case of tumor extension into the stomach a caudal margin of 2 cm was chosen. In addition, the CTV included a radial margin around the GTV of 0.5 cm, adjusted for anatomical structures. The planning target volume (PTV) was defined as the CTV plus a margin of 1 cm in all directions. Patients were treated by either three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT).

Surgical treatment consisted of a transthoracic esophagectomy with en-bloc two-field lymphadenectomy and gastric conduit reconstruction. A linear stapler (GIATM 80, 3.8 mm, Covidien, Mansfield, MA, USA) was used to create a gastric conduit 4 cm wide, and the gastric conduit staple line was oversewn by hand. A cervical esophagogastric anastomosis was performed end-to-side with hand-sewn continuous sutures (3-0 PDS) in monolayer. For the end-to-side anastomosis, the distal end of the cervical esophagus was positioned perpendicular to the side of the proximal gastric conduit. The surplus of the gastric conduit was removed with a stapling device (GIATM 80, 3.8 mm, Covidien, Mansfield, MA, USA) in all patients.

DATA COLLECTION

Clinical patient characteristics (i.e. gender, age, body mass index [BMI], ASA score, co-morbidities, history of smoking, tumor location, clinical stage and histologic type), treatment details (i.e. radiation modality, total radiation dose, and intraoperative blood loss), and surgical outcome data (i.e. anastomotic leakage, and

hospital stay) were collected from the prospectively acquired database. Anastomotic leakage was defined as postoperative demonstration of saliva through the cervical wound, extravasation of water-soluble contrast during a contrast swallow study or CT scan, or visualization of anastomotic dehiscence or fistulae during endoscopy or surgical re-intervention⁹.

IMAGE ANALYSIS

The gastric fundus was retrospectively contoured on the pre-treatment planning CT (section thickness: 3.0 mm) using Volumetool software²¹. After consultation with the authors of a previous study¹⁹, the boundaries of the delineated gastric fundus were standardized in accordance with the applied method in that study: the most proximal part of the stomach located within the diaphragmatic dome was determined in the transverse plane. From that point, four consecutive transverse sections in caudal direction were delineated following the boundaries of the stomach at these levels. The resulting region of interest (ROI) in three dimensions was defined as the gastric fundus. The following dose-volume histogram parameters were calculated from the ROI: volume, mean dose, minimum dose, D50 (i.e. dose that covered at least 50% of the volume), maximum dose, V20, V25, V30, and V35 (i.e. percentage of the volume that received at least 20, 25, 30, and 35 Gy, respectively).

STATISTICAL ANALYSIS

The association of baseline characteristics with anastomotic leakage was studied univariably. The Chi-square test (or Fisher's exact test in case of small cell counts) was used to compare categorical parameters, whereas the Student's T-test and Mann-Whitney U test were used to compare parametric and non-parametric continuous parameters, respectively. Univariable logistic regression models were used to analyze whether the different radiation dose and volume characteristics of the gastric fundus influenced the risk of anastomotic leakage. Odds ratios (ORs) with 95% confidence intervals (CIs) were provided. For the radiation dose parameters that were significantly related to anastomotic leakage, receiver operating characteristics (ROC) analysis was performed to identify ideal cut-off values in which equal weight was given to sensitivity and specificity.

Three baseline characteristics including tumor location, clinical T-stage and radiation modality, were thought to potentially confound the association between radiation dose to the gastric fundus and anastomotic leakage, by potentially influencing both predictor (radiation dose) and outcome (anastomotic leakage).

Therefore, the (mean) radiation dose to the gastric fundus was entered in a multivariable logistic regression model together with the three potential confounders to study the independent influences on the risk of anastomotic leakage. Statistical analysis was performed using SPSS 23.0 (IBM Corp., Armonk, NY). A p -value of <0.05 was considered statistically significant.

RESULTS

In the study period a total of 115 patients with esophageal cancer were treated with nCRT followed by transthoracic esophagectomy. Of these patients, 18 were excluded because they received radiotherapy at another institution ($n=15$), the treatment planning CT did not include the level of the gastric fundus ($n=1$), the quality of the treatment planning CT was insufficient ($n=1$), or no surgical resection was performed due to unsuspected metastatic disease ($n=1$).

Among the 97 included patients, 25 (26%) developed postoperative anastomotic leakage. The median length of hospital stay was significantly longer in patients with anastomotic leakage compared to patients without anastomotic leakage (median [interquartile range (IQR)]: 31 days [26-36] versus 13 days [11-18], respectively; $p<0.001$). Postoperative in-hospital mortality occurred in 3 of 97 patients (3.1%), of which two suffered from anastomotic leakage. Baseline characteristics and their univariable association with anastomotic leakage are presented in **Table 1**. None of the studied baseline characteristics were significantly associated with the occurrence of postoperative anastomotic leakage.

A comparison of gastric fundus radiation dose characteristics for patients with versus without anastomotic leakage is demonstrated in **Table 2**. In univariable logistic regression analysis, the mean radiation dose to the gastric fundus was significantly higher in patients with anastomotic leakage compared to patients without anastomotic leakage (median [IQR]: 35.6 Gy [20.2-39.9] versus 24.9 Gy [11.9-35.1], respectively; $p=0.047$). Also, in patients with anastomotic leakage the minimum radiation dose to the gastric fundus was significantly higher compared to patients without leakage (15.1 Gy [11.9-26.1] versus 8.9 Gy [2.8-16.9]; $p=0.006$) (**Figure 1a**). In addition, univariable analysis showed that percentages of the gastric fundus volume receiving a minimal dose of 25, 30, and 35 Gy (i.e. V25, V30, V35, respectively) were significantly higher in patients with anastomotic leakage (**Figure 1b**). The volume of the gastric fundus and other radiation dose characteristics were not significantly associated with anastomotic leakage. Two typical examples of dose distributions in relation to the gastric fundus in patients with and without anastomotic leakage are depicted in **Figure 2**.

Table 1 Baseline characteristics

| Characteristic | Anastomotic leakage (n = 25) | No anastomotic leakage (n = 72) | p value |
|--|---------------------------------|------------------------------------|---------|
| Male gender | 19 (76.0) | 53 (73.6) | 0.814 |
| Age (years)* | 64.9 ± 7.6 | 66.3 ± 7.3 | 0.414 |
| BMI (kg/m²)* | 25.6 ± 4.6 | 25.5 ± 4.7 | 0.947 |
| ASA score | | | 0.262 |
| I | 5 (20.0) | 14 (19.4) | |
| II | 12 (48.0) | 48 (66.7) | |
| III | 8 (32.0) | 10 (13.9) | |
| COPD | 6 (24.0) | 9 (12.5) | 0.203 |
| Cardiac co-morbidity | 7 (28.0) | 25 (34.7) | 0.538 |
| Vascular co-morbidity | 12 (48.0) | 33 (45.8) | 0.852 |
| Diabetes mellitus | 4 (16.0) | 10 (13.9) | 0.751 |
| History of smoking | 17 (68.0) | 52 (72.2) | 0.688 |
| Clinical T-stage | | | 0.104 |
| cT1 | 0 (0.0) | 1 (1.4) | |
| cT2 | 3 (12.0) | 19 (26.4) | |
| cT3 | 19 (76.0) | 47 (65.3) | |
| cT4 | 3 (12.0) | 5 (6.9) | |
| Clinical N-stage | | | 0.529 |
| cN0 | 5 (20.0) | 19 (26.4) | |
| cN1 | 12 (48.0) | 34 (47.2) | |
| cN2 | 7 (28.0) | 15 (20.8) | |
| cN3 | 1 (4.0) | 4 (5.6) | |
| Tumor histology | | | 0.799 |
| Adenocarcinoma | 17 (68.0) | 43 (59.7) | |
| Squamous cell carcinoma | 8 (32.0) | 27 (37.5) | |
| Other | 0 (0.0) | 2 (2.8) | |
| Tumor location | | | 0.629 |
| Proximal third of esophagus | 2 (8.0) | 6 (8.3) | |
| Middle third of esophagus | 5 (20.0) | 18 (25.0) | |
| Distal third of esophagus | 15 (60.0) | 41 (56.9) | |
| Gastro-esophageal junction | 3 (12.0) | 7 (9.7) | |
| Radiation modality | | | 0.339 |
| 3D-CRT | 11 (44.0) | 24 (33.3) | |
| IMRT | 14 (56.0) | 48 (66.7) | |
| Total radiation dose | | | 1.000 |
| 41.4 Gy (23 x 1.8 Gy) | 23 (92.0) | 67 (93.1) | |
| 50.4 Gy (28 x 1.8 Gy) | 2 (8.0) | 5 (6.9) | |
| Intraoperative blood loss (mL)* | 500 ± 295 | 502 ± 336 | 0.985 |

Note. Data are numbers of patients with percentages in parentheses.

*Data are mean ± standard deviation.

3D-CRT: three-dimensional conformal radiotherapy. IMRT: intensity-modulated radiotherapy.

Table 2 Univariable logistic regression analysis of gastric fundus dose characteristics among patients with versus without anastomotic leakage

| Characteristic | Anastomotic leakage (n = 25) | No anastomotic leakage (n = 72) | OR (95% CI) | p value |
|-------------------|---------------------------------|------------------------------------|-------------------------------|---------|
| Volume (mL) | 11.1 [8.1-12.8] | 11.8 [8.3-15.9] | 0.92 (0.83-1.02) | 0.121 |
| Mean dose (Gy) | 35.6 [20.2-39.9] | 24.9 [11.9-35.1] | 1.04 (1.00-1.08) | 0.047* |
| Minimum dose (Gy) | 15.1 [11.9-26.1] | 8.9 [2.8-16.9] | 1.06 (1.02-1.11) | 0.006* |
| D50 (Gy) | 39.0 [16.7-41.2] | 21.8 [11.7-38.9] | 1.03 (1.00-1.07) | 0.054 |
| Maximum dose (Gy) | 42.5 [40.9-43.0] | 41.9 [23.2-42.7] | 1.02 (0.98-1.05) | 0.328 |
| V20 (%) | 94.5 [27.5-100] | 60.0 [2.6-93.9] | 1.12 (0.99-1.27) [†] | 0.066 |
| V25 (%) | 90.1 [22.3-99.8] | 38.3 [0.0-81.3] | 1.15 (1.02-1.30) [†] | 0.025* |
| V30 (%) | 73.1 [17.9-96.1] | 26.2 [0.0-76.5] | 1.16 (1.02-1.31) [†] | 0.021* |
| V35 (%) | 63.4 [13.2-93.3] | 17.4 [0.0-65.2] | 1.16 (1.03-1.32) [†] | 0.018* |

Data presented as median with interquartile range (IQR) between brackets.

*Significant difference between patients with versus without anastomotic leakage ($p < 0.05$).

[†]Odds ratio per 10% increase in volume-percentage.

OR: odds ratio. CI: confidence interval.

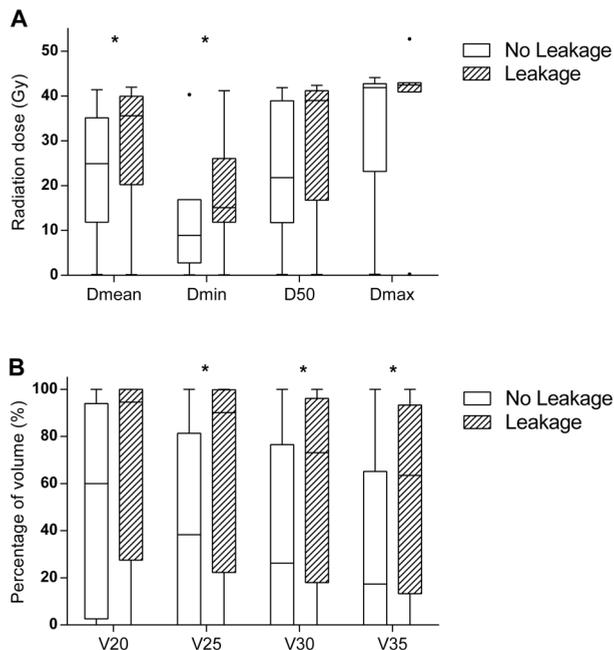


Figure 1 Box plots showing (A) the distribution of gastric fundus dose parameters (Dmean, Dmin, D50, Dmax), and (B) the distribution of gastric fundus volume percentages receiving a minimum amount of Gy (V20, V25, V30, V35) between patients with and without anastomotic leakage. The asterisk (*) indicates parameters significantly associated with anastomotic leakage. The single dots (•) represent individual patient outliers (more than 1.5 times the interquartile range below the first quartile or above the third quartile).

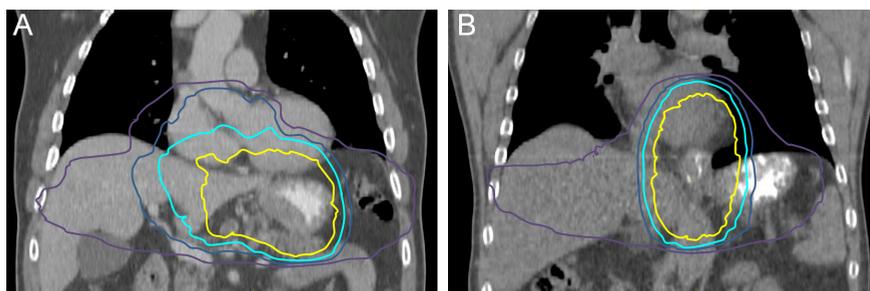


Figure 2 Examples of treatment planning CT scans with dose distributions in (A) a patient who developed postoperative anastomotic leakage after receiving a mean dose to the gastric fundus of 41.2 Gy, and in (B) a patient who did not experience postoperative anastomotic leakage after receiving a mean dose to the gastric fundus of 11.8 Gy. The areas within the yellow, light blue, dark blue and purple lines received at least 40, 30, 20, and 10 Gy, respectively.

Ideal cut-off values as determined by ROC analysis for the parameters that were significantly related to anastomotic leakage are presented in **Table 3**. The mean dose to the gastric fundus above which the risk of anastomotic leakage increased significantly was determined at 31.4 Gy. Patients with a mean dose above versus below this threshold developed anastomotic leakage in 43% versus 15% of cases, respectively. The minimum radiation dose threshold to the gastric fundus above which the risk of anastomotic leakage increased significantly was 10.9 Gy. Patients with a minimum radiation dose above versus below this threshold had a chance of 39% versus 9%, respectively, to develop anastomotic leakage. The ideal cut-off value for the percentage of the gastric fundus volume receiving at least 30 Gy (i.e. V30) was determined at 59%. Patients with a V30 above versus below the threshold of 59% developed anastomotic leakage in 42% versus 16% of cases, respectively.

In multivariable analysis, the association between the (mean) neoadjuvant radiation dose to the gastric fundus and postoperative anastomotic leakage appeared not confounded by tumor location, clinical T-stage or radiation modality (**Table 4**). Adjusted for these factors, the mean radiation dose to the gastric fundus remained significantly and independently associated with an increased risk of anastomotic leakage (adjusted OR 1.05 per 1 Gy increase, 95% CI: 1.002-1.10, $p=0.043$).

Table 3 Receiver operating characteristics analysis of gastric fundus dose characteristics among patients with versus without anastomotic leakage

| Characteristic | AUC | Ideal cut-off | SE (%) | SP (%) | PPV (%) | NPV (%) |
|----------------|------|---------------|--------|--------|---------|---------|
| Mean dose | 0.66 | 31.4 Gy | 64.0 | 70.8 | 43.2 | 85.0 |
| Minimum dose | 0.65 | 10.9 Gy | 84.0 | 54.2 | 38.9 | 90.7 |
| V25 | 0.65 | 89.7% | 52.0 | 80.6 | 48.1 | 82.9 |
| V30 | 0.65 | 59.3% | 60.0 | 70.8 | 41.7 | 83.6 |
| V35 | 0.65 | 54.7% | 60.0 | 72.2 | 42.9 | 83.9 |

AUC: area under the curve. SE: sensitivity. SP: specificity. PPV: positive predictive value. NPV: negative predictive value.

Table 4 Results of multivariable logistic regression analysis with anastomotic leakage as outcome parameter

| Characteristic | OR (95% CI) | <i>p</i> value |
|--|-------------------|----------------|
| Tumor location | | 0.432 |
| Proximal or middle third of esophagus | 1.00 (ref) | |
| Distal third of esophagus or GEJ | 0.60 (0.16-2.17) | |
| Clinical T-stage | | 0.132 |
| cT1-2 | 1.00 (ref) | |
| cT3-4 | 2.81 (0.73-10.77) | |
| Radiation modality | | 0.398 |
| 3D-CRT | 1.00 (ref) | |
| IMRT | 0.65 (0.25-1.74) | |
| Mean radiation dose to gastric fundus | 1.05 (1.002-1.10) | 0.043* |

GEJ: gastro-esophageal junction. 3D-CRT: three-dimensional conformal radiotherapy. IMRT: intensity-modulated radiotherapy. OR: odds ratio. CI: confidence interval.

DISCUSSION

This study demonstrates that the neoadjuvant radiation dose to the gastric fundus in patients with esophageal cancer has a significant impact on the risk of anastomotic leakage after transthoracic esophagectomy with cervical anastomosis. Several radiation dose characteristics appeared to be significant predictors of anastomotic leakage, including the mean and minimum dose, V25, V30, and V35. These findings suggest that efforts should be made to limit the dose to the gastric fundus when planning neoadjuvant radiation for esophageal cancer with planned transthoracic esophagectomy. Overall, 26% of patients developed anastomotic leakage in this series. According to the results of this study, limiting the mean

or minimum dose to 31 Gy or 11 Gy, respectively, or the V30 (i.e. percentage of volume receiving at least 30 Gy) to 59%, could decrease the risk of anastomotic leakage to 9-16% in this setting.

Two previous studies have reported on the relationship between neoadjuvant radiation dose to the gastric fundus and the risk of postoperative anastomotic leakage^{19,20}. Similar to the current series, one study that included 54 patients treated with nCRT followed by Ivor-Lewis esophagectomy with intrathoracic anastomosis reported that the radiation dose to the gastric fundus was significantly related to the risk of anastomotic leakage¹⁹. However, in that study a different neoadjuvant treatment regimen (36 Gy in 20 fractions combined with 5-FU and cisplatin) and surgical procedure (Ivor-Lewis esophagectomy with intrathoracic anastomosis) were applied¹⁹. Of note, neoadjuvant treatment according to the CROSS-regimen as applied in the present study is currently regarded as the standard of care in many countries worldwide for patients with resectable locally advanced esophageal cancer⁴.

In contrast, another recent study with 53 patients that underwent nCRT followed by transhiatal esophagectomy with cervical anastomosis found no influence of radiation dose to the gastric fundus on the occurrence of anastomotic leakage²⁰. That study applied a similar neoadjuvant treatment regimen to the current series, but the surgical procedure (transhiatal esophagectomy with cervical anastomosis) was different²⁰. However, transthoracic esophagectomy with en-bloc radical lymphadenectomy as was performed in the present study is currently considered the preferred approach of oncologic esophagectomy^{22,23}. Therefore, in contrast to other studies, the association between radiation dose to the gastric fundus and anastomotic leakage was analyzed under the circumstances of present-day standardized radical surgery and standardized neoadjuvant chemoradiotherapy in the current study. In addition, sample sizes across the two previous reports^{19,20} were small with only few events of anastomotic leakage (n=7 and n=13, respectively), which resulted in a substantial uncertainty of estimates and conclusions. This may be the reason for the more nuanced discriminatory ability of the mean dose to the gastric fundus to differentiate between patients with versus without leakage found in the current series (i.e. area under the ROC curve [AUC] 0.66; **Table 3**) compared to those found in the other two studies (AUC 0.77¹⁹, and approximately 0.50²⁰).

The current evidence concerning the influence of nCRT on postoperative anastomotic leakage rates remains equivocal. A recent meta-analysis including 11 randomized controlled trials (RCTs) comparing outcomes of patients undergoing

nCRT followed by surgery with patients who undergo surgery alone found that nCRT did not seem to increase the risk of postoperative anastomotic leakage (pooled risk ratio 1.00, 95% CI 0.74-1.35; $p=0.878$)¹¹. However, another recent meta-analysis including 12 RCTs reported that nCRT potentially increases the risk of surgical morbidity, but that surgical morbidity was inconsistently reported across trials which impeded direct comparisons². A recent retrospective analysis of 686 patients reported that anastomotic leakage developed more frequently in 376 patients who received nCRT than in the remaining patients who underwent surgery alone (28% versus 17%, respectively; $p<0.01$)¹⁵. The current study was not designed - and hence does not allow - to answer the question whether nCRT *per se* increases the risk of postoperative anastomotic leakage, but rather to determine whether the variability of radiation doses to the gastric fundus relates to the risk of leakage.

The conflicting evidence in the literature on the influence of nCRT on the risk of postoperative anastomotic leakage may in part be explained by the various definitions that are used for leakage. In some studies, anastomotic leakage is defined as clinical or radiologic evidence of anastomotic dehiscence, whereas other definitions include only clinical leakage or anastomotic leakage that requires re-intervention only. In the current study, anastomotic leakage was defined as any postoperative evidence of leakage (either clinically or radiologically confirmed, and either or not requiring re-intervention), explaining the relatively high incidence rate of 26% in this study compared with other series^{7,8,10,11}. However, the leakage rate in this study appears to be comparable to the leakage rates of 22% to 30% that were reported in the recent CROSS-trial³ which used the same nCRT regimen as the current study. Also, in accordance with the CROSS-trial³, the used definition for anastomotic leakage in this study included subclinical leakage diagnosed on radiologic examination or endoscopy without clinical signs.

Sparing of the gastric fundus in radiation treatment planning for esophageal cancer could be achieved in various ways. The most obvious method would be the use of IMRT as highly conformal radiation therapy technique providing greater target volume conformality, greater dose homogeneity, and an increased ability to control dose to adjacent normal structures including the gastric fundus if desired. In addition, one could think of reducing the caudal CTV margin in distal esophageal and GEJ tumors in the neoadjuvant setting to spare the gastric fundus, as the microscopic spread beyond the gross tumor is likely dealt with by surgical resection. This suggestion is supported by the finding that an irradiated (R1) resection after nCRT, which occurs in 8% of patients³, mostly involves microscopically positive

surgical margins at the lateral (circumferential) borders rather than the caudal border²⁴. On the other hand, such a margin-reducing strategy may increase the amount of residual tumor after nCRT outside the radiation field, which has been shown to negatively impact survival²⁵.

Certain limitations apply to this study. First, although the largest study in this field, the sample size was relatively small hindering a more extensive multivariable analysis. Second, this study is limited by the retrospective nature of the analysis, which impedes adjustment for all potential factors that could explain our findings. Third, the gastric fundus is susceptible to breathing-induced organ motion, which could have altered radiation dose calculations. Since no daily imaging information was available the authors were not able to compensate for organ motion of the stomach nor for day-to-day treatment variations. Finally, unlike in other studies^{19,20}, the authors decided not to exclude patients with proximal and middle esophageal tumors. However, this decision was made deliberately to increase the observed variability of gastric fundus doses across patients, which increases the statistical power and precision of the effect estimates. The potential confounding effect of the resulting heterogeneity on the studied association between radiation dose and anastomotic leakage was corrected for in multivariable analysis.

In conclusion, this study demonstrates that the neoadjuvant radiation dose to the gastric fundus is associated with the risk of postoperative anastomotic leakage in patients with esophageal cancer treated with neoadjuvant chemoradiotherapy followed by transthoracic esophagectomy and cervical anastomosis. This finding is important for clinical practice because it suggests that efforts should be made to minimize the radiation dose to the gastric fundus when planning neoadjuvant chemoradiotherapy for esophageal cancer.

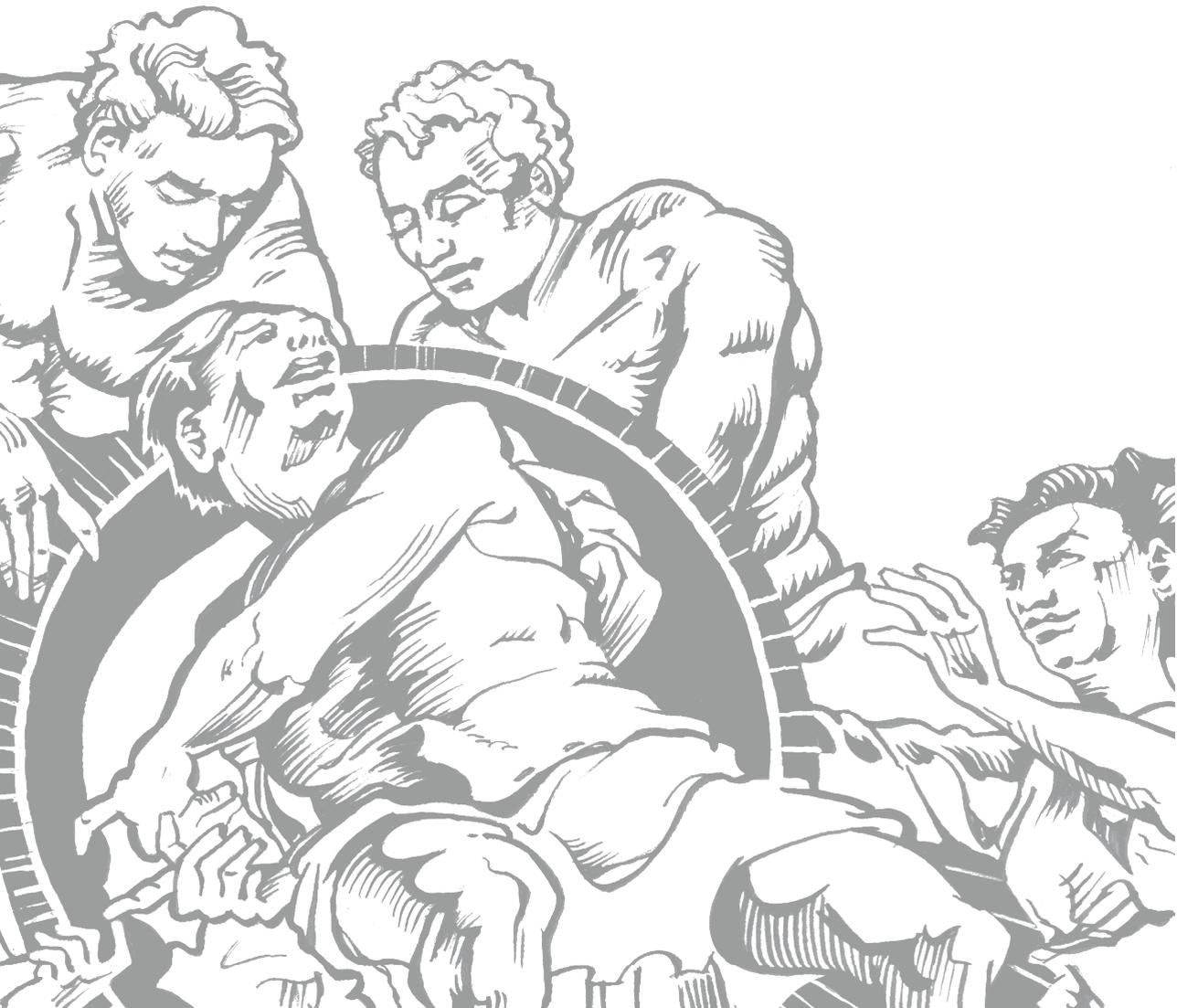
ACKNOWLEDGEMENTS

The authors thank Dr. G.H. Bol, computer scientist at the Department of Radiotherapy, University Medical Center Utrecht, The Netherlands, for his valuable contribution to the radiation dose calculations involved in this manuscript. Also, the authors thank the research group of Prof. P. Pattyn from the University Hospital Gent, Belgium, for their input in determining a proper contouring method.

REFERENCES

1. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. *Lancet* 2013;381:400-12
2. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011;12:681-92
3. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
4. Shapiro J, van Lanschot JJ, Hulshof MC, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol* 2015;16:1090-8
5. Lagarde SM, de Boer JD, ten Kate FJ, et al. Postoperative complications after esophagectomy for adenocarcinoma of the esophagus are related to timing of death due to recurrence. *Ann Surg* 2008;247:71-6
6. Parekh K, Iannettoni MD. Complications of esophageal resection and reconstruction. *Semin Thorac Cardiovasc Surg* 2007;19:79-88
7. Hulscher JB, van Sandick JW, de Boer AG, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 2002;347:1662-9
8. Merritt RE, Whyte RI, D'Arcy NT, et al. Morbidity and mortality after esophagectomy following neoadjuvant chemoradiation. *Ann Thorac Surg* 2011;92:2034-40
9. Nederlof N, Tilanus HW, Tran TC, et al. End-to-end versus end-to-side esophago-gastrostomy after esophageal cancer resection: a prospective randomized study. *Ann Surg* 2011;254:226-33
10. Gronnier C, Trechot B, Duhamel A, et al. Impact of neoadjuvant chemoradiotherapy on postoperative outcomes after esophageal cancer resection: results of a European multicenter study. *Ann Surg* 2014;260:764-70; discussion 770-1
11. Kumagai K, Rouvelas I, Tsai JA, et al. Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers. *Br J Surg* 2014;101:321-38
12. Hagry O, Coosemans W, De Leyn P, et al. Effects of preoperative chemoradiotherapy on postsurgical morbidity and mortality in cT3-4 +/- cM1 lymph cancer of the esophagus and gastro-oesophageal junction. *Eur J Cardiothorac Surg* 2003;24:179-86; discussion 186
13. Reynolds JV, Ravi N, Hollywood D, et al. Neoadjuvant chemoradiation may increase the risk of respiratory complications and sepsis after transthoracic esophagectomy. *J Thorac Cardiovasc Surg* 2006;132:549-55
14. Steyerberg EW, Neville BA, Koppert LB, et al. Surgical mortality in patients with esophageal cancer: development and validation of a simple risk score. *J Clin Oncol* 2006;24:4277-84
15. Morita M, Masuda T, Okada S, et al. Preoperative chemoradiotherapy for esophageal cancer: factors associated with clinical response and postoperative complications. *Anticancer Res* 2009;29:2555-62
16. Lee HK, Vaporciyan AA, Cox JD, et al. Postoperative pulmonary complications after preoperative chemoradiation for esophageal carcinoma: correlation with pulmonary dose-volume histogram parameters. *Int J Radiat Oncol Biol Phys* 2003;57:1317-22

17. Tucker SL, Liu HH, Wang S, et al. Dose-volume modeling of the risk of postoperative pulmonary complications among esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. *Int J Radiat Oncol Biol Phys* 2006;66:754-61
18. Wang SL, Liao Z, Vaporciyan AA, et al. Investigation of clinical and dosimetric factors associated with postoperative pulmonary complications in esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. *Int J Radiat Oncol Biol Phys* 2006;64:692-9
19. Vande Walle C, Ceelen WP, Boterberg T, et al. Anastomotic complications after Ivor Lewis esophagectomy in patients treated with neoadjuvant chemoradiation are related to radiation dose to the gastric fundus. *Int J Radiat Oncol Biol Phys* 2012;82:e513-9
20. Koeter M, van der Sagen MJ, Hurkmans CW, et al. Radiation dose does not influence anastomotic complications in patients with esophageal cancer treated with neoadjuvant chemoradiation and transhiatal esophagectomy. *Radiat Oncol* 2015;10:59
21. Bol GH, Kotte AN, van der Heide UA, et al. Simultaneous multi-modality ROI delineation in clinical practice. *Comput Methods Programs Biomed* 2009;96:133-40
22. Omloo JM, Lagarde SM, Hulscher JB, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. *Ann Surg* 2007;246:992-1000; discussion 1000-1
23. Kutup A, Nentwich MF, Bollschweiler E, et al. What should be the gold standard for the surgical component in the treatment of locally advanced esophageal cancer: transthoracic versus transhiatal esophagectomy. *Ann Surg* 2014;260:1016-22
24. Oppedijk V, van der Gaast A, van Lanschot JJ, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. *J Clin Oncol* 2014;32:385-91
25. Muijs C, Smit J, Karrenbeld A, et al. Residual tumor after neoadjuvant chemoradiation outside the radiation therapy target volume: a new prognostic factor for survival in esophageal cancer. *Int J Radiat Oncol Biol Phys* 2014;88:845-52



Chapter 19

Management and outcome of
cervical versus intrathoracic manifestation of
cervical anastomotic leakage after
transthoracic esophagectomy for cancer

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Diseases of the Esophagus 2016

ABSTRACT

PURPOSE

The aim of this study was to evaluate management strategies and related outcomes for cervical versus intrathoracic manifestation of cervical anastomotic leakage after transthoracic esophagectomy for cancer with gastric conduit reconstruction.

MATERIALS AND METHODS

Patients with esophageal cancer undergoing transthoracic esophagectomy with cervical anastomosis from October 2003 to December 2014 were identified from a prospectively acquired database. Management strategies and related outcomes among patients with anastomotic leakage confined to the neck were compared to patients with intrathoracic manifestation of anastomotic leakage.

RESULTS

From a total of 286 patients, leakage of the cervical anastomosis occurred in 60 patients (21%) at a median time of 7 days after esophagectomy. Leakage was confined to the neck in 23 of 60 patients (38%), whereas 37 of 60 patients (62%) presented with intrathoracic spread. Leakages with intrathoracic manifestation were more frequently accompanied by a positive SIRS score compared to leakages confined to the neck (73% versus 35%, respectively; $p=0.004$). Drainage of the anastomotic leakage through the neck wound was effective in all of 23 patients (100%) with cervical manifestation. In patients with intrathoracic manifestation, mediastinal drainage through the neck was successful in 15 of 37 patients (41%), whereas 22 patients (59%) required an intervention through the thoracic cavity. Compared to patients with leakage confined to the neck, patients with intrathoracic manifestation showed prolonged intensive care unit (ICU) stay (median 6 versus 2 days, respectively; $p=0.001$), hospital stay (median 34 versus 19 days, respectively; $p<0.001$), and time to oral intake (32 versus 23 days, respectively; $p=0.018$).

CONCLUSIONS

Intrathoracic manifestation of cervical anastomotic leakage occurs in more than half of patients with anastomotic leakage after transthoracic esophagectomy for cancer. A SIRS reaction should raise the suspicion of intrathoracic spread of leakage. Intrathoracic manifestation can be managed effectively by mediastinal drainage through the neck in 41% of patients, but a re-intervention through the thoracic cavity is required in 59%. Intrathoracic manifestation of leakage results in prolonged ICU/hospital stay and delays time to oral intake compared with leakage confined to the neck.

INTRODUCTION

Esophagectomy is the standard treatment for resectable non-metastatic esophageal cancer and is increasingly applied in combination with neoadjuvant or perioperative chemo(radio)therapy¹⁻³. Transthoracic esophagectomy with en-bloc radical lymphadenectomy is currently considered the preferred type of oncologic esophagectomy according to a prospective randomized trial^{4,5}. Improvements of surgical techniques and perioperative management have led to a steady decrease in postoperative mortality over the years⁶. However, the incidence of anastomotic leakage after cervical esophagogastromy - one of the major complications after esophagectomy negatively impacting surgical and oncologic outcomes⁶⁻⁸ - remains relatively high (10-30%)^{2,9,10}. Although the incidence of leakage from intrathoracic anastomosis may be lower, many surgeons prefer to perform cervical anastomosis because of the less severe complications in case of leakage¹¹⁻¹³. However, even after cervical anastomosis a substantial proportion of the leakages may exhibit potentially life-threatening intrathoracic manifestation including mediastinal abscess, pleural empyema, and esophago-bronchial fistula^{14,15}.

The efficacy of treatment for anastomotic leakage after esophagectomy for cancer depends on early detection and adequate drainage, but the optimal management strategies for cervical and intrathoracic manifestation of cervical anastomotic leakage after transthoracic esophagectomy for cancer are unclear¹⁴⁻¹⁶. Therefore, the primary aim of this study was to evaluate management strategies and related outcomes for cervical versus intrathoracic manifestation of anastomotic leakage after transthoracic esophagectomy with cervical anastomosis for cancer. A secondary aim was to determine differences in associated signs and symptoms between cervical and intrathoracic manifestation of cervical anastomotic leakage in order to provide information that may aid the clinician in early suspicion and detection of intrathoracic manifestation.

MATERIALS AND METHODS

STUDY POPULATION

Institutional review board (IRB) approval was obtained, and the informed consent requirement was waived for this study. From October 2003 to December 2014, all consecutive patients that underwent transthoracic esophagectomy for adenocarcinoma or squamous cell carcinoma of the esophagus at our tertiary referral center were included in this study. Patient records were retrieved from a prospectively acquired database. Exclusion criteria were benign disease, premature

discontinuation of surgery due to the discovery of T4b or M1 disease during surgery, no gastric tube reconstruction, urgent non-elective surgery, combined laryngeal resection, intrathoracic anastomosis, and transhiatal resection. Patient and treatment-related characteristics were collected from the prospective database.

The surgical procedure consisted of a three-stage transthoracic esophagectomy in all patients. An en-bloc two-field lymphadenectomy was performed, which was extended up to the levels of the upper and lower paratracheal lymph nodes (levels 2 and 4, respectively). Continuity of the alimentary tract was restored by cervical esophagogastric anastomosis after gastric conduit formation along the greater curvature. The cervical anastomosis was truly located in the neck and not in or below the thoracic inlet. Generally, the cervical esophageal remnant was about 2 cm in length from the upper esophageal sphincter. All anastomoses were cervical and hand-sewn in monolayer in an end-to-side fashion¹⁷. The surplus of the gastric conduit was removed with the use of a stapler (Endo GIA™ Stapler, Covidien, Dublin, Ireland). At the end of the procedure, a feeding jejunostomy was constructed in all patients. Placement of a cervical drain at the end of the operation was not routinely performed^{18,19}.

LEAKAGE DIAGNOSIS

The presence of anastomotic leakage was reviewed in all patients according to clinical and radiologic definitions. Clinical symptoms suspicious for leakage included cervical wound infection, subcutaneous emphysema, persistent fever, sepsis, respiratory or circulatory distress and enteric drainage from a thoracic tube. Recognition of these symptoms guided wound exploration and/or a diagnostic procedure (computed tomography [CT] scan, contrast swallow examination or endoscopy). Cervical manifestation was defined as demonstration of saliva through the cervical wound, extravasation of water-soluble contrast during a contrast swallow study or CT scan, or visualization of anastomotic dehiscence or fistulae during endoscopy, without signs of intrathoracic or mediastinal involvement. Intrathoracic manifestation was defined as anastomotic leakage associated with pus drainage from the thoracic tube, pleural empyema, mediastinitis or mediastinal pus collection. Diagnostic tests to identify anastomotic leakage were conducted on indication only; no routine contrast swallow examination was performed²⁰⁻²².

ASSOCIATED CLINICAL FACTORS

Postoperative signs and symptoms of patients were reviewed and compared between the two groups in order to determine factors associated with intrathoracic

manifestation that could aid the clinician in decision-making. Studied signs and symptoms included cervical wound infection, cervical wound crepitus, fever (temperature $\geq 38.5^{\circ}\text{C}$), leukocytosis, and positive SIRS score (according to the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference criteria²³). In addition, the potential associations between intrathoracic versus cervical manifestation of leakage and accompanying postoperative complications including pneumonia, recurrent nerve injury, chylothorax and cardiac arrhythmia were evaluated.

MANAGEMENT ALGORITHM

The following management algorithm was applied in all patients diagnosed with postoperative anastomotic leakage at our center. First, patients were put on a nil-per-os regimen including gastric tube decompression and enteral feeding through jejunostomy. In case of cervical leakage, the neck wound was opened for local drainage. In case signs of mediastinitis were detected on a CT scan, the neck wound was opened and a reoperation was performed to drain the mediastinum through the neck wound. In case of radiologic evidence of pleural collection, cleansing of the pleural cavity was conducted by either thoracoscopy or thoracotomy. Endoscopic stent placement was considered in patients with persistent leakage after drainage. In general, anastomotic leakages confined to the cervical region were treated by neck wound opening and dressing only. Esophageal diversion – implying a complete take-down of the gastric conduit with cervical esophagostomy - was performed in case of severe necrosis of the gastric conduit. Severe necrosis was defined as diffuse rather than localized necrosis, precluding the possibility of a partial resection of a localized necrotic portion only.

OUTCOME PARAMETERS

The following outcome parameters were evaluated and compared for patients with cervical versus intrathoracic manifestation of anastomotic leakage: length of intensive care unit (ICU) stay, length of hospital stay, time to oral intake, and postoperative mortality (defined as in-hospital death or death within 30 days after surgery). In addition, overall survival was compared between the two groups, which was calculated from the date of surgery until death. Similarly, overall survival was compared between patients without anastomotic leakage and patients with cervical or intrathoracic manifestation of leakage, respectively. Patients were followed for 5 years after surgery at the outpatient clinic on a regular basis every 3 months in the first year, every 6 months in the second year and every 12 months

afterwards. For the patients that were discharged after 5 years of follow-up, the general practitioners were consulted for additional follow-up data.

STATISTICAL ANALYSIS

First, the association of the specified postoperative signs and symptoms with cervical versus intrathoracic manifestation of anastomotic leakage was studied. Second, the following outcome parameters were evaluated and compared between patients with cervical and patients with intrathoracic manifestation of anastomotic leakage: length of intensive care unit (ICU) stay, length of hospital stay, time to oral intake, and postoperative mortality. Chi-square testing was used for categorical parameters (or Fisher's exact testing in case of small count), and Mann-Whitney *U* testing was used for continuous parameters. Third, the Kaplan-Meier method was applied to estimate the overall survival differences among patients according to presence and type of leakage, with the log-rank test to determine significance. Statistical analysis was performed using SPSS version 23.0 (SPSS Inc, Chicago, IL, USA). A *p*-value of <0.05 was considered statistically significant.

RESULTS

Patient flow and management are summarized in **Figure 1**. From 432 patients who underwent esophagectomy in the study period, 37 patients were excluded because of benign disease ($n=11$), premature discontinuation of the operation due to unsuspected T4b or M1 disease ($n=10$), use of colon interposition graft ($n=5$), intrathoracic rather than cervical anastomosis ($n=2$), urgent non-elective resection ($n=4$), and combination with laryngeal resection ($n=5$). In addition, 109 patients who underwent a transhiatal resection were excluded. Among these 109 excluded patients, 36 (33%) experienced postoperative anastomotic leakage, of which 29 (81%) was confined to the neck and 7 (19%) demonstrated intrathoracic spread. Baseline characteristics of the remaining 286 patients who were included in the analysis are presented in **Table 1**. The mean age among the eligible subjects was 63.6 years (range 39 to 79), and 210 (73%) of the patients were male.

Anastomotic leakage occurred in 60 (21%) of 286 included patients. Intrathoracic manifestation of leakage occurred in 37 (62%) of these 60 patients, whereas the leakage among 23 (38%) of 60 patients remained confined to the neck region only. Of note, the proportion of intrathoracic manifestation among patients with cervical anastomotic leakage was considerably higher in the current transthoracic esophagectomy series as compared to the excluded transhiatal esophagectomy

Table 1 Baseline characteristics of the 286 included patients that underwent esophagectomy for cancer

| Characteristic | n (%) |
|---|------------------|
| Male gender | 210 (73.4) |
| Age (years)[†] | 63.6 ± 8.7 |
| Body Mass Index (kg/m²)[†] | 25.5 ± 4.3 |
| ASA score | |
| 1 | 73 (25.5) |
| 2 | 177 (61.9) |
| 3 | 36 (12.6) |
| COPD | 30 (10.5) |
| Diabetes mellitus | 33 (11.5) |
| Cardiovascular comorbidity | 57 (19.9) |
| Smoking | |
| No | 128 (44.8) |
| Past smoker | 95 (33.2) |
| Current smoker | 63 (22.0) |
| Histologic tumor type | |
| Adenocarcinoma | 206 (72.0) |
| Squamous cell carcinoma | 77 (27.0) |
| Other | 3 (1.0) |
| Tumor location | |
| Proximal third of esophagus | 4 (1.4) |
| Middle third of esophagus | 46 (16.1) |
| Distal third of esophagus | 136 (47.5) |
| Gastro-esophageal junction | 88 (30.8) |
| Cardia | 12 (4.2) |
| Clinical T-stage | |
| T1b | 19 (6.6) |
| T2 | 40 (14.0) |
| T3 | 215 (75.2) |
| T4a | 12 (4.2) |
| Clinical N-stage | |
| N0 | 71 (24.8) |
| N1 | 138 (48.3) |
| N2 | 54 (18.9) |
| N3 | 23 (8.0) |
| Neoadjuvant treatment | |
| No | 95 (33.2) |
| Chemotherapy | 86 (30.1) |
| Chemoradiotherapy | 105 (36.7) |
| Surgical approach | |
| Thoracoscopic | 217 (75.9) |
| Thoracotomy | 43 (15.0) |
| Thoracoscopic-laparotomy | 26 (9.1) |
| Duration of operation (minutes)[†] | 398 ± 66.4 |
| Blood loss during surgery (mL)[‡] | 400 [50-1550] |
| Year of surgery[‡] | 2011 [2003-2014] |

Data presented as numbers of patients with column-based percentages in parentheses.

[†]: Data presented as mean ± standard deviation.

[‡]: Data presented as median [range].

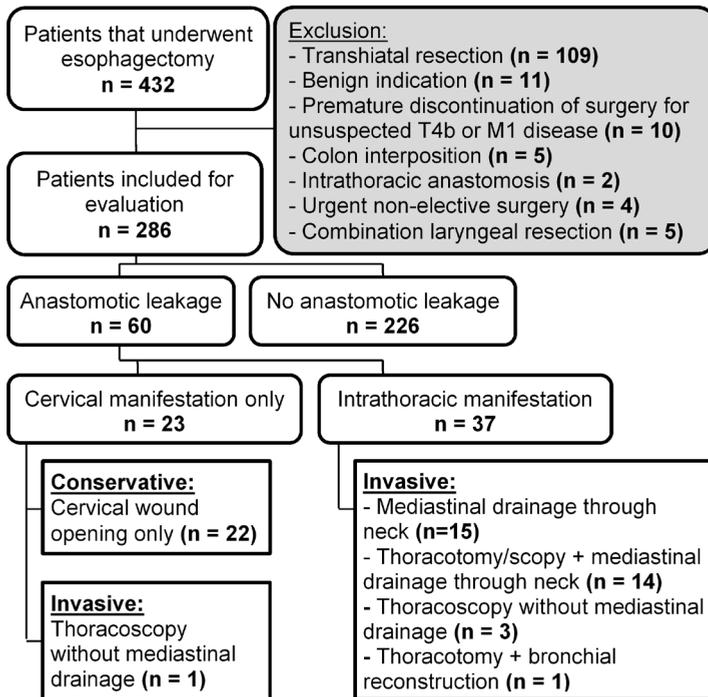


Figure 1 Flowchart summarizing patient flow and management of anastomotic leakage with cervical versus intrathoracic manifestation. The specified treatment options represent the final effective re-interventions, performed in either one or more procedures.

series (37 of 60 [62%] versus 7 of 36 [19%], respectively; $p < 0.001$). Only 15 (41%) of 37 patients developing intrathoracic manifestation of leakage after transthoracic esophagectomy also showed cervical manifestation. Leakage confined to the neck was diagnosed clinically without radiologic or endoscopic confirmation in 15 of 23 patients (65%), by contrast swallow examination in 5 (22%), by endoscopy in 2 (9%), and by CT in 1 (4%) (**Figure 2a**). Intrathoracic manifestation was confirmed by CT in all of 37 patients (100%) (**Figure 2b-c**). The overall median interval between surgery and anastomotic leakage diagnosis was 7 days (range 2 to 18 days), and this time to diagnosis was not significantly different for patients with cervical versus intrathoracic manifestation of leakage (median [range]: 8 days [2 to 14] versus 6 days [2 to 18], respectively; $p = 0.351$).

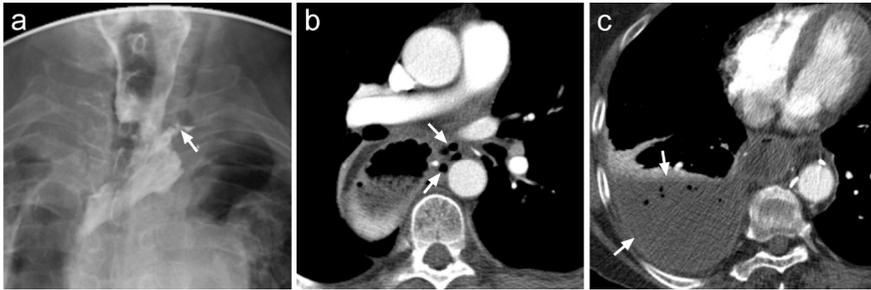


Figure 2 Examples of patients with leakage of the cervical esophagogastrostomy. Contrast swallow examination revealed a small fistula at the left side of the anastomotic site (*arrow*) without extension to the thoracic cavity in a patient with cervical wound crepitus without altered SIRS criteria as a result of leakage confined to the neck (**a**). CT demonstrated mediastinal extra-luminal air collections (*arrows*) in another patient in who pus was successfully evacuated by mediastinal drainage through the neck (**b**). In a third patient, cervical leakage exhibited a right dorsal pleural empyema (*arrows*) which required evacuation through video-assisted thoracoscopy (**c**).

ASSOCIATED CLINICAL FACTORS

A comparison of potentially associated signs and symptoms and accompanying complications of patients with cervical versus intrathoracic manifestation of leakage is presented in **Table 2**. The cervical wound more often showed signs of infection in patients with leakage confined to the neck region compared with patients with intrathoracic manifestation of leakage (96% versus 41%, respectively; $p < 0.001$). Patients with intrathoracic manifestation of leakage, on the other hand, more frequently scored positive on SIRS criteria compared with leakage patients who developed cervical manifestation only (73% versus 35%, respectively; $p = 0.004$). The incidences of other symptoms including cervical wound crepitus, fever, and leukocytosis, were not significantly different among the two groups.

Although the incidences of chylothorax and cardiac arrhythmia seemed slightly higher among patients with intrathoracic manifestation of leakage (32% versus 17%, and 30% versus 17%, respectively), these differences were not statistically significant. In addition, the incidence of accompanying pneumonia or recurrent nerve injury did not differ significantly between the two groups. Severe gastric conduit necrosis occurred in 4 patients with resulting intrathoracic manifestation in all cases.

Table 2 Comparison of associated signs and symptoms and accompanying complications of patients with cervical versus intrathoracic manifestation of cervical anastomotic leakage

| | Manifestation of anastomotic leakage | | <i>p</i> value |
|--|--------------------------------------|----------------------|----------------|
| | Cervical only (n=23) | Intrathoracic (n=37) | |
| Signs and symptoms | | | |
| Cervical wound infection | 22 (95.7) | 15 (40.5) | <0.001* |
| Cervical wound crepitus | 8 (34.8) | 7 (18.9) | 0.168 |
| Fever (temperature $\geq 38.5^{\circ}\text{C}$) | 17 (73.9) | 23 (62.2) | 0.348 |
| Leukocytosis ($>11.0 \times 10^9/\text{L}$) | 19 (82.6) | 31 (83.8) | 0.905 |
| Positive on SIRS criteria | 8 (34.8) | 27 (73.0) | 0.004* |
| Complications | | | |
| Pneumonia | 9 (39.1) | 13 (35.1) | 0.755 |
| Chylothorax | 4 (17.4) | 12 (32.4) | 0.200 |
| Recurrent nerve injury | 3 (13.0) | 3 (8.1) | 0.666 |
| Cardiac arrhythmia | 4 (17.4) | 11 (29.7) | 0.283 |
| Gastric conduit necrosis | 0 (0.0) | 4 (10.8) | 0.288 |

Data presented as numbers of patients with percentages in parentheses.

*: Significant difference between patients with cervical versus intrathoracic manifestation of cervical anastomotic leakage ($p < 0.05$).

MANAGEMENT

All of the 23 patients (100%) with only cervical manifestation of leakage were treated conservatively by cervical wound opening (**Figure 1**). Among these patients, one patient (4%) underwent an invasive re-intervention that included thoracoscopy for respiratory insufficiency revealing a thoracic hematoma rather than a manifestation of leakage. Of the 37 patients who developed intrathoracic manifestation of leakage, mediastinal drainage through the neck as sole treatment was the first re-intervention in 20 patients (54%). Among these 20 patients, 5 (25%) eventually required a subsequent re-intervention through the thoracic cavity. Hence, in 15 of 37 patients (41%), the mediastinal drainage was sufficient as sole treatment, whereas in the other 22 patients (59%) thoracoscopy or thoracotomy was required to effectively establish intrathoracic drainage.

Diversion and esophagostomy for severe necrosis of the gastric conduit was performed in 4 (7%) of 60 patients with anastomotic leakage. A self-expandable stent was placed by endoscopy for persistent leakage in 1 (4%) of 23 patients with only cervical manifestation of leakage, and in 7 (19%) of 37 patients with intrathoracic manifestation.

OUTCOME

A comparison of studied outcomes for patients with cervical versus intrathoracic manifestation of leakage is presented in **Table 3**. The postoperative ICU stay and hospital stay were significantly longer among patients with intrathoracic manifestation of leakage compared with patients developing cervical manifestation only (median [range]: 6 days [1 to 65] versus 2 days [0 to 33], respectively; $p=0.001$, and 34 days [11 to 98] versus 19 days [11 to 36], respectively; $p<0.001$). Also, time to oral intake was longer for patients with intrathoracic versus cervical manifestation of leakage (median [range]: 32 days [7 to 122] versus 23 days [7 to 115], respectively; $p=0.018$). Although postoperative in-hospital mortality and 90-day mortality rates among patients with leakage appeared higher when intrathoracic manifestation was present (14% versus 4%, and 16% versus 4%, respectively), these differences were not statistically significant.

Table 3 Comparison of outcome of patients with cervical versus intrathoracic manifestation of cervical anastomotic leakage

| Outcome | Manifestation of anastomotic leakage | | p value |
|---|--------------------------------------|----------------------|---------|
| | Cervical only (n=23) | Intrathoracic (n=37) | |
| ICU stay (days) [‡] | 2 [0-33] | 6 [1-65] | 0.001* |
| Hospital stay (days) [‡] | 19 [11-36] | 34 [11-98] | <0.001* |
| Time to oral intake (days) [‡] | 23 [7-115] | 32 [7-122] | 0.018* |
| In-hospital mortality | 1 (4.3) | 5 (13.5) | 0.391 |
| 30-day postoperative mortality | 0 (0.0) | 2 (5.4) | 0.519 |
| 90-day postoperative mortality | 1 (4.3) | 6 (16.2) | 0.233 |

Data presented as numbers of patients with percentages in parentheses.

*: Significant difference between patients with cervical versus intrathoracic manifestation of cervical anastomotic leakage ($p<0.05$).

[‡]: Data presented as median [range].

For patients alive at last follow-up, the median follow-up duration was 38 months (range, 3 to 143). The 23 patients with leakage confined to the neck had a median overall survival of 17 months as compared to 16 months in the 37 patients with intrathoracic manifestation of leakage (**Figure 3**). The overall survival among the two leakage groups was not significantly different ($p=0.919$). The overall survival among patients without postoperative anastomotic leakage (median, 32 months) appeared favorable compared to patients with leakage particularly in the first two

years after surgery (**Figure 3**). However, the difference between patients without leakage and patients with leakage confined to the neck was not statistically significant in the long term ($p=0.161$). The survival difference between patients without leakage and patients with intrathoracic manifestation of leakage showed a more pronounced trend in favor of patients without leakage, but no statistical significance was observed ($p=0.053$).

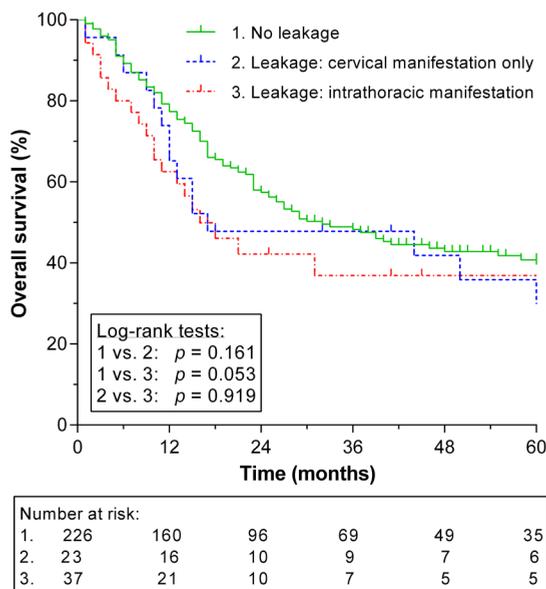


Figure 3 Kaplan-Meier analysis for overall survival according to presence and type of postoperative anastomotic leakage after transthoracic esophagectomy for cancer.

DISCUSSION

Leakage of the cervical esophagogastric anastomosis is expected to result in less severe complications compared to intrathoracic anastomosis because of its accessibility and possibility of local drainage. However, this study demonstrates that intrathoracic manifestation of leakage after transthoracic esophagectomy with cervical anastomosis can occur in up to 62%. This results in a prolonged ICU stay, hospital stay and time to oral intake compared with leakage confined to the neck. A substantial proportion of patients with intrathoracic manifestation of leakage (41%) can be managed by mediastinal drainage through the neck, deviating the route of the leakage without the need for re-intervention through the thoracic cavity.

Recognition of intrathoracic involvement of cervical leakage is pivotal, as this complication may require extensive re-intervention and can negatively impact the outcome of patients developing leakage after esophagectomy^{14,15}. The current study showed that a positive SIRS score is associated with a higher chance of intrathoracic rather than cervical manifestation of leakage. In clinical practice, this finding is important to identify patients with intrathoracic manifestation of leakage in an early stage, preventing the development of severe mediastinitis and sepsis. In patients developing cardio-respiratory distress or unspecific inflammatory response, there should be a high suspicion of intrathoracic spread of anastomotic leakage, requiring prompt evaluation of the anastomosis.

Previous studies suggested that anastomotic leakage with manifestation confined to the cervical region can be sufficiently treated through local drainage by opening the cervical wound^{14,15,24}, which is supported by the current study. However, when cervical anastomotic leakage involves the mediastinum, effective drainage of the mediastinum should be carried out. In our systematic step-up approach, the placement of drains through the neck wound to the mediastinum was initially performed in 54% of patients with intrathoracic manifestation in order to deviate the route of the leakage from the mediastinum towards the neck. This is a limited and fast surgical intervention that allows external drainage of collected material from the mediastinum and the possibility to flush with saline. In 75% of these patients, this approach was sufficiently effective without need for re-intervention through the thoracic cavity. Overall, management of intrathoracic manifestation without accessing the thoracic cavity was effectively carried out in 15 of 37 patients (41%) and esophago-gastric continuity was preserved in 33 of 37 of patients (89%).

In our series, surgical drainage was the treatment of choice for anastomotic leakage, which was combined with endoscopic stent placement in case of persistent leakage. Recently, endoscopic management of leakage by means of stent placement has been proposed as alternative to surgery^{25,26}. In one study, endoscopic management of leakages has been demonstrated to result in improved outcomes in terms of ICU/hospital stay and time to oral intake when compared to a conventional surgical approach²⁷. However, in case of placement of a stent, the drainage of the area surrounding the stent is essential to prevent abscess formation. Another suggested approach to treat cervical anastomotic leakage includes the routine placement of a cervical (closed-suction) drain at the end of the operation^{18,19}. Such a drain allows for early diagnosis of anastomotic leakage, while simultaneously serving as an effective treatment²⁸. Theoretically, this strategy might also prevent intrathoracic manifestation of cervical anastomotic leakage. A disadvantage is the possible air leakage through the neck drain towards the pleural cavity. Current evidence on the potential benefits of this approach is limited and further investigation is required.

In the current study, anastomotic leakage was defined as any postoperative evidence of leakage (either clinically or radiologically confirmed, and either or not requiring re-intervention), explaining the relatively high incidence rate of 21% in this study compared with other series²⁹⁻³². However, the leakage rate in this study appears to be comparable to the leakage rates of 22% to 30% that were reported in the recent Dutch multi-center CROSS-trial². In accordance with the CROSS-trial², the used definition for anastomotic leakage in this study also included subclinical leakage diagnosed on radiologic examination or endoscopy without clinical signs. In our center, transhiatal (instead of transthoracic) esophagectomy is mainly applied in patients with a poor condition as this procedure is associated with lower postoperative morbidity in an unselected population²⁹. The selection of patients with a poor condition may explain our rather high incidence of postoperative anastomotic leakage in the transhiatal group (33%).

Certain limitations apply to this study. First, although the used data was collected in a prospective fashion, the analysis was retrospective by nature. Second, the sample size of patients with leakage was too small to prove or reject the potential existence of small differences between the two studied subgroups. For example, in the current series a trend towards reduced overall survival rates in patients with postoperative anastomotic leakage was observed, but this could not be proven in terms of statistical significance. However, in larger recent series this association was convincingly confirmed^{33,34}. Third, our described step-up approach was not directly compared to other strategies, such as conventional surgical strategies or emerging endoscopic approaches. However, the analysis was strengthened by its extensiveness and by the use of a dedicated prospectively acquired database from a high volume upper gastrointestinal surgery center.

In conclusion, leakage of the cervical anastomosis occurred in 21% of patients that underwent transthoracic esophagectomy for cancer of which 38% was confined to the neck and 62% spread intrathoracically. Awareness of possible intrathoracic spread of leakage after a cervical anastomosis is important for early recognition. A positive SIRS score should raise the clinician's suspicion of anastomotic leakage with intrathoracic manifestation, regardless of the findings at cervical wound inspection. Mediastinal drainage through the neck wound was effective in 41% of all patients with intrathoracic manifestation. Patients with intrathoracic manifestation showed longer time to oral intake and prolonged ICU/hospital stay when compared to patients with leakage confined to the neck region, without significant differences in long-term overall survival rates.

REFERENCES

1. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011;12:681-92
2. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
3. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20
4. Omloo JM, Lagarde SM, Hulscher JB, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. *Ann Surg* 2007;246:992-1000; discussion 1000-1
5. Kutup A, Nentwich MF, Bollschweiler E, et al. What should be the gold standard for the surgical component in the treatment of locally advanced esophageal cancer: transthoracic versus transhiatal esophagectomy. *Ann Surg* 2014;260:1016-22
6. Lagarde SM, de Boer JD, ten Kate FJ, et al. Postoperative complications after esophagectomy for adenocarcinoma of the esophagus are related to timing of death due to recurrence. *Ann Surg* 2008;247:71-6
7. Parekh K, Iannettoni MD. Complications of esophageal resection and reconstruction. *Semin Thorac Cardiovasc Surg* 2007;19:79-88
8. Crestanello JA, Deschamps C, Cassivi SD, et al. Selective management of intrathoracic anastomotic leak after esophagectomy. *J Thorac Cardiovasc Surg* 2005;129:254-60
9. Urschel JD. Esophagogastrostomy anastomotic leaks complicating esophagectomy: a review. *Am J Surg* 1995;169:634-40
10. Walther B, Johansson J, Johnsson F, et al. Cervical or thoracic anastomosis after esophageal resection and gastric tube reconstruction: a prospective randomized trial comparing sutured neck anastomosis with stapled intrathoracic anastomosis. *Ann Surg* 2003;238:803-12; discussion 812-4
11. Swanson SJ, Batirel HF, Bueno R, et al. Transthoracic esophagectomy with radical mediastinal and abdominal lymph node dissection and cervical esophagogastrostomy for esophageal carcinoma. *Ann Thorac Surg* 2001;72:1918-24; discussion 1924-5
12. Orringer MB, Marshall B, Chang AC, et al. Two thousand transhiatal esophagectomies: changing trends, lessons learned. *Ann Surg* 2007;246:363-72; discussion 372-4
13. Biere SS, Maas KW, Cuesta MA, et al. Cervical or thoracic anastomosis after esophagectomy for cancer: a systematic review and meta-analysis. *Dig Surg* 2011;28:29-35
14. van Heijl M, van Wijngaarden AK, Lagarde SM, et al. Intrathoracic manifestations of cervical anastomotic leaks after transhiatal and transthoracic oesophagectomy. *Br J Surg* 2010;97:726-31
15. Korst RJ, Port JL, Lee PC, et al. Intrathoracic manifestations of cervical anastomotic leaks after transthoracic esophagectomy for carcinoma. *Ann Thorac Surg* 2005;80:1185-90
16. Scheepers JJ, van der Peet DL, Veenhof AA, et al. Systematic approach of postoperative gastric conduit complications after esophageal resection. *Dis Esophagus* 2010;23:117-21

17. Haverkamp L, van der Sluis PC, Verhage RJ, et al. End-to-end cervical esophagogastric anastomoses are associated with a higher number of strictures compared with end-to-side anastomoses. *J Gastrointest Surg* 2013;17:872-6
18. Li J, Shen Y, Tan L, et al. Cervical triangulating stapled anastomosis: technique and initial experience. *J Thorac Dis* 2014;6 Suppl 3:S350-4
19. Choi HK, Law S, Chu KM, et al. The value of neck drain in esophageal surgery: a randomized trial. *Dis Esophagus* 1998;11:40-2
20. Boone J, Rinkes IB, van Leeuwen M, et al. Diagnostic value of routine aqueous contrast swallow examination after oesophagectomy for detecting leakage of the cervical oesophagogastric anastomosis. *ANZ J Surg* 2008;78:784-90
21. Cools-Lartigue J, Andalib A, Abo-Alsaud A, et al. Routine contrast esophagram has minimal impact on the postoperative management of patients undergoing esophagectomy for esophageal cancer. *Ann Surg Oncol* 2014;21:2573-9
22. Solomon DG, Sasaki CT, Salem RR. An evaluation of the routine use of contrast radiography as a screening test for cervical anastomotic integrity after esophagectomy. *Am J Surg* 2012;203:467-71
23. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;20:864-74
24. Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy for treatment of benign and malignant esophageal disease. *World J Surg* 2001;25:196-203
25. Schubert D, Scheidbach H, Kuhn R, et al. Endoscopic treatment of thoracic esophageal anastomotic leaks by using silicone-covered, self-expanding polyester stents. *Gastrointest Endosc* 2005;61:891-6
26. Roy-Choudhury SH, Nicholson AA, Wedgwood KR, et al. Symptomatic malignant gastroesophageal anastomotic leak: management with covered metallic esophageal stents. *Am J Roentgenol* 2001;176:161-5
27. Hunerbein M, Stroszczyński C, Moesta KT, et al. Treatment of thoracic anastomotic leaks after esophagectomy with self-expanding plastic stents. *Ann Surg* 2004;240:801-7
28. Tang H, Xue L, Hong J, et al. A method for early diagnosis and treatment of intrathoracic esophageal anastomotic leakage: prophylactic placement of a drainage tube adjacent to the anastomosis. *J Gastrointest Surg* 2012;16:722-7
29. Hulscher JB, van Sandick JW, de Boer AG, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 2002;347:1662-9
30. Merritt RE, Whyte RI, D'Arcy NT, et al. Morbidity and mortality after esophagectomy following neoadjuvant chemoradiation. *Ann Thorac Surg* 2011;92:2034-40

31. Gronnier C, Trechot B, Duhamel A, et al. Impact of neoadjuvant chemoradiotherapy on postoperative outcomes after esophageal cancer resection: results of a European multicenter study. *Ann Surg* 2014;260:764-70; discussion 770-1
32. Kumagai K, Rouvelas I, Tsai JA, et al. Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers. *Br J Surg* 2014;101:321-38
33. Markar S, Gronnier C, Duhamel A, et al. The impact of severe anastomotic leak on long-term survival and cancer recurrence after surgical resection for esophageal malignancy. *Ann Surg* 2015;262:972-80
34. Kofoed SC, Calatayud D, Jensen LS, et al. Intrathoracic anastomotic leakage after gastroesophageal cancer resection is associated with increased risk of recurrence. *J Thorac Cardiovasc Surg* 2015;150:42-8



Chapter 20

Summary

Despite recent improvements in staging, multimodality treatment, and perioperative care, esophageal cancer remains a devastating disease with a 5-year overall survival rate of only 15-25%. As prognosis is often poor, multimodality (rather than single modality) treatment approaches are frequently applied to increase the chances of cure. For patients the multitude of burdening treatment modalities are hard to undergo and exhibit substantial risks of serious side effects without knowing whether all components (e.g. chemotherapy, radiotherapy, surgery) contribute to the desired outcome on an individual basis. The studies presented in this thesis aimed to open a window to move towards individualized care for patients with esophageal cancer enabling selection of only those treatments that are best for the individual patient and omission of components that contribute little to (or even deteriorate) the well-being of the patient. To reach this goal, important current limitations were exposed and improvements were proposed with regard to the diagnostic work-up, multimodality treatment strategies, treatment response assessment, and the risk prediction, prevention, and management of postoperative complications.

PART I. IMAGING OF ESOPHAGEAL CANCER

In this part of the thesis the current value and future potential of MRI, PET and CT scanning techniques for individualizing the treatment for esophageal cancer were examined. To this regard, opportunities for further clinical research were sought in the relevant literature.

The narrative review in **Chapter 2** highlighted the limitations in the current diagnostic work-up in esophageal cancer patients. It was demonstrated that the imaging quality of magnetic resonance imaging (MRI) in esophageal cancer has markedly improved in recent years due to technological progress, reaching similar or even better results for staging compared with currently applied imaging strategies. In addition, promising recent innovations are expected to enable (real-time) MRI-guided radiotherapy in the near future. Finally, a few recent pilot studies were outlined which found that functional MRI may be capable of predicting tumor response to chemotherapy and radiotherapy.

The pictorial review in **Chapter 3** aimed to guide clinicians in the optimal use and understanding of ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET)/ computed tomography (CT) and MRI in esophageal cancer as these advancing technologies yield high potential to contribute to individualized treatment decision-making. The importance of ^{18}F -FDG PET/CT as a useful adjunct

to conventional staging modalities, with particular value for detecting unexpected distant metastases, was illustrated. In addition, the growing evidence for MRI was outlined, suggesting a complementary role for MRI in staging, radiation treatment planning, and treatment response assessment.

In the narrative review in **Chapter 4** attention was given to the potential role of the emerging field of extracting additional information from standard medical images, also referred to as ‘radiomics’. The current evidence was outlined suggesting that quantification of tumor heterogeneity – through its relation to biologic tumor characteristics – may provide incremental value in esophageal cancer for staging, predicting treatment response, and predicting survival. As such, radiomics approaches may contribute to the ongoing movement towards more individualized treatment strategies.

In **Chapter 5** the aim was to systematically review and meta-analyze the diagnostic performance of ¹⁸F-FDG PET and PET/CT for diagnosing recurrent esophageal cancer after initial treatment with curative intent. CT and endoscopy are frequently applied for this purpose, but the interpretation of these modalities is often difficult due to local anatomic changes caused by surgery. The meta-analysis revealed that ¹⁸F-FDG PET and PET/CT are reliable imaging modalities with a high sensitivity (96%) and moderate specificity (78%) for detecting recurrent esophageal cancer. This implies that ¹⁸F-FDG PET and PET/CT particularly allow for a minimal false-negative rate, but that histopathologic confirmation of suspected lesions remains required, because a considerable false-positive rate is noticed. ¹⁸F-FDG PET(/CT) appears more sensitive for recurrent esophageal cancer than conventional modalities (CT and endoscopy) and could therefore largely replace these techniques for this indication resulting in less unjustified reassurances and improved patient selection for treatment.

PART II. MULTIMODALITY TREATMENT STRATEGIES

In this part various multimodality treatment strategies for esophageal cancer were compared. Treatment strategies with curative intent and also strategies with palliative intent were studied.

In **Chapter 6** two of the most frequently applied multimodality treatment strategies in locally advanced esophageal or gastroesophageal junction adenocarcinoma (i.e. neoadjuvant chemoradiotherapy and perioperative chemotherapy) were compared in terms of treatment-related toxicity, pathologic outcome, and survival. Since the two treatment strategies were applied in a non-randomized fashion and in

a consecutive order at our institution, propensity score matching was applied to create comparable groups. Both regimens were associated with substantial regimen-specific adverse events. Although neoadjuvant chemoradiotherapy improved pathologic response rates and significantly reduced the risk of locoregional recurrence, these achievements did not translate into an overall survival benefit.

Chapter 7 contains a narrative review on palliative treatment options in unresectable, metastatic, and recurrent esophageal cancer that share the aims of controlling dysphagia and other cancer-related symptoms, improving quality of life, and prolonging survival. The individual indications for different treatment strategies including chemotherapy, targeted agents, external radiotherapy, intraluminal brachytherapy, surgery, self-expanding metal stent placement, and thermal or chemical ablative techniques, and their associated outcomes were discussed. Combinations of treatment modalities appear to provide improved outcomes.

The aim of the descriptive cohort study in **Chapter 8** was to identify prognostic factors that affect survival when recurrent esophageal cancer is diagnosed after initial treatment with curative intent. The finding that 50% of patients had already died at only 3 months after diagnosis of recurrence highlights the importance and complexity of finding a proper balance between treatment efficacy and associated burden in each individual patient. Distant (rather than locoregional) recurrence and more than 3 recurrent locations were independent prognostic factors associated with worse post-recurrence survival, irrespective of primary tumor characteristics. These findings are helpful to guide patient selection for treatment.

PART III. TREATMENT RESPONSE PREDICTION

The aim of the studies presented in this part was to gain the ability to accurately select those components of multimodality treatment that are favorable for the individual patient and to omit those components that add little to (or even deteriorate) the well-being of the individual patient.

Chapter 9 focused on potential improvements in the role of endoscopic biopsy and endoscopic ultrasound (EUS) in the work-up of esophageal cancer by evaluating the accuracy of these modalities for detecting residual cancer after neoadjuvant chemoradiotherapy. A reliable diagnosis of residual cancer before surgery would enable a tailored treatment strategy in which complete responders after neoadjuvant chemoradiotherapy could be offered close clinical follow-up instead of surgery. It was found that endoscopic biopsy after neoadjuvant chemoradiotherapy appears

negative in 91% of patients with a true pathologic complete response, but also in 65% of patients with residual cancer. On the other hand, EUS after neoadjuvant chemoradiotherapy appears positive in 96% of patients with residual cancer, but also in 89% of patients with a pathologic complete response. Based on these findings, we recommended that these endoscopic modalities cannot be used to withhold surgical treatment in test-negative patients after neoadjuvant chemoradiotherapy.

In the retrospective cohort study in **Chapter 10** four prediction models were constructed to study the incremental values of subjective assessment of baseline and post-chemoradiation ^{18}F -FDG PET, conventional quantitative metabolic features, and ^{18}F -FDG PET radiomics features, for predicting a pathologic complete response to neoadjuvant chemoradiotherapy in esophageal cancer beyond clinical predictors. Although subjective and quantitative assessment of ^{18}F -FDG PET provided statistical incremental value for predicting a pathologic complete response (corrected *c*-index increased from 0.67 to 0.77), the discriminatory improvement beyond clinical predictors did not translate into a clinically relevant benefit that could change decision-making. This finding indicates that ^{18}F -FDG PET gives a fair indication of the response to chemotherapy and radiotherapy, but that by itself the modality is not accurate enough to guide individualized multimodality treatment in esophageal cancer.

In **Chapter 11 and 12** the results of a prospective pilot study exploring the value of diffusion-weighted MRI (Chapter 11) and dynamic contrast-enhanced MRI (Chapter 12) for the prediction of pathologic response to neoadjuvant chemoradiotherapy in patients with esophageal cancer were reported. MRI scanning was performed before treatment, after the first 2-3 weeks of chemoradiotherapy, and before surgery. On the diffusion-weighted MRI scans the tumor apparent diffusion coefficient (ADC), which indicates the free mobility of water molecules within the tumor as a marker for microstructural density, was determined at these 3 time points. On the dynamic contrast-enhanced MRI scans the tumor area-under-the-concentration versus time curve was determined at the 3 time points (reflecting tumor blood flow, vascular permeability, and the fraction of interstitial space).

The treatment-induced changes in tumor ADC (diffusion) and AUC (vascularization) during neoadjuvant chemoradiotherapy for esophageal cancer appeared highly predictive for histopathologic response. In 20 patients the change in tumor ADC during the first 2-3 weeks of chemoradiotherapy was 100% accurate in predicting a pathologic complete response after treatment and the prediction of

residual cancer was correct in 94% of patients. Also, in 26 patients the change in tumor AUC after chemoradiotherapy was 71% accurate in predicting a pathologic complete response and the prediction of residual cancer was correct in 93%. Both ADC and AUC measurements also appeared capable of identifying esophageal tumors that did not (or barely) respond to chemoradiotherapy. Because of these promising results in this first small study, larger studies with more patients are necessary to determine the exact value of diffusion-weighted and dynamic contrast-enhanced MRI in this setting. We are currently conducting such a multicenter study, which could directly open a window to individualize care and greatly improve the quality of life for many esophageal cancer patients.

The study in **Chapter 13** aimed to determine the value of ^{18}F -FDG PET for the prediction of pathologic response to another increasingly applied multimodality treatment strategy. In an attempt to eliminate micrometastases, additional induction chemotherapy before preoperative chemoradiotherapy is sometimes applied depending on institutional preferences. In this setting, ^{18}F -FDG PET before and after induction chemotherapy appeared useful for the early prediction of a poor pathologic response to subsequent preoperative chemoradiotherapy. As such, ^{18}F -FDG PET has the potential to enable individualized treatment decision-making in this setting.

PART IV. PERIOPERATIVE CARE

After esophagectomy for cancer the continuity of the alimentary tract is often restored by the construction a gastric tube and an esophagogastric anastomosis in the neck. Leakage of the cervical anastomosis is a feared complication after esophagectomy occurring in 10-30% of patients and results in increased morbidity and mortality. Preoperative prediction of the individual risk of a patient to develop anastomotic leakage is very difficult as predictive risk factors are missing. Therefore, in this part of the thesis risk factors for anastomotic leakage were sought along with preventative strategies and treatment strategies.

In **Chapter 14** we proposed a practical vascular calcification scoring system that reflects the amount and location of calcification in the arteries supplying the gastric tube as determined on a routine diagnostic CT scan in esophageal cancer. In a cohort of 246 patients who underwent esophagectomy with cervical anastomosis, both minor and major aortic calcification were associated with an increased risk of postoperative anastomotic leakage. Also, an independent association with leakage was found for calcification of the right post-celiac arteries. The identification of

this new risk factor is important as it could aid in patient selection for preventative strategies.

Since calcification of the arteries supplying the gastric tube was identified as risk factor for anastomotic leakage for the first time in the study mentioned above, validation of this finding was warranted and performed in **Chapter 15**. Indeed, in a cohort of 164 patients who underwent esophagectomy with intrathoracic (rather than cervical) anastomosis, the independent association of minor and major aortic calcification with the risk of anastomotic leakage was confirmed.

The narrative review in **Chapter 16** outlines the current experimental and clinical evidence on preoperative ischemic conditioning of the stomach, which seems a promising method before surgery to reduce the risk of postoperative anastomotic leakage. The technique includes partial gastric devascularization through embolization or laparoscopy in order to provide the time for the gastric tube to adapt to the acute ischemia at the time of its formation at a second stage. An important finding was that ischemic conditioning increases the perfusion of the gastric tube most effectively after a time interval of at least 2-3 weeks. In addition, the available studies investigated the effect of ischemic conditioning to all candidates for esophagectomy while no attempt was made to identify a subgroup who may actually benefit from the technique (i.e. who are at high risk of leakage). This finding provides room for improved patient selection.

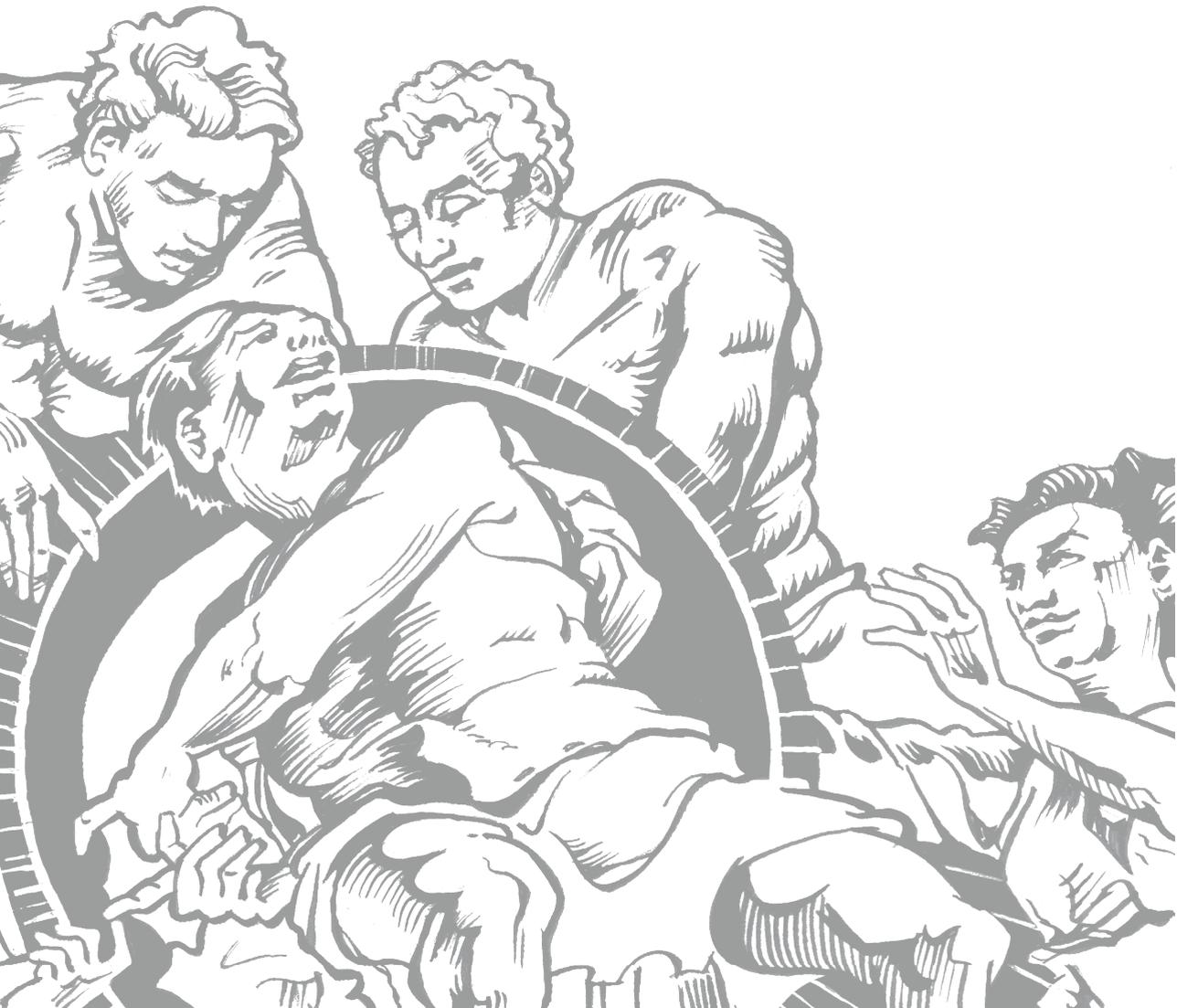
In the cohort study described in **Chapter 17** the relationships of intraoperative and postoperative vital parameters with anastomotic leakage and pneumonia after esophagectomy were assessed in 82 patients. A minimum intraoperative pH below 7.25 was associated with an increased risk of anastomotic leakage after esophagectomy (51% versus 12%). A maximum intraoperative pH above 7.34 and an average MAP in the first 12 hours after surgery below 83 mmHg were associated with an increased risk of postoperative pneumonia (52% versus 23%, and 49% versus 9%, respectively). These findings indicate the importance of setting strict perioperative goals to be protected intensively.

Another potential risk factor for anastomotic leakage after esophagectomy described sporadically in literature is the neoadjuvant radiation dose to the gastric fundus, which was investigated in more detail in **Chapter 18**. In 97 consecutive patients with esophageal cancer who underwent neoadjuvant chemoradiotherapy followed by transthoracic esophagectomy, the radiation dose to the gastric fundus – which is the vulnerable part of the future anastomosis – was calculated. Higher dose levels to the gastric fundus were associated with an increased risk of

anastomotic leakage, suggesting that efforts should be made to minimize this dose when planning neoadjuvant chemoradiotherapy for esophageal cancer.

Cervical anastomotic leakage after esophagectomy for cancer may exhibit both cervical and intrathoracic manifestation, and a comparison between these two manifestations in terms of associated signs and symptoms, management and outcomes is described in **Chapter 19**. In 60 patients with cervical anastomotic leakage, it was found that a positive SIRS score should raise the clinician's suspicion of anastomotic leakage with intrathoracic manifestation, regardless of the findings at cervical wound inspection. Mediastinal drainage through the neck wound was effective in 41% of all patients with intrathoracic manifestation. Patients with intrathoracic manifestation showed longer time to oral intake and prolonged ICU/hospital stay.

In conclusion, each patient with esophageal cancer is a unique and autonomous person with a unique set of patient- and tumor-related characteristics. In order to secure structure and comparativeness in quality of care and research, historically all these unique patients have been lumped together in groups through protocols and guidelines. This paradigm in care and research have brought many improvements in the prognosis of patients with esophageal cancer in the past decades. However, it also resulted in the fact that currently most patients undergo a multitude of burdening treatment modalities in which many individuals do not benefit from 1 or more of these modalities (over-treatment) and in which many individuals still do not receive (enough of) their most appropriate treatment (under-treatment). Now the time has come to tailor the treatment to the individual patient with esophageal cancer. The research projects presented in this thesis contributed to this development through the use of advanced imaging techniques and prediction models for the estimation of individual efficacies and risks.



Chapter 21

General discussion
and future perspectives

INDIVIDUALIZED TREATMENT

Why does a man prefer a tailor-made suit? Because it fits him, and him alone. Because each and every stitch was threaded over with him in mind. A man either fits the jacket or the jacket fits him. Currently, groups of patients with esophageal cancer fit in certain protocolled treatment approaches in esophageal cancer, but the treatment is rarely a perfect fit for the individual patient. This thesis indicates that in order to enable tailor-made treatment for the individual patient with esophageal cancer, improvements in the diagnostic work-up, multimodality treatment strategies, treatment response assessment, and the risk prediction, prevention, and management of postoperative complications are indicated. Although the research presented in this thesis has opened several doors regarding these topics, further research is crucial.

STAGING

MRI

The research in Chapters 2 and 3 demonstrated that in the past few years, several technical innovations in magnetic resonance imaging (MRI) for the first time enabled a clear visualization of the esophagus. In the University Medical Center Utrecht, we have specifically optimized the MRI scan protocol to improve image quality for esophageal cancer. This work has provided interesting new high-resolution anatomical and functional information on esophageal tumors. Initial staging of the primary tumor, lymph nodes, and possible distant metastases is currently the most important method to select patients for treatment approaches. However, current initial staging is known to be suboptimal in many respects and in need of improvement. Therefore, ongoing studies are focusing on the potential added value of modern MRI to this regard.

RADIOMICS

The emerging field of radiomics is another promising development that has the potential to improve on the current staging accuracy and individualized patient selection for treatment as described in Chapter 4¹. It is increasingly being recognized that the amount of information currently extracted from computed tomography (CT) and ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET) images in esophageal cancer may be substantially enhanced by quantitative imaging analysis². However, current evidence is still exploratory in nature and further validation in larger studies is required before implementation

in clinical practice could be considered. To this regard, standardization of imaging and radiomics approaches, multivariable prediction modeling, and validation of findings are key to successful future introduction of radiomics in the clinical management of esophageal cancer.

TREATMENT RESPONSE PREDICTION

Another important field of research aiming to develop tailor-made treatment strategies in esophageal cancer focuses on the prediction and assessment of response to chemotherapy and radiotherapy. Ultimately, if high accuracy in this field can be reached this means that in case of great effectiveness of chemoradiotherapy a more restrained policy could be considered in relation to surgical resection of the esophagus, thereby greatly improving the quality of life. Vice versa, burdening chemoradiotherapy could be omitted, stopped or modified in case of unresponsive disease, and by advancing surgery detrimental delays could be minimized. Consequently, a more restrained and tailored approach towards unnecessary surgery or chemoradiotherapy is then expected along with an improved quality of life.

ENDOSCOPIC BIOPSY

A meta-analysis presented in Chapter 9 demonstrated that endoscopic biopsy results after chemoradiotherapy yields a high specificity of 91% (95% confidence interval [CI]: 86-95%), but low sensitivity of 35% (95% CI: 26-44%) for residual cancer. Endoscopic sampling error due to the irradiated luminal surface with remaining small tumor foci combined with inflammation and fibrosis/scarring, and the presence of non-mucosal residual cancer in deeper esophageal wall layers are thought to account for the low sensitivity³⁻⁸. Extensive sampling protocols and deeper bite-on-bite submucosal biopsies have been proposed in recent studies to improve the sensitivity of endoscopic biopsy after chemoradiotherapy^{4,6}. These protocols deserve further investigation with special caution regarding the potential risk of esophageal perforations.

EUS

Also, a meta-analysis in Chapter 9 demonstrated that endoscopic ultrasound (EUS) yields a high sensitivity of 96% (95% CI: 92-99%), but very low specificity of 11% (95% CI: 4-29%) for detecting residual cancer at the primary tumor site after chemoradiotherapy. In fact, EUS is not able to reliably distinguish between disruption of the esophageal wall due to residual tumor and disruption secondary

to inflammation and fibrosis/scarring after chemoradiotherapy⁹⁻¹¹. Recently, a potentially superior method to determine residual cancer status with EUS has been proposed in a Swiss prospective multicenter study¹². An EUS-based maximum tumor thickness after chemoradiotherapy of >6 mm appeared promising for detecting residual cancer with a sensitivity of 86% and specificity of 64%¹². These findings suggest that this method is superior to the diagnostic performance resulting from our meta-analysis on EUS-based T-restaging, but the method and used threshold have not yet been validated and further studies are required.

¹⁸F-FDG PET

The University of Texas MD Anderson Cancer Center has the largest experience with ¹⁸F-FDG PET scanning in esophageal cancer worldwide. In Chapters 10 and 13, the value of ¹⁸F-FDG PET for treatment response assessment was evaluated in a cohort of their patients with esophageal adenocarcinoma receiving multimodality treatment. Although subjective and quantitative (radiomics) assessment of ¹⁸F-FDG PET provided statistical incremental value for predicting pathologic response, the predictive ability is considered not good enough to truly enable individualized treatment decision-making. It has been suggested that response assessment with ¹⁸F-FDG PET might be improved by extending the time period from the end of neoadjuvant treatment, because after 12 or more weeks the artifacts due to radiation-induced inflammation are expected to have largely dissolved¹³. This suggestion deserves further attention.

MRI

The prospective pilot studies in Chapters 11 and 12 presented initial evidence that functional MRI (including diffusion-weighted MRI and dynamic contrast-enhanced MRI) yields high potential for treatment response prediction in esophageal cancer. This finding was supported by a recent Italian study in gastric and esophageal cancer¹⁴, and by studies in several other malignancies including brain, head-and-neck, breast, prostate, and rectal cancer¹⁵⁻²⁰. However, further studies are required to optimize MRI scan protocols, timing of scans, and confirm the preliminary clinical evidence in larger populations of patients with esophageal cancer. In addition, future clinical studies in esophageal cancer should aim to determine the potential value of the recently developed MR-linac system that integrates an MRI system with a radiotherapy accelerator, allowing for simultaneous irradiation and real-time MR imaging.

MULTIMODALITY DIAGNOSTIC APPROACHES

In addition, it is more likely that in future research a multimodality imaging approach might prove to provide sufficient predictive value for pathologic response to safely guide tailored treatment decision-making, rather than using ^{18}F -FDG PET or MRI alone for example. Therefore, in a recently embarked prospective multicenter study we aim to determine the complementary values of diffusion-weighted MRI, dynamic contrast-enhanced MRI, and ^{18}F -FDG PET for the prediction of treatment response by performing both MRI and ^{18}F -FDG PET before, during, and after neoadjuvant chemoradiotherapy for esophageal cancer²¹. Future efforts should include large high-quality studies focusing on multimodality diagnostic approaches and standardization of techniques.

MOLECULAR BIOMARKERS

It should be noted that several studies also have demonstrated potential of a number of molecular biomarkers for predicting treatment response in esophageal cancer, but most of these studies included small patient populations²². Molecular biomarkers that hold most promise to this regard include epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), serum microRNA, and some genes extracted from gene expression profiling²²⁻²⁵. In the near future, an approach combining information from multimodality imaging ('radiomics') and molecular biomarkers ('genomics') – for which 'radiogenomics' may be the appropriate term – could prove most optimal for guiding multimodality treatment decision-making tailored to the individual patient with esophageal cancer.

TREATMENT STRATEGIES

The optimal treatment approach for locally advanced esophageal adenocarcinoma is controversial. Neoadjuvant chemoradiotherapy followed by surgery is the preferred treatment strategy in many countries (e.g. United States, The Netherlands), while perioperative chemotherapy remains the standard of treatment in other countries (e.g. United Kingdom). Chapter 6 described an important comparison in terms of toxicity, pathologic outcome, and survival of two of the most frequently applied regimens (perioperative chemotherapy according to the modified MAGIC-regimen versus neoadjuvant chemoradiotherapy according to the CROSS-regimen)²⁶⁻²⁹. No significant improvements were achieved with neoadjuvant chemoradiotherapy compared to perioperative chemotherapy in terms of radical resection rates or progression-free survival and overall survival. However, chemoradiotherapy was associated with improved tumor downstaging, higher pathologic complete

response rates (18% vs. 11%), higher pathologic near-complete response rates (19% vs. 6%), and a reduced risk of locoregional recurrence compared to chemotherapy (15% vs. 37% after 3 years).

The pathologic findings of the comparative study are important in the light of the desired shift towards individualized treatment approaches, as apparently after chemoradiotherapy a substantial proportion of patients (18%) may benefit from a wait-and-see approach with omission of surgery. Also, the fact that a relatively large proportion of patients (19%) has a near-complete response (i.e. microscopic residual cancer only) after chemoradiotherapy offers interesting opportunities for individualized treatment as these patients might benefit from treatment intensification strategies. In contrast, the low incidence of pathologic complete and near-complete response rates after preoperative chemotherapy (11% and 6%, respectively) yields little opportunity for such tailored treatment strategies.

From diagnosis of recurrent disease after initial treatment with curative intent, patients have a median survival of only 3 months. Distant (rather than locoregional) recurrence and more than 3 recurrent locations were independent prognostic factors associated with worse post-recurrence survival, irrespective of primary tumor characteristics in a cohort study presented in chapter 8. These findings are helpful as they contribute to informed decision-making by doctors and patients. For example, patients with unfavorable disease characteristics (distant recurrence and >3 locations) burdening treatment with little chance of benefit may be omitted. In addition, future trials may select patients with favorable prognostic factors (i.e. locoregional recurrence and ≤ 3 locations) to study the feasibility and potentially superior efficacy of new (more aggressive) treatment approaches. In addition, the current follow-up strategy after treatment with curative intent may need revision. Currently, follow-up includes imaging on indication only, but it could be hypothesized that routine imaging may result in the detection of recurrent disease at earlier stages. In light of the concept of oligometastases, the fact that most recurrences manifest within 2 years following primary treatment, and the superior diagnostic performance of ^{18}F -FDG PET/CT in this setting, I suggest to perform routine ^{18}F -FDG PET/CT in the first 2 years following primary treatment. Consequently, more patients may be eligible for effective treatment focused on tumor reduction to improve their survival or even achieve cure.

PERIOPERATIVE MANAGEMENT

Anastomotic leakage is a frequently encountered and feared complication after esophagectomy that is associated with increased postoperative morbidity, length of hospital stay, and mortality. Clinicians are currently unable to accurately predict which patient will develop this complication and which patient will not. This is unfortunate, because such an accurate prediction could aid in patient selection for preoperative preventative strategies and postoperative early recognition of anastomotic leakage. In Chapters 14-15 a new hypothesis-driven risk factor for anastomotic leakage (i.e. minor and major calcification of the aorta as determined on routine preoperative CT scans) was identified and validated in an external cohort. In fact, the risks of anastomotic leakage in patients with major aortic calcification, minor aortic calcification, and no aortic calcification in the two cohorts were 35-37%, 27-32%, and 9-16%, respectively.

Ischemic conditioning of the stomach through embolization or laparoscopy, at least 2-3 weeks before esophagectomy and gastric tube reconstruction, appears to be a promising strategy for preventing postoperative anastomotic leakage (Chapter 16). Across experimental and initial clinical feasibility studies, gastric ischemic conditioning appeared moderately –but consistently– effective to prevent anastomotic leakage. However, it is important to note that the studies investigated the effect of ischemic conditioning to all candidates for esophagectomy while no attempt was made to identify a subgroup who may actually benefit from the technique (i.e. who are at high risk of leakage). In order to improve the efficacy of gastric ischemic conditioning, selection of patients at high risk of leakage could prove beneficial, for example by using the calcification scoring system presented in Chapter 14-15. Future efforts should include patients at high risk of leakage only and aim to determine the feasibility of the technique in a properly powered phase II study, and the efficacy in a subsequent phase III randomized controlled trial.

Further improvements in preventing anastomotic leakage in esophageal cancer include setting strict perioperative goals to be protected intensively during esophagectomy and during the first 24 postoperative hours (Chapter 17) and minimizing the neoadjuvant radiation dose to the gastric fundus (Chapter 18). Again, these strategies may be of particular importance in individual patients at high risk of anastomotic leakage. However, ideally the found associations of the risk of anastomotic leakage with perioperative vital parameters and neoadjuvant radiation dosimetry should be validated in larger studies.

FINAL REMARKS

As in every part of medicine, the goal of future work in esophageal oncology should be to maximize the efficacy of treatment and to minimize the burden to the patient. In this respect, I envision that (among others) two exciting recent developments described in this thesis will likely have a major impact in the nearby future. First, in the years to come I expect that clinicians will become able to accurately estimate patients' individual probability of a certain efficacy (i.e. tumor regression grade) after chemoradiotherapy based on quantitative imaging parameters and/or molecular biomarkers. Such an estimation would tremendously help clinicians and patients with informed and shared treatment decision-making. In particular the preoperative probability of a pathologic complete response is of interest for the patient, as this parameter reflects the need for additional surgical treatment. Vice versa, early identification of a high probability of non-response may be reason to modify or stop neoadjuvant treatment. Future trials should stratify patients according to their biological tumor characteristics, of which response to chemoradiotherapy is a very important parameter. For example, trials could focus on improving the treatment strategies separately per response category.

Second, the development of the MR-guided linear accelerator (MR-linac) by the UMC Utrecht and partners is transforming the field of radiotherapy. The MR-linac enables physicians to visualize and adapt radiation therapy in real-time during treatment based on detailed MR images. As such, the MR-linac yields unprecedented levels of precision and accuracy for each individual patient resulting in improved efficacy and reduced toxicity. In addition, it implies that in the nearby future standard (rather conservative) total radiation doses –already leading to a complete disappearance of esophageal tumor cells in approximately 30% of cases– may be safely escalated using the MR-linac. Meanwhile, treatment response could be continuously monitored during treatment using the MRI component. These features are expected to result in a higher proportion of local cure (and good tumor responses) for esophageal cancer with fewer side effects. If so, a more restrained policy towards surgery may be practiced in a significant proportion of patients, while current non-surgical patients (due to advanced local tumor characteristics) may become new surgical candidates.

CONCLUSIONS

The conclusions reached in this thesis can be summarized as follows:

PART I. IMAGING OF ESOPHAGEAL CANCER

- Chapter 2** MRI has the potential to bring improvement in staging, tumor delineation and real-time guidance for radiotherapy, and assessment of treatment response in esophageal cancer.
- Chapter 3** ^{18}F -FDG PET/CT is of particular importance for the detection of unexpected distant metastases and recurrent disease.
- Chapter 4** The evidence on radiomics in esophageal cancer has been growing steadily suggesting potential added value for staging, prediction of response to treatment, and prediction of survival.
- Chapter 5** ^{18}F -FDG PET/CT allows for a minimal false-negative rate in the detection of recurrent esophageal cancer after treatment with curative intent, but histopathologic confirmation of suspected lesion remains required as a considerable false-positive rate is noticed.

PART II. MULTIMODALITY TREATMENT STRATEGIES

- Chapter 6** Neoadjuvant chemoradiotherapy for esophageal adenocarcinoma improves pathologic response rates and reduces the risk of locoregional recurrence compared to perioperative chemotherapy, without significantly improving overall survival.
- Chapter 7** Concurrent chemoradiotherapy is the preferred treatment option for patients with inoperable locally advanced esophageal cancer, whereas combination chemotherapy is indicated for metastatic disease, and self-expanding metal stent placement is the most widely applied method for palliating dysphagia.
- Chapter 8** In patients with recurrent disease after esophagectomy for cancer, distant recurrence and more than 3 recurrent locations are independently associated with worse post-recurrence survival, irrespective of primary tumor characteristics.

PART III. TREATMENT RESPONSE ASSESSMENT

- Chapter 9** Endoscopic biopsy has a low sensitivity and EUS a very low specificity for detecting residual cancer after neoadjuvant chemoradiotherapy, and therefore both modalities cannot be used to withhold surgical treatment in test-negative patients after neoadjuvant chemoradiotherapy.
- Chapter 10** Although subjective and quantitative assessment of ^{18}F -FDG PET provides statistical incremental value for predicting a pathologic complete response after neoadjuvant chemoradiotherapy in esophageal cancer, the discriminatory improvement beyond clinical predictors does not translate into a clinically relevant benefit for treatment decision-making.
- Chapter 11** The change of tumor apparent diffusion coefficient values as determined on diffusion-weighted MRI during the first 2-3 weeks of neoadjuvant chemoradiotherapy for esophageal cancer appears highly predictive for pathologic response to treatment.
- Chapter 12** Determining changes in the area-under-the-time-versus-concentration-curve within the tumor based on dynamic contrast-enhanced MRI after the first 2-3 weeks of neoadjuvant chemoradiotherapy and prior to surgery appears useful for predicting pathologic response to treatment.
- Chapter 13** ^{18}F -FDG PET appears useful to predict a poor pathologic response as well as progression-free survival early after induction chemotherapy in patients with esophageal adenocarcinoma undergoing a three-step treatment strategy.

PART IV. PERIOPERATIVE CARE

- Chapter 14** Atherosclerotic calcification of the arteries that supply the gastric tube, defined by a visual grading system with good to excellent inter- and intraobserver reproducibility, is independently associated with anastomotic leakage of the cervical esophagostomy.
- Chapter 15** Atherosclerotic calcification of the aorta, defined by the same visual grading system, is also an independent risk factor for anastomotic leakage after esophagectomy with intrathoracic anastomosis.
- Chapter 16** Preoperative ischemic conditioning of the stomach appears to be a promising strategy for preventing postoperative anastomotic leakage.
- Chapter 17** A lower minimum intraoperative pH is associated with an increased risk of anastomotic leakage after esophagectomy, whereas a lower postoperative average mean arterial pressure and a higher intraoperative pH increase the risk of postoperative pneumonia.
- Chapter 18** Higher neoadjuvant radiation dose levels to the gastric fundus are associated with an increased risk of anastomotic leakage after transthoracic esophagectomy.
- Chapter 19** Intrathoracic manifestation of cervical anastomotic leakage occurs in more than half of patients with anastomotic leakage after transthoracic esophagectomy for cancer, results in prolonged ICU/hospital stay and delays time to oral intake compared with leakage confined to the neck, and can be managed effectively by mediastinal drainage or a re-intervention through the thoracic cavity.

REFERENCES

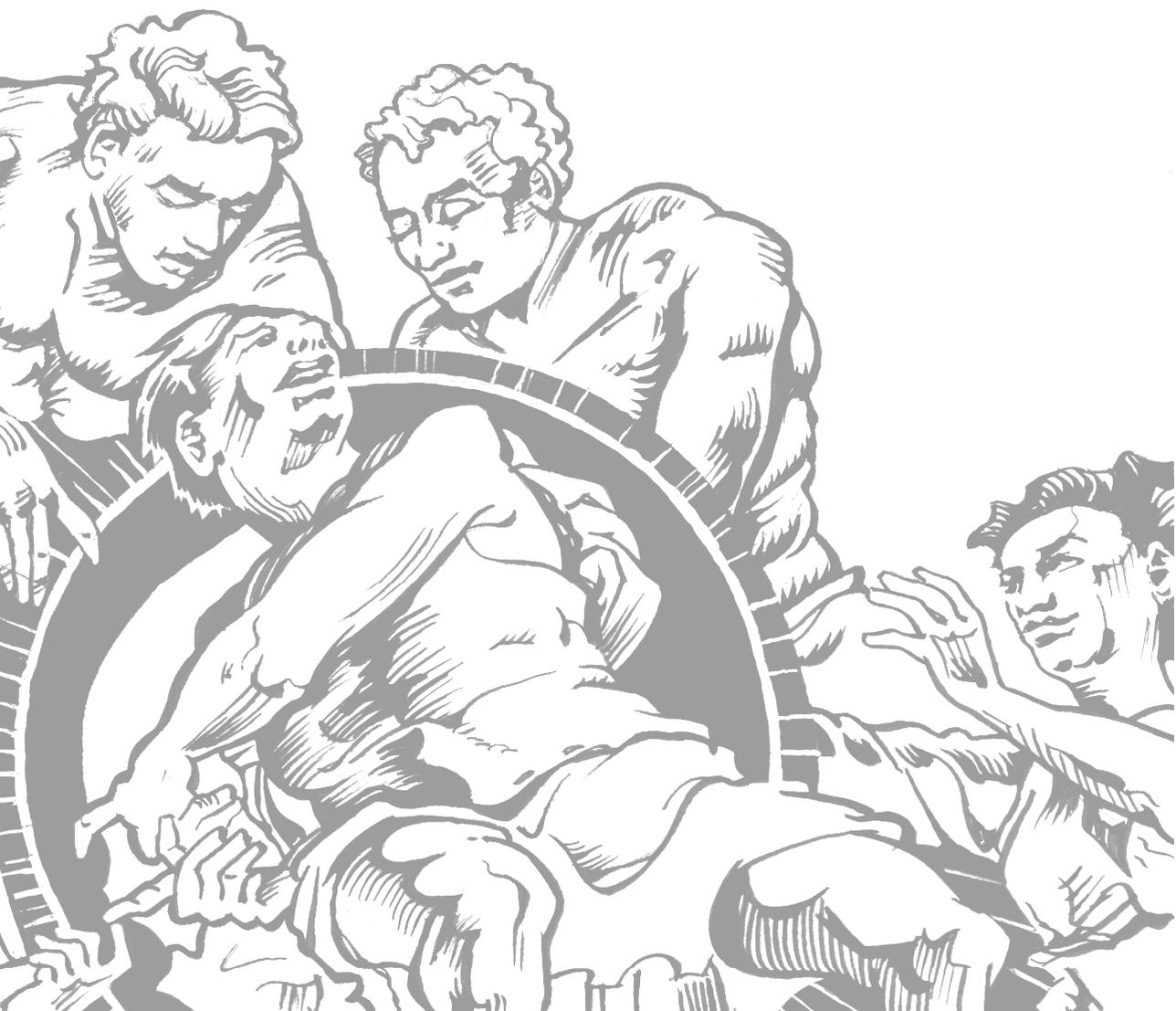
1. Lambin P, Rios-Velazquez E, Leijenaar R, et al. Radiomics: extracting more information from medical images using advanced feature analysis. *Eur J Cancer* 2012;48:441-6
2. Ganeshan B, Skogen K, Pressney I, et al. Tumour heterogeneity in oesophageal cancer assessed by CT texture analysis: preliminary evidence of an association with tumour metabolism, stage, and survival. *Clin Radiol* 2012;67:157-64
3. Yang Q, Cleary KR, Yao JC, et al. Significance of post-chemoradiation biopsy in predicting residual esophageal carcinoma in the surgical specimen. *Dis Esophagus* 2004;17:38-43
4. Shapiro J, ten Kate FJ, van Hagen P, et al. Residual esophageal cancer after neoadjuvant chemoradiotherapy frequently involves the mucosa and submucosa. *Ann Surg* 2013;258:678-88; discussion 688-9
5. Chao YK, Yeh CJ, Lee MH, et al. Factors associated with false-negative endoscopic biopsy results after neoadjuvant chemoradiotherapy in patients with esophageal squamous cell carcinoma. *Medicine (Baltimore)* 2015;94:e588
6. Chao YK, Tsai CY, Chang HK, et al. A pathological study of residual cancer in the esophageal wall following neoadjuvant chemoradiotherapy: focus on esophageal squamous cell carcinoma patients with false negative preoperative endoscopic biopsies. *Ann Surg Oncol* 2015;22:3647-52
7. Shaukat A, Mortazavi A, Demmy T, et al. Should preoperative, post-chemoradiotherapy endoscopy be routine for esophageal cancer patients? *Dis Esophagus* 2004;17:129-35
8. Sarkaria IS, Rizk NP, Bains MS, et al. Post-treatment endoscopic biopsy is a poor-predictor of pathologic response in patients undergoing chemoradiation therapy for esophageal cancer. *Ann Surg* 2009;249:764-7
9. Beseth BD, Bedford R, Isacoff WH, et al. Endoscopic ultrasound does not accurately assess pathologic stage of esophageal cancer after neoadjuvant chemoradiotherapy. *Am Surg* 2000;66:827-31
10. Yen TJ, Chung CS, Wu YW, et al. Comparative study between endoscopic ultrasonography and positron emission tomography-computed tomography in staging patients with esophageal squamous cell carcinoma. *Dis Esophagus* 2012;25:40-7
11. Kalha I, Kaw M, Fukami N, et al. The accuracy of endoscopic ultrasound for restaging esophageal carcinoma after chemoradiation therapy. *Cancer* 2004;101:940-7
12. Jost C, Binek J, Schuller JC, et al. Endosonographic radial tumor thickness after neoadjuvant chemoradiation therapy to predict response and survival in patients with locally advanced esophageal cancer: a prospective multicenter phase II study by the Swiss Group for Clinical Cancer Research (SAKK 75/02). *Gastrointest Endosc* 2010;71:1114-21
13. Noordman BJ, Shapiro J, Spaander MC, et al. Accuracy of detecting residual disease after Cross neoadjuvant chemoradiotherapy for esophageal cancer (preSANO trial): rationale and protocol. *JMIR Res Protoc* 2015;4:e79
14. De Cobelli F, Giganti F, Orsenigo E, et al. Apparent diffusion coefficient modifications in assessing gastro-oesophageal cancer response to neoadjuvant treatment: comparison with tumour regression grade at histology. *Eur Radiol* 2013;23:2165-74

15. Vandecaveye V, Dirix P, De Keyzer F, et al. Diffusion-weighted magnetic resonance imaging early after chemoradiotherapy to monitor treatment response in head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2012;82:1098-1107
16. Mardor Y, Pfeffer R, Spiegelmann R, et al. Early detection of response to radiation therapy in patients with brain malignancies using conventional and high b-value diffusion-weighted magnetic resonance imaging. *J Clin Oncol* 2003;21:1094-1100
17. Decker G, Murtz P, Gieseke J, et al. Intensity-modulated radiotherapy of the prostate: dynamic ADC monitoring by DWI at 3.0 T. *Radiother Oncol* 2014;113:115-20
18. Cho N, Im SA, Park IA, et al. Breast cancer: early prediction of response to neoadjuvant chemotherapy using parametric response maps for MR imaging. *Radiology* 2014;272:385-96
19. Chawla S, Kim S, Dougherty L, et al. Pre-treatment diffusion-weighted and dynamic contrast-enhanced MRI for prediction of local treatment response in squamous cell carcinomas of the head and neck. *Am J Roentgenol* 2013;200:35-43
20. Intven M, Monninkhof EM, Reerink O, et al. Combined T2w volumetry, DW-MRI and DCE-MRI for response assessment after neo-adjuvant chemoradiation in locally advanced rectal cancer. *Acta Oncol* 2015;54:1729-36
21. University Medical Center Utrecht. Preoperative identification of response to neoadjuvant chemoradiotherapy for esophageal cancer (PRIOR). In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). Available from: <http://clinicaltrials.gov/show/NCT02125448>; NLM Identifier: NCT02125448.
22. Bain GH, Petty RD. Predicting response to treatment in gastroesophageal junction adenocarcinomas: combining clinical, imaging, and molecular biomarkers. *Oncologist* 2010;15:270-84
23. Odenthal M, Hee J, Gockel I, et al. Serum microRNA profiles as prognostic/predictive markers in the multimodality therapy of locally advanced adenocarcinomas of the gastroesophageal junction. *Int J Cancer* 2015;137:230-7
24. Skinner HD, Lee JH, Bhutani MS, et al. A validated miRNA profile predicts response to therapy in esophageal adenocarcinoma. *Cancer* 2014;120:3635-41
25. Wen J, Luo K, Liu H, et al. MiRNA expression analysis of pretreatment biopsies predicts the pathological response of esophageal squamous cell carcinomas to neoadjuvant chemoradiotherapy. *Ann Surg* 2016;263:942-8
26. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20
27. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;358:36-46
28. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84
29. Shapiro J, van Lanschot JJ, Hulshof MC, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol* 2015;16:1090-8



ADDENDA





Summary in Dutch
(Nederlandse samenvatting)

Slokdarmkanker is de achtste meest voorkomende kankersoort wereldwijd met ruim 450.000 nieuwe gevallen per jaar en ruim 400.000 sterftegevallen per jaar. Ondanks recente verbeteringen in de diagnostiek en behandeling van slokdarmkanker blijft de aandoening een verwoestende ziekte met een 5-jaarsoverleving van slechts 15-25%. Omdat de prognose veelal slecht is wordt vaak voor verschillende combinaties van chirurgie, chemotherapie en radiotherapie gekozen (in plaats van een enkele behandeling) om zo de kansen op genezing te vergroten. Voor patiënten is het grote aantal invasieve behandelingen zwaar om te ondergaan, mede omdat de behandelingen substantiële risico's op bijwerkingen en complicaties met zich mee brengen, terwijl men op individueel niveau niet weet of alle componenten van de behandeling daadwerkelijk bijdragen aan de gewenste uitkomst. De onderzoeken die gepresenteerd zijn in dit proefschrift zijn erop gericht om een individuele behandeling op maat mogelijk te maken voor patiënten met slokdarmkanker. Het doel is om componenten van de behandeling die het beste zijn voor de individuele patiënt nauwkeurig te kunnen selecteren en componenten van de behandeling die weinig bijdragen aan het welzijn van de patiënt (of deze zelfs verslechteren) achterwege te kunnen laten. Om dit doel te bereiken werden belangrijke huidige beperkingen blootgelegd en verbeteringen aangedragen ten aanzien van de diagnostiek, de behandelingsstrategieën, het evalueren van het effect van gecombineerde chemotherapie en radiotherapie op de slokdarmtumor en de risicoschatting, preventie en behandeling van complicaties na een slokdarmoperatie.

DEEL I. BEELDVORMING BIJ SLOKDARMKANKER

In dit deel van het proefschrift werd de huidige waarde en toekomstige potentie van MRI, PET en CT scantechieken voor het op maat maken van de behandeling voor slokdarmkanker onderzocht. In dat kader werden aanknopingspunten gezocht vanuit de literatuur met potentie voor nader klinisch onderzoek.

MRI speelt momenteel geen belangrijke rol in de standaardzorg voor patiënten met slokdarmkanker. Echter, in **Hoofdstuk 2 en 3** werd aangetoond dat de beeldkwaliteit van MRI voor slokdarmkanker sterk is verbeterd in de afgelopen jaren door technologische vooruitgang, waardoor gelijkwaardige of zelfs betere resultaten worden bereikt voor diagnostiek vergeleken met de technieken (PET, CT, endoscopische echografie) die momenteel standaard toegepast worden. Recente innovaties werden beschreven die in de nabije toekomst MRI-gestuurde radiotherapie voor slokdarmkanker mogelijk maken, waardoor gericht bestraald kan gaan worden met meer effect en minder bijwerkingen. Tot slot werd beschreven

dat er groeiend bewijs is dat bepaalde nieuwe MRI technieken (al dan niet in combinatie met PET/CT) het effect van radiotherapie en chemotherapie op de tumor kunnen voorspellen (zie ook Deel III). Als zodanig hebben moderne MRI scantechnieken (al dan niet in combinatie met PET/CT) grote potentie voor het bijdragen aan een behandeling op maat voor ieder individu met slokdarmkanker in de nabije toekomst.

In **Hoofdstuk 4** werd aandacht besteed aan de potentiële rol van het opkomende wetenschappelijke veld genaamd ‘radiomics’, waarin additionele informatie uit standaard medische beelden wordt geëxtraheerd. De wetenschappelijke literatuur suggereert dat kwantificatie van de heterogeniteit van tumoren op beeldvorming –door de relatie met biologische tumorkarakteristieken– van toegevoegde waarde kan zijn bij slokdarmkanker voor diagnostiek, het voorspellen van het effect van de behandeling (zie ook Deel III) en het voorspellen van de prognose. Als zodanig zouden ‘radiomics’ benaderingen kunnen bijdragen aan het afstemmen van de behandeling op individueel niveau.

Uit het onderzoek gepresenteerd in **Hoofdstuk 5** blijkt dat PET of geïntegreerde PET/CT scans betrouwbaar zijn voor het detecteren of uitsluiten van teruggekeerde slokdarmkanker na een slokdarmoperatie. De teruggekeerde slokdarmkanker kan gedetecteerd worden op PET(/CT) in 96% van de patiënten die daadwerkelijk teruggekeerde kanker hebben; in 78% van de patiënten die geen teruggekeerde kanker hebben toont PET(/CT) ook geen verdachte afwijkingen. Daarmee lijkt PET(/CT) gevoeliger voor teruggekeerde slokdarmkanker dan de standaard toegepaste technieken voor deze indicatie (CT en endoscopie). Daarom dient PET(/CT) in grote lijnen de andere technieken te vervangen voor deze indicatie, zodat minder patiënten onterecht gerustgesteld worden en geen behandeling (op maat) krijgen.

DEEL II. GECOMBINEERDE BEHANDELINGSSTRATEGIEËN

In dit deel van het proefschrift werden de verscheidene behandelingsstrategieën voor slokdarmkanker vergeleken. Zowel behandelingsstrategieën met als doel te genezen (curatieve intentie) alsook strategieën met als doel de kwaliteit van leven te optimaliseren en de overleving te verlengen indien genezing niet meer mogelijk is (palliatieve intentie) werden bestudeerd.

Wereldwijd worden twee behandelingsstrategieën met curatieve intentie het meeste toegepast bij patiënten met slokdarmkanker zonder uitzaaiingen, namelijk een combinatie van gelijktijdig chemotherapie en radiotherapie gevolgd door

een operatie (preoperatieve chemoradiatie) of chemotherapie gevolgd door een operatie en daarna wederom chemotherapie (perioperatieve chemotherapie). In **Hoofdstuk 6** werden deze strategieën met elkaar vergeleken in een groep patiënten uit het UMC Utrecht ten aanzien van bijwerkingen, het effect van de preoperatieve behandeling op de tumor bij pathologisch onderzoek na de operatie en de prognose op lange termijn. Beide strategieën bleken geassocieerd met een vergelijkbare kans op ernstige bijwerkingen. Hoewel preoperatieve chemoradiatie een groter effect had op de slokdarmtumoren bij pathologisch onderzoek en de kans op teruggekeerde slokdarmkanker in het operatiegebied en nabijgelegen lymfeklieren reduceerde, leidden deze bevindingen niet tot betere algehele overlevingskansen vergeleken met perioperatieve chemotherapie.

Hoofdstuk 7 is een uiteenzetting van de palliatieve behandelingsmogelijkheden voor patiënten met slokdarmkanker die niet geopereerd kunnen worden en waarbij het doel is om passageklachten en andere kanker-gerelateerde symptomen te bestrijden, de kwaliteit van leven te verbeteren en de overlevingsduur te verlengen. Recente wetenschappelijke onderzoeken omtrent de individuele indicaties voor de verschillende behandelingsstrategieën zoals chemotherapie, zogenaamde ‘targeted’ agentia, uitwendige en inwendige radiotherapie, chirurgie en stentplaatsing werden bediscussieerd. Het doel was om behandelend artsen een leidraad aan te reiken voor klinische besluitvorming op het niveau van de individuele patiënt.

Het doel van het onderzoek in **Hoofdstuk 8** was om factoren te identificeren die de overleving beïnvloeden vanaf het moment dat er teruggekeerde slokdarmkanker is vastgesteld na een eerdere slokdarmoperatie. De bevinding dat 50% van de patiënten reeds 3 maanden na het vaststellen van de teruggekeerde slokdarmkanker overleden was, benadrukt het belang en de complexiteit van het vinden van een goede balans tussen de (veelal beperkte) effectiviteit van behandeling en de (vaak zware) last daarvan in iedere individuele patiënt afzonderlijk. Terugkeer van slokdarmkanker in de vorm van uitzaaiingen (in plaats van lokaal in het operatiegebied of nabijgelegen lymfeklieren) en meer dan 3 teruggekeerde plekken waren onafhankelijke prognostische factoren geassocieerd met een slechtere overleving, ongeacht de primaire tumorkarakteristieken. Deze bevindingen kunnen helpen in het selecteren van welke patiënten met teruggekeerde slokdarmkanker te behandelen en welke niet.

DEEL III. VOORSPELLING VAN BEHANDELINGSEFFECT

Het doel van de onderzoeken in dit deel van het proefschrift was om componenten van de behandeling die het beste zijn voor de individuele patiënt accuraat te kunnen selecteren en componenten van de behandeling die weinig bijdragen aan het welzijn van de patiënt (of deze zelfs verslechteren) achterwege te kunnen laten.

In **Hoofdstuk 9** werd gekeken naar de waarde van endoscopische biopsie en endoscopische echografie om na het afronden van preoperatieve chemoradiatie te bepalen of er nog resttumor is of dat de tumor geheel verdwenen is. Een nauwkeurige bepaling hiervan voorafgaand aan de operatie zou een orgaansparend beleid mogelijk kunnen maken waarbij de ingrijpende operatie (waarbij de slokdarm verwijderd) achterwege gelaten zou kunnen worden. Uit het onderzoek kwam naar voren dat endoscopische biopten inderdaad geen resttumor tonen bij 91% van de patiënten met daadwerkelijk geen resterende tumor in de slokdarm, maar ook in 65% van de patiënten die nog wel ergens in de slokdarm resterend tumorweefsel hebben. Endoscopische echografie toont daarentegen een beeld van resttumor in 96% van de patiënten met daadwerkelijk een resttumor, maar ook in 89% van de patiënten zonder resterend tumorweefsel. De onbetrouwbaarheid van deze endoscopische technieken maakt dat ze niet gebruikt kunnen worden om bij patiënten (waarbij de tumor helemaal weg lijkt) de operatie achterwege te laten.

Het onderzoek in **Hoofdstuk 10** betreft een onderzoek in een patiëntenpopulatie van het MD Anderson Cancer Center, Houston (Texas), waarin de toegevoegde waarde werd bestudeerd van (1) de subjectieve beoordeling van PET scans vóór en na preoperatieve chemoradiatie, (2) traditionele kwantitatieve PET-metingen en (3) kwantitatieve 'radiomics' metingen op PET, voor het voorspellen van de aanwezigheid versus afwezigheid van resttumor na preoperatieve chemoradiatie. Hoewel de drie bestudeerde mogelijkheden voor het interpreteren van PET scans statistisch gezien tot een betere voorspelling van de uitkomst leidden, was het onderscheidend vermogen van deze voorspelling nog niet goed genoeg om op grond daarvan te besluiten een individuele patiënt wel of niet te opereren. Deze bevinding wijst erop dat PET een redelijke indicatie geeft van het effect van chemoradiatie op slokdarmtumoren, maar dat het op zichzelf staand niet nauwkeurig genoeg is om de klinische besluitvorming te veranderen en dat andere (aanvullende) methoden dus erg wenselijk zijn.

In **Hoofdstuk 11 en 12** werden de eerste resultaten beschreven van een klinische studie die werd uitgevoerd in het UMC Utrecht en het Antoni van Leeuwenhoek/Nederlands Kanker Instituut bij patiënten met slokdarmkanker met als doel

de waarde van twee nieuwe MRI scantechnieken genaamd 'diffusie-gewogen' MRI (Hoofdstuk 11) en 'dynamische contrast-versterkte' MRI (Hoofdstuk 12) te bepalen voor het voorspellen het effect van preoperatieve chemoradiatie op slokdarmtumoren. MRI scans werden vervaardigd voorafgaand aan de behandeling, na de eerste 2-3 weken van chemoradiatie en na afloop van de chemoradiatie (vlak vóór de operatie). Op de diffusie-gewogen MRI scans – verkregen op deze 3 tijdstippen– werd de 'apparent diffusion coefficient' (ADC) waarde van de tumor bepaald, wat een maat is voor de vrije beweeglijkheid van water moleculen binnen de tumor als een marker voor microstructurele dichtheid. Op de dynamische contrast-versterkte MRI scans werd de zogenaamde 'area-under-the-concentration versus time curve' (AUC) waarde van de tumor bepaald op de 3 tijdstippen, wat een maat is voor de bloedstroom, vasculaire permeabiliteit en de fractie van interstitiële weefselruimte van de tumor.

De door behandeling geïnduceerde veranderingen van de tumor ADC (diffusie) en AUC (vascularisatie) waarden gedurende de chemoradiatie is sterk voorspellend gebleken voor het daadwerkelijke effect op de tumor zoals bepaald door de patholoog na de operatie. Zo bleek bij 20 patiënten dat de verandering in tumor ADC gedurende de eerste 2-3 weken 100% nauwkeurig was in het voorspellen van afwezigheid van resttumor na de behandeling en dat een voorspelling van resttumor in 94% van de gevallen juist was. Ook bleek bij 26 patiënten dat de verandering in tumor AUC na chemoradiatie 71% nauwkeurig was in het voorspellen van afwezigheid van resttumor na de behandeling en dat een voorspelling van resttumor in 93% van de gevallen juist was. Zowel ADC als AUC metingen bleken tevens redelijk goed in staat om vroeg tijdens de behandeling slokdarmtumoren die niet (of nauwelijks) reageerden op chemoradiatie te identificeren. Vanwege deze veelbelovende resultaten in een relatief kleine eerste studie, zijn grotere studies met meer patiënten nodig om de exacte waarde van diffusie-gewogen en dynamische contrast-versterkte MRI scans in deze setting te bepalen. Wij zijn reeds een dergelijke studie gestart, die direct tot gevolg kan hebben dat de zeer intensieve slokdarmbehandeling beter kan worden afgestemd op de individuele patiënt (en zijn of haar wensen) en dat overbehandeling kan worden voorkomen met een betere kwaliteit van leven tot gevolg.

Het doel van het onderzoek in **Hoofdstuk 13** was om de waarde van PET scans te bepalen voor het voorspellen van het effect van een andere steeds meer toegepaste behandelingsstrategie. Additionele inductie chemotherapie voorafgaand aan preoperatieve chemoradiatie wordt soms toegepast in een poging onzichtbare

(micro-)uitzaaiingen te elimineren. In deze setting werd in een serie uit het MD Anderson Cancer Center gevonden dat het maken van PET scans vóór en na inductie chemotherapie (vóór preoperatieve chemoradiatie) nuttig lijkt om vroegtijdig die patiënten te identificeren die niet of nauwelijks baat hebben van de opvolgende preoperatieve chemoradiatie. Als zodanig heeft PET de potentie om een behandeling op maat mogelijk te maken in deze setting.

DEEL IV. ZORG RONDOM DE OPERATIE

Bij een operatie voor slokdarmkanker wordt de continuïteit van het verteringskanaal veelal hersteld door de maag tot een buis te vormen (buismaag). De buismaag wordt dan door de borstkas omhoog opgetrokken en vervolgens wordt vaak een nieuwe verbinding (naad) gemaakt in de hals. Lekkage van deze naad in de hals is een gevreesde complicatie na een slokdarmoperatie, dat ongeveer bij 10 tot 30% van de patiënten voorkomt en gepaard gaat met een verhoogde kans op een gecompliceerd beloop en overlijden na de operatie. Preoperatieve voorspelling van het individuele risico van een patiënt op het krijgen van naadlekkage is erg lastig door het ontbreken van goede voorspellende factoren. Hiertoe werd in dit deel van het proefschrift op zoek gegaan naar oorzaken en risicofactoren voor naadlekkage en mogelijke preventieve maatregelen en behandelingen.

In **Hoofdstuk 14** werd een praktisch scoresysteem aangedragen waarmee de hoeveelheid en locatie van calcificaties in de slagaders die de buismaag van bloed voorzien kan worden gescoord op routinematig verkregen diagnostische CT scans bij slokdarmkanker. In een groep van 246 patiënten behandeld in het UMC Utrecht werd gevonden dat zowel milde als majeure calcificatie van de aorta geassocieerd was met een verhoogd risico op ontwikkelen van naadlekkage na de operatie. Ook werd een onafhankelijke associatie gevonden tussen calcificaties in kleinere aanvoerende slagaders van de buismaag en de kans op naadlekkage. Deze nieuw ontdekte risicofactor is belangrijk, omdat het kan helpen met het selecteren van hoog-risico patiënten die baat kunnen hebben van preventieve maatregelen.

Omdat calcificatie van de aanvoerende slagaders van de buismaag voor het eerst als risicofactor voor naadlekkage werd geïdentificeerd, was validatie van deze bevindingen noodzakelijk en dit werd gedaan in **Hoofdstuk 15**. In een externe serie patiënten behandeld in Ziekenhuisgroep Twente, Almelo en het Catharina Ziekenhuis, Eindhoven, werd inderdaad bevestigd dat calcificatie van de aorta geassocieerd was met het risico op naadlekkage na de operatie.

In **Hoofdstuk 16** werd het huidige experimentele en klinisch-wetenschappelijke bewijs voor preoperatieve ischemische conditionering van de maag uiteengezet, dat als doel heeft om het risico op naadlekkage te verkleinen. De verschillende technieken werden beschreven die een deel van de bloedaanvoer van de maag af te sluiten om tijd te geven aan de overgebleven bloedvaten om zich aan te passen aan de acute ischemie die optreedt bij de formatie van de buismaag in tweede instantie. De beschikbare onderzoeken hebben het effect van preoperatieve ischemische conditionering slechts bestudeerd in ongeselecteerde patiëntgroepen zonder dat werd geprobeerd een subgroep te selecteren die er het meeste baat bij zou kunnen hebben (een hoog-risico groep). Deze bevinding laat ruimte voor verbetering in het selecteren van patiënten voor ischemische conditionering in de toekomst, bijvoorbeeld door middel van de calcificatiescore.

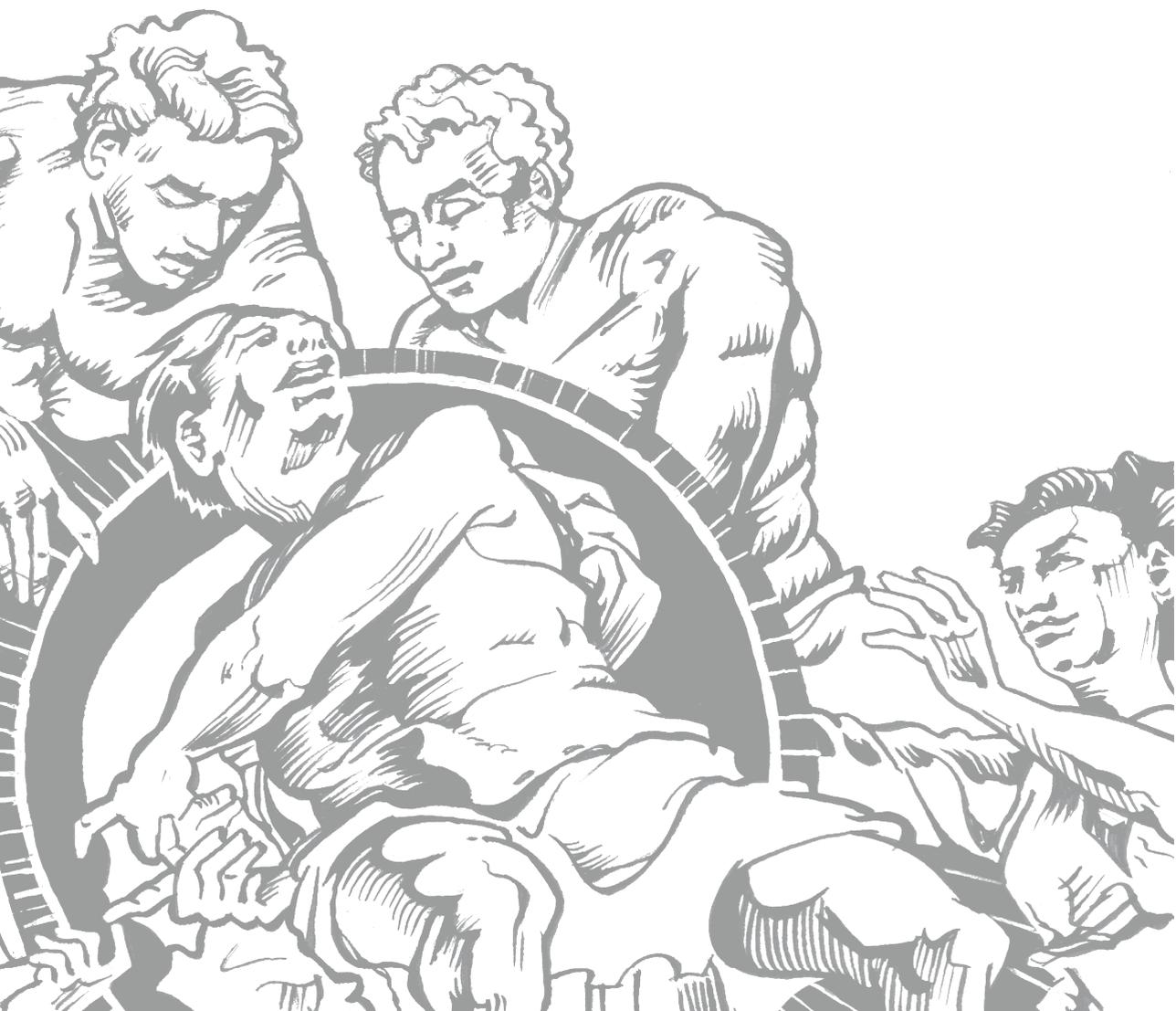
In **Hoofdstuk 17** werd de potentiële relatie tussen postoperatieve complicaties (naadlekkage en longontsteking) en vitale parameters tijdens de operatie en in de eerste dag na de operatie op de Intensive Care bestudeerd. Bij een laagste pH waarde gemeten tijdens de operatie lager dan 7.25 was het risico op naadlekkage aanzienlijk verhoogd (51% versus 12%). Bij een hoogste pH waarde gemeten tijdens de operatie hoger dan 7.34 en een gemiddelde arteriële druk in de eerste 12 uur na de operatie onder 88 mmHg was het risico op longontsteking aanzienlijk verhoogd (52% versus 23% en 49% versus 9%, respectively). Deze bevindingen onderstrepen het belang van het stellen van strikte doelen tijdens de operatie met betrekking tot vitale parameters en dragen bij aan een individuele risicoschatting voor belangrijke complicaties.

Een andere potentiële risicofactor voor naadlekkage na een slokdarmoperatie die reeds sporadisch werd beschreven in de literatuur betreft de bestralingsdosis op het bovenste deel van de maag voorafgaand aan de operatie, wat in meer detail werd onderzocht in **Hoofdstuk 18**. In een groep patiënten die preoperatieve chemoradiatie gevolgd door een slokdarmoperatie onderging werd de bestralingsdosis berekend op het bovenste deel van de maag (wat later het kwetsbare deel is van de naad in de hals). Hogere dosis levels op het bovenste deel van de maag waren geassocieerd met een verhoogd risico op naadlekkage, wat suggereert dat men de dosis daar zou moeten minimaliseren bij het plannen van preoperatieve radiotherapie.

Als er dan lekkage van de naad in de hals optreedt kan het zich op 2 manieren manifesteren: alleen in de hals of in de hals en in de borstkas. Een vergelijking tussen deze 2 manifestaties ten aanzien van geassocieerde symptomen, behandelingen en uitkomsten werd gepresenteerd in **Hoofdstuk 19**. Bij patiënten met een

naadlekkage in de hals werd gevonden dat een positieve SIRS score sterk verdacht is voor manifestatie tot in de borstkas, ongeacht de bevindingen bij inspectie van de halswond. Drainage van de borstkas via de halswond was effectief in 41% van alle patiënten met manifestatie tot in de borstkas. Patiënten met manifestatie tot in de borstkas hadden een langere tijd nodig om weer tot eten te komen en waren langer opgenomen in het ziekenhuis. Als zodanig bieden de bevindingen in dit hoofdstuk handvaten voor de zorg van individuele patiënten met naadlekkage.

Concluderend is iedere patiënt met slokdarmkanker een uniek en autonoom persoon met unieke patiëntgerelateerde en tumorgerelateerde kenmerken. Om structuur en vergelijkbaarheid in zorgkwaliteit en wetenschap te borgen worden al deze unieke patiënten van oudsher middels zorgprotocollen 'in hokjes gestopt'. Deze manier van zorg en wetenschap heeft erg veel verbetering gebracht in de overlevingskansen van patiënten met slokdarmkanker in de afgelopen decennia. Echter, deze ontwikkelingen hebben ertoe geleid dat grote groepen patiënten heden een veelvoud van zware behandelingen moeten ondergaan waarvan bekend is dat een groot aantal individuen geen baat heeft van 1 of meer van die behandelingen (overbehandeling) of nog steeds onterecht 1 of meer behandelingen niet of onvoldoende krijgt (onderbehandeling). Nu is de tijd om vanuit de goede basis van behandelingsopties de unieke patiënt zelf centraal te stellen en niet het bijbehorende hokje. De onderzoeken in dit proefschrift dragen bij aan deze ontwikkeling waarin steeds meer gestreefd wordt naar een behandeling op maat voor de individuele patiënt met slokdarmkanker door gebruik te maken van geavanceerde beeldvormende technieken en voorspellende mathematische modellen voor individuele effect- en risicoschattingen.



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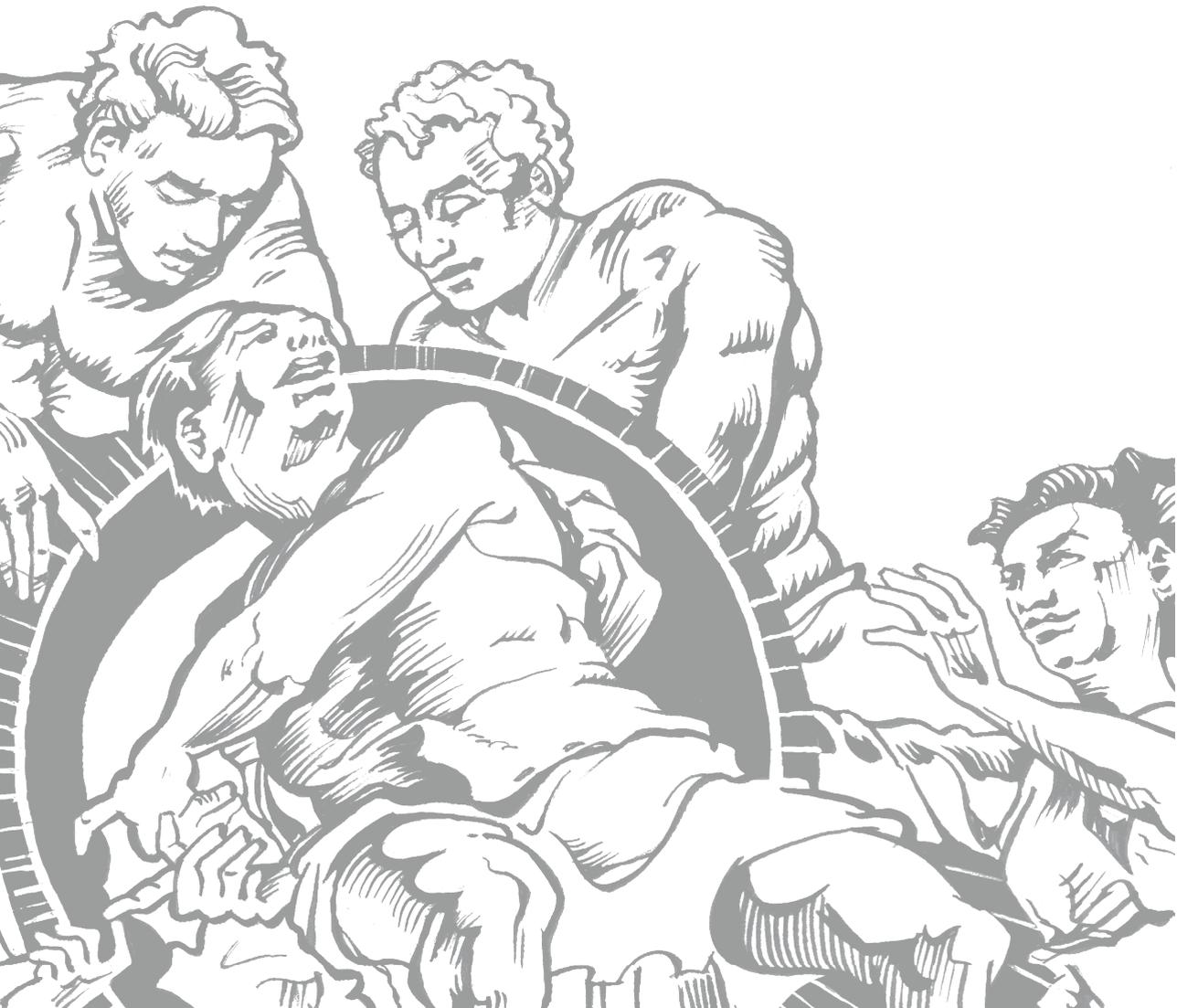
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Acknowledgements (Dankwoord)

Dit proefschrift was dit proefschrift niet geweest zonder de directe en indirecte bijdragen van vele personen. In de eerste plaats wil ik alle patiënten met slokdarmkanker die deel hebben genomen aan de onderzoeken in dit proefschrift – en hun familie of nabestaanden – heel hartelijk bedanken voor hun bereidwilligheid belangeloos bij te dragen aan een verbeterde behandeling van toekomstige patiënten. Ik heb daar zeer veel respect voor. Voorts wil ik onderstaande personen in het bijzonder bedanken.

PROMOTIECOMMISSIE

Geachte Prof. dr. R. van Hillegersberg, beste professor, eind 2009 was u het die mij –toen derdejaars student– de kans bood mijn eerste voetstappen in de medische wetenschap te zetten. Ik ben dankbaar voor de enorme ontwikkelingen die ik heb door mogen maken in de jaren onder uw hoede. Vanaf 2012 heb ik deel mogen uitmaken van uw oesofagus/maag onderzoeksgroep, die ik mede heb zien uitgroeien tot de grootste in zijn soort in Nederland en misschien zelfs in Europa. U bent een icoon geweest in mijn leven in de afgelopen jaren en ik hoop nog lange tijd met u samen te werken.

Geachte Prof. dr. M. van Vulpen, beste Marco, jouw enthousiasme en energie voor wetenschap zijn ongeëvenaard en hebben mij gemotiveerd groots te denken en groots te doen. Bedankt voor de vele deuren die je voor mij geopend hebt, zoals de promotieplek, de postgraduate Master Epidemiologie, de buitenlandse fellowships en het uitzonderlijke symposium rondom mijn promotie. Ik ben je ook erg dankbaar dat je me geïnspireerd hebt voor het prachtige specialisme Radiotherapie.

Geachte Dr. J.P. Ruurda, beste Jelle, wat ik nooit zal vergeten is dat de ‘oesofagus-imaging’ researchlijn die geresulteerd heeft in dit proefschrift is begonnen met ons tweeën toen jij het idee had om de literatuur over de potentiële rol van MRI bij slokdarmkanker op een rij te zetten. Dat die researchlijn vervolgens zo groot en belangrijk zou worden met betrokkenheid van diverse centra en diverse afdelingen wisten wij toen nog niet. We hebben er wat moois van gemaakt en gaan nog mooiere dingen samen doen. Bedankt voor je onvergetelijke toespraak bij mijn buluitreiking, voor je altijd snelle en heldere reacties op mijn vragen en manuscripten, voor je gedrevenheid en voor onze inspirerende gesprekken over het leven.

Geachte Dr. G.J. Meijer, beste Gert, wat hebben wij veel samen gezeten en dingen uitgedacht, de grote lijnen maar juist ook veel details. Jouw kennis is van levensgroot belang geweest voor de belangrijkste imaging projecten van dit proefschrift.

Ook de erg vruchtbare samenwerkingen met onze consortium-partners zijn in belangrijke mate door jou tot stand gekomen. Veel dank dat je daardoor niet alleen dit proefschrift, maar ook mij persoonlijk, naar een aanzienlijk hoger wetenschappelijk niveau en impact hebt getild. Bedankt ook voor je gezelligheid, je laagdrempeligheid en ook jij voor onze inspirerende gesprekken over het leven.

Geachte leden van de beoordelingscommissie, Prof. dr. R.L.A.W. Bleys, Prof. dr. M.R. Vriens, Prof. dr. M.A.A.J. van den Bosch, Prof. dr. ir. J.J.W. Lagendijk, Prof. dr. K. Haustermans, zeer veel dank voor uw interesse, tijd en energie voor het beoordelen van dit proefschrift.

PARANIMFEN

Lucas Goense, eerst mijn uitblinkende student, toen mijn opvolger, nu vooral één van mijn beste kameraden en paranimf. Door jouw komst is onze researchlijn in een stroomversnelling geraakt die niet meer te stoppen is. Op het eerste oog zijn we misschien erg verschillend, maar er zijn maar weinig mensen met wie ik zo goed kan levelen. De meeste tijd van mijn werkende leven in de afgelopen jaren heb ik denk ik met jou doorgebracht, op de werkvloer, op congressen, borrels en feestjes. Dank voor de gezelligheid en lol die we altijd hadden en voor je enorme inzet en klasse voor 'onze' researchlijn!

Ruben van Eijk, maatje vanaf het eerste moment, jaar 1, dag 1 van Geneeskunde in Utrecht en nu mijn paranimf. Onze vriendschap bestaat daarmee nu exact 10 jaar. Bedankt voor het sparren al die jaren over de studie, maar vooral ook daarbuiten. Erg gezellig dat –ondanks dat we altijd onze eigen weg zijn gegaan– je nu ook al een poosje PhD student in het UMC Utrecht bent. Onze relativerende borrelavonden hebben mij en dit proefschrift veel goeds gebracht.

COLLEGA'S EN ONDERSTEUNERS

Beste collega slokdarm-radiotherapie onderzoekers, Astrid van Lier, Irene Lips, Onne Reerink, Sophie Heethuis en Stella Mook, jullie zijn de drijvende krachten geweest achter vele ontwikkelingen die onze researchlijn en mijn proefschrift de afgelopen jaren hebben doorgemaakt. Zeer veel dank daarvoor, voor alle dingen die ik van jullie heb mogen leren en voor jullie gedeelde enthousiasme en inzet voor onze onderzoekslijn!

Beste collega slokdarm-chirurgie onderzoekers, Teus Weijs, Leonie Haverkamp, Margriet Prins, Pieter van der Sluis, Sylvia van der Horst, Kevin Parry, Els Visser, Alicia Borggreve, Hylke Brenkman en Maarten Seesing, wat is chirurgie toch een

mooi vak met mooie mensen! Veel dank voor de onvergetelijke tijd in de 'oes-maag' onderzoeksgroep, van de dynamische onderzoeksbesprekingen tot de memorabele congressen. Dank ook voor jullie inhoudelijke bijdragen aan dit proefschrift. Ik hoop de komende jaren nog veel zijdelings betrokken te zijn, want ik kan de groep maar moeilijk missen!

Dear Dr. Steven H. Lin, it has been such an honor for me to do a research fellowship at MD Anderson Cancer Center under your supervision two times during my PhD program. Your exceptional intelligence and extraordinary enthusiasm for research and radiation oncology have been very inspiring for me both as researcher and clinician. Thank you for all your trust in me in the past years and it would be my great pleasure to initiate many more collaborative projects with you in the future.

Beste overige co-auteurs van artikelen in dit proefschrift, allen hartelijk dank voor jullie individuele bijdragen. Dear other co-authors of articles presented in this thesis, thank you all for your individual contributions.

Beste oud-kamergenoten, Danny Young-Afat, Maarten Burbach, Sofie Gernaat en wederom Lucas Goense, niets is belangrijker dan dat je met plezier naar je werk gaat. Nou, dat deed ik zeker de afgelopen jaren en dat heeft voor een groot deel te maken met de gezelligheid op onze kamer. Dank voor alle mooie, leuke en hilarische momenten!

Beste andere (oud-)collega onderzoekers van de Radiotherapie en Chirurgie, Ramona Charaghvandi, Joris Hartman, Fieke Prins, Juliette van Loon, Max Peters, Sophie Gerlich, Boris Peltenburg, Alice Couwenberg, Madelijn Gregorowitsch, Tristan van Heijst, Christel Nomden, Tim Schakel, Jennifer Jongen, Marieke Walma, Morsal Samim, Stefanie Peeters Weem, Sjoerd Nell, Steffi Rombouts, Steven van Haelst, Tesse Leunissen, Vanessa Pourier, Thomas Vellinga, Pieter Leliefeld, Laurien Waaijer, Amy Gunning en Jacqueline van Laarhoven, wat was het mooi onderdeel uit te mogen maken van zulke gezellige groepen onderzoekers, waarvoor veel dank!

Beste dames van het secretariaat Radiotherapie en secretariaat Chirurgie, dames van het afsprakenbureau, dames van het trialbureau en laboranten van de MRI, jullie ondersteuning was onmisbaar voor de totstandkoming van dit proefschrift. Veel dank voor jullie inzet en betrokkenheid!

Beste Roy Sanders en Wim Rebergen, ik ben jullie erg dankbaar voor het maken van de prachtige lay-out respectievelijk cover van dit proefschrift!

Beste collega AIOS, opleiders Dr. J.L. Noteboom/Drs. I.E. van Dam en overige staf van de Radiotherapie, een nieuwe periode is voor mij aangebroken en met veel plezier ben ik aan de slag gegaan als jullie nieuwe collega. Ik ben erg dankbaar voor het motiverende opleidingsklimaat en zie uit naar onze samenwerking de komende jaren!

VRIENDEN EN FAMILIE

Hugo Adams en Joost Rüsche, bedankt voor jullie vriendschap en inspirerende gesprekken over de medische (onderzoeks)wereld en daarbuiten!

Veel andere vrienden hebben me in de afgelopen jaren bijgestaan met hun gezelligheid en kameraadschap en dat waardeer ik enorm. In het bijzonder veel dank daarvoor aan Arian van Dijk, Masco en Nikkie Beker, René en Lian van Kooten, Wilco en José Koudijs en anderen.

Dear Houstonian friends, Cody and Kelly Nicholson, Lee Hsia, Sam Song, Eric Mingle, and others, thank “y’all” for making my time as research fellow in H-town unforgettable. It was great to be able to come back to Houston a second time when your welcome was very memorable. Also, it was awesome to welcome some of you back in The Netherlands, and I hope to spent much more time with you guys in the near future.

Ralph en Ineke van Manen, mijn schoonouders, voor velen misschien onzichtbaar, maar jullie support in de afgelopen jaren is gigantisch en onmisbaar geweest. Daar ben ik jullie zeer dankbaar voor!

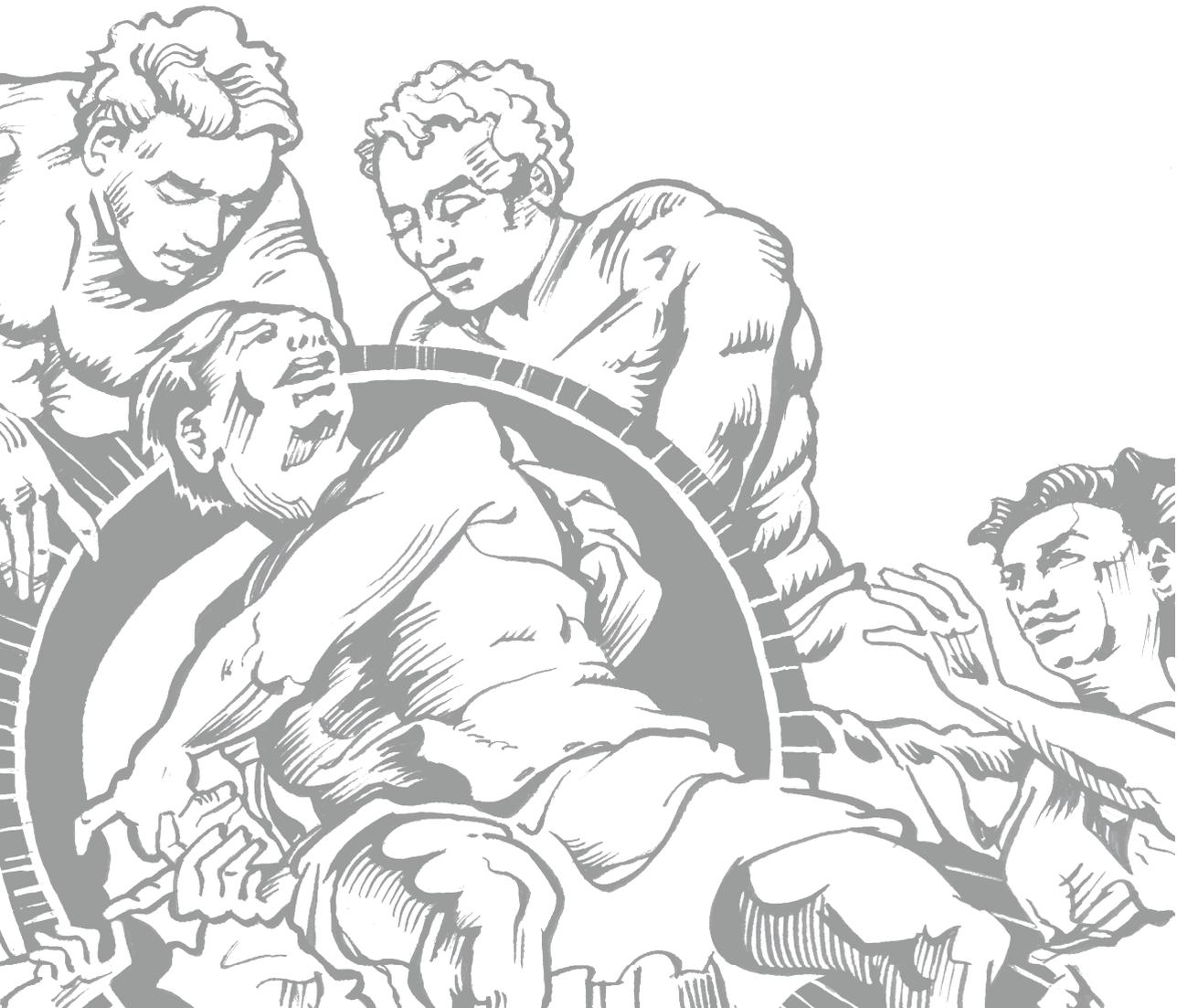
Lieve familie en in het bijzonder Lucien, Theo-Marien, Annemiek, Joni, Simon, oma Els, oma Nel en opa Joop†, dank voor jullie gezelligheid, steun, zorgzaamheid en kameraadschap en bedankt dat jullie altijd achter me staan!

Lieve mam, heel veel dank voor al jouw steun, liefde en toewijding waarmee je mij altijd geholpen hebt alles uit mezelf en mijn opleidingen te halen, soms ten koste van jezelf. Bedankt voor de stabiele thuissituatie en mogelijkheden die je me hebt gegeven. Zonder jou had ik dit nooit kunnen bereiken.

Lieve pa, de afgelopen jaren op afstand maar toch altijd dichtbij. Je hebt het goed gedaan.

Liefste Rosa, mijn grote liefde en grootste supporter. Zonder jouw steun was dit proefschrift er nooit gekomen. Bedankt dat je mijn betere helft bent, bedankt voor je flexibiliteit en geduld. Ik draag dit proefschrift aan jou op.

Elliot en Lauren, blijven jullie maar lekker klein.



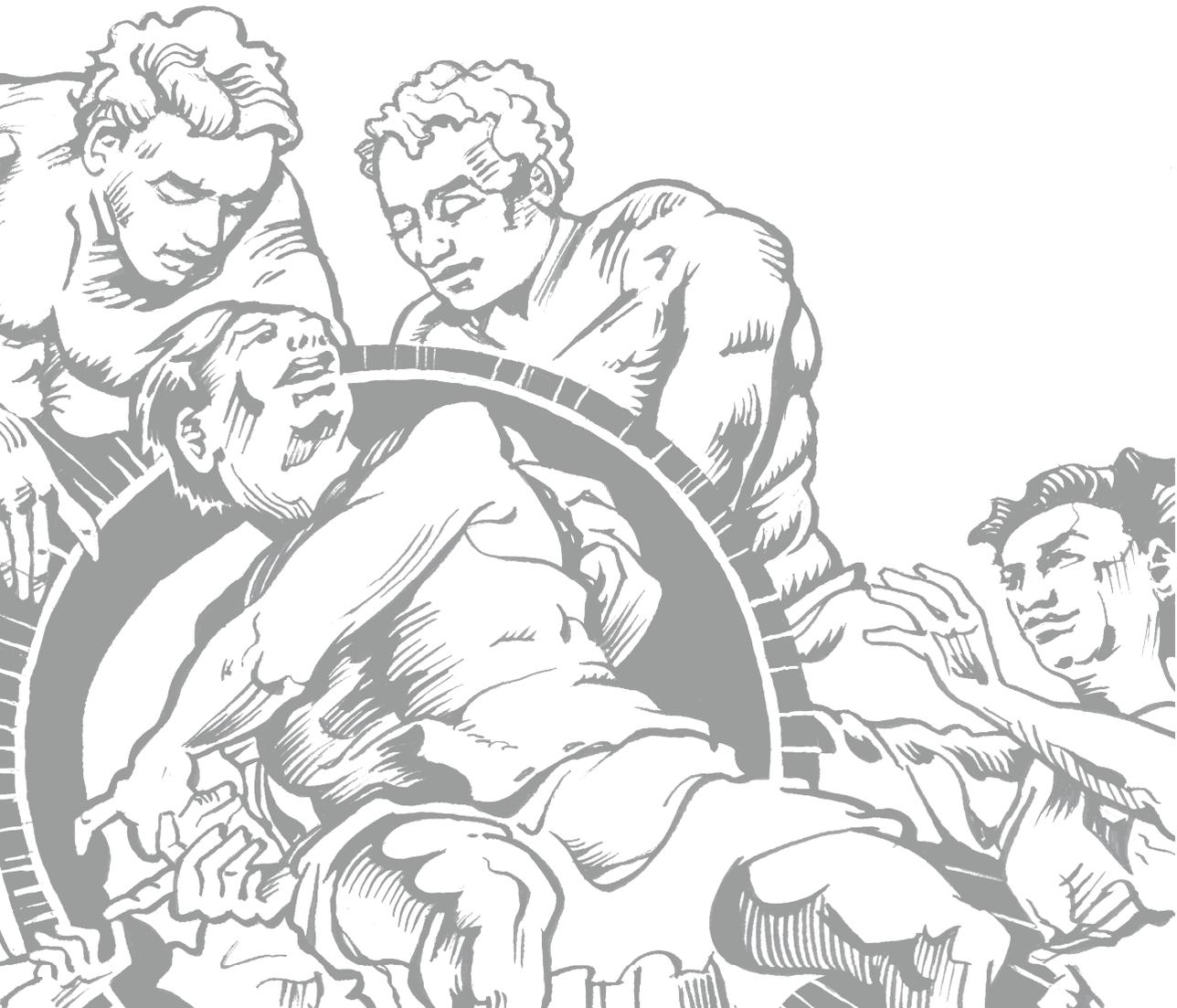
List of publications

1. **van Rossum PSN**, Goense L, Meziani J, Reitsma JB, Siersema PD, Vleggaar FP, van Vulpen M, Meijer GJ, Ruurda JP, van Hillegersberg R. Endoscopic biopsy and EUS for the detection of pathologic complete response after neoadjuvant chemoradiotherapy in esophageal cancer: a systematic review and meta-analysis. *Gastrointest Endosc* 2016;83:866-79
2. **van Rossum PSN**, Fried DV, Zhang L, Hofstetter WL, van Vulpen M, Meijer GJ, Court LE, Lin SH. The incremental value of subjective and quantitative assessment of ¹⁸F-FDG PET for the prediction of pathologic complete response to preoperative chemoradiotherapy in esophageal cancer. *J Nucl Med* 2016;57:691-700
3. **van Rossum PSN**, Fried DV, Zhang L, Hofstetter WL, Ho L, Meijer GJ, Carter BW, Court LE, Lin SH. The value of ¹⁸F-FDG PET before and after induction chemotherapy for the early prediction of a poor pathologic response to subsequent preoperative chemoradiotherapy in oesophageal adenocarcinoma. *Eur J Nucl Med Mol Imaging* 2016 [In press]
4. **van Rossum PSN**, Xu C, Fried DV, Goense L, Court LE, Lin SH. The emerging field of radiomics in esophageal cancer: current evidence and future potential. *Transl Cancer Res* 2016 [In press]
5. **van Rossum PSN***, Goense L*, Ruurda JP, van Vulpen M, Mook S, Meijer GJ, van Hillegersberg R. Neoadjuvant radiation to the gastric fundus increases the risk of anastomotic leakage after transthoracic esophagectomy for esophageal cancer. *Ann Thorac Surg* 2016 [In press; *Shared first authorship]
6. **van Rossum PSN***, Goense L*, Tromp M, Joore HC, van Dijk D, Kroese AC, Ruurda JP, van Hillegersberg R. Intraoperative and postoperative risk factors for anastomotic leakage and pneumonia after esophagectomy for cancer. *Dis Esophagus* 2016 [Epub ahead of print; *Shared first authorship]
7. **van Rossum PSN**, Haverkamp L, Carvello M, Ruurda JP, van Hillegersberg R. Management and outcome of cervical versus intrathoracic manifestation of cervical anastomotic leakage after transthoracic esophagectomy for cancer. *Dis Esophagus* 2016 [Epub ahead of print]
8. Heethuis SE, **van Rossum PSN**, Lips IM, Goense L, Voncken FE, Reerink O, van Hillegersberg R, Ruurda JP, Philippens ME, van Vulpen M, Meijer GJ, Lagendijk JJW, van Lier ALHMW. Dynamic contrast-enhanced MRI for treatment response assessment in patients with oesophageal cancer receiving neoadjuvant chemoradiotherapy. *Radiother Oncol* 2016 [Epub ahead of print]

9. Visser E, **van Rossum PSN**, Verhoeven RHA, Ruurda JP, van Hillegersberg R. Impact of weekday of esophagectomy on short-term and long-term oncological outcomes – a nationwide population-based cohort study in the Netherlands. *Ann Surg* 2016 [*In press*]
10. Parry K, **van Rossum PSN**, Haj Mohammad N, Ruurda JP, van Hillegersberg R. The effect of perioperative chemotherapy for patients with an adenocarcinoma of the gastroesophageal junction: a propensity score matched analysis. *Eur J Surg Oncol* 2016 [*Epub ahead of print*]
11. Goense L, **van Rossum PSN**, Kandioler D, Ruurda JP, Goh KL, Luyer MD, Krasna MJ, van Hillegersberg R. Stage-directed individualized therapy in esophageal cancer. *Ann N Y Acad Sci* 2016 [*In press*]
12. Kechagias A, **van Rossum PSN**. Letter to the Editor on the article “The role of low CRP values in the prediction of the development of acute diverticulitis”. *Int J Colorect Dis* 2016 [*Epub ahead of print*]
13. Goense L, **van Rossum PSN**, Weijs TJ, van Det MJ, Nieuwenhuijzen GA, Luyer MD, van Leeuwen MS, van Hillegersberg R, Ruurda JP, Kouwenhoven EA. Aortic calcification increases the risk of anastomotic leakage after Ivor-Lewis esophagectomy. *Ann Thorac Surg* 2016;102:247-52
14. Visser E, Leefstink AG, **van Rossum PSN**, Siesling S, van Hillegersberg R, Ruurda JP. Waiting time from diagnosis to treatment has no impact on survival in patients with esophageal cancer. *Ann Surg Oncol* 2016;23:2679-89
15. Peters M, van der Voort van Zyp JR, Moerland MA, Hoekstra CJ, van de Pol S, Westendorp H, Maenhout M, Kattevilder R, Verkooijen HM, **van Rossum PSN**, Ahmed HU, Shah TT, Emberton M, van Vulpen M. Development and internal validation of a multivariable prediction model for biochemical failure after whole-gland salvage iodine-125 prostate brachytherapy for recurrent prostate cancer. *Brachytherapy* 2016;15:296-305
16. Peters M, van der Voort van Zyp JR, Moerland MA, Hoekstra CJ, van de Pol S, Westendorp H, Maenhout M, Kattevilder R, Verkooijen HM, **van Rossum PSN**, Ahmed HU, Shah TT, Emberton M, van Vulpen M. Multivariable model development and internal validation for prostate cancer specific survival and overall survival after whole-gland salvage Iodine-125 prostate brachytherapy. *Radiother Oncol* 2016;119:104-10

17. Weijs TJ, Seesing MFJ, **van Rossum PSN**, Koëter M, Luyer MDP, Ruurda JP, Nieuwenhuijzen GAP, van Hillegersberg R. Internal and external validation of a multivariable model to define hospital-acquired pneumonia after esophagectomy. *J Gastrointest Surg* 2016;20:680-7
18. Kechagias A, **van Rossum PSN**, Ruurda JP, van Hillegersberg R. Ischemic conditioning of the stomach in the prevention of esophago-gastric anastomotic leakage after esophagectomy. *Ann Thorac Surg* 2016;101:1614-23
19. **van Rossum PSN**, Goense L, van Hillegersberg R, Ruurda JP. Comment on: Hölscher AH, Bollschweiler E, Bogoevski D, Schmidt H, Semrau R, Izbiccki JR. Prognostic impact of neoadjuvant chemoradiation in cT3 oesophageal cancer – A propensity score matched analysis. *Eur J Cancer* 2015;51:2095-6
20. **van Rossum PSN**, van Lier ALHMW, van Vulpen M, Reerink O, Lagendijk JJW, Lin SH, van Hillegersberg R, Ruurda JP, Meijer GJ, Lips IM. Diffusion-weighted magnetic resonance imaging for the prediction of pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer. *Radiother Oncol* 2015;115:163-70
21. **van Rossum PSN**, van Hillegersberg R, Meijer GJ, Ruurda JP. Residual esophageal cancer after neoadjuvant chemoradiotherapy frequently involves the mucosa and submucosa. *Ann Surg* 2015;262:e83-4
22. **van Rossum PSN***, Goense L*, Reitsma JB, Lam MGEH, Meijer GJ, van Vulpen M, Ruurda JP, van Hillegersberg R. Diagnostic performance of ¹⁸F-FDG PET and PET/CT for the detection of recurrent esophageal cancer after treatment with curative intent: a systematic review and meta-analysis. *J Nucl Med* 2015;56:995-1002 [*Shared first authorship]
23. **van Rossum PSN**, van Hillegersberg R, Reerink O, Ruurda JP. Neoadjuvant chemoradiotherapy for stage I and II esophageal cancer. *J Clin Oncol* 2015;33:287-8
24. **van Rossum PSN**, Haverkamp L, Verkooijen HM, van Leeuwen MS, van Hillegersberg R, Ruurda JP. Calcifications of the arteries supplying the gastric tube: a new risk factor for anastomotic leakage in esophageal surgery. *Radiology* 2015;274:124-32
25. **van Rossum PSN**, van Lier ALHNW, Lips IM, Meijer GJ, Reerink O, van Vulpen M, Lam MG, van Hillegersberg R, Ruurda JP. Imaging of oesophageal cancer with FDG-PET/CT and MRI: a pictorial review. *Clin Radiol* 2015;70:81-95

26. Parry K*, Visser E*, **van Rossum PSN**, Haj Mohammad N, Ruurda JP, van Hillegersberg R. Prognosis and treatment of patients with recurrent esophageal carcinoma following curative resection. *Ann Surg Oncol* 2015;22 Suppl 3:1292-300 [**Shared first authorship*]
27. Akkerman RD, Haverkamp L, **van Rossum PSN**, van Hillegersberg R, Ruurda JP. Long-term quality of life after oesophagectomy with gastric conduit interposition for cancer. *Eur J Cancer* 2015;51:1538-45
28. **van Rossum PSN**, Ruurda JP, Siersema PD. [Nutrition and esophageal diseases]. Book chapter in Dutch. *Informatorium voor Voeding & Diëtetiek* 2015
29. **van Rossum PSN**, Ruurda JP, van Vulpen M, van Hillegersberg R. [MRI for staging, radiation treatment planning and response evaluation in esophageal cancer]. Article in Dutch. *Oncology News International* 2014;8:5
30. Blom RL, Bogush T, Brücher BL, Chang AC, Davydov M, Dudko E, Leong T, Polotsky B, Swanson PE, **van Rossum PSN**, Ruurda JP, Sagaert X, Tjulandin S, Schraepen MC, Sosef MN, van Hillegersberg R. Therapeutic approaches to gastroesophageal junction adenocarcinomas. *Ann N Y Acad Sci* 2014;1325:197-210
31. Waaijer L, Krebs DL, Fernandez Gallardo MA, **van Rossum PSN**, Postma E, Koelemij R, van Diest PJ, Klaessens JH, Witkamp AJ, van Hillegersberg R. Radiofrequency ablation of small breast tumours: evaluation of a novel bipolar cool-tip application. *Eur J Surg Oncol* 2014;40:1222-9
32. Wijnhoven BP, Toxopeus EL, Vallböhmer D, Knoefel WT, Krasna MJ, Perez K, **van Rossum PSN**, Ruurda JP, van Hillegersberg R, Schiesser P, Felix VN. New therapeutic strategies for squamous cell cancer and adenocarcinoma. *Ann N Y Acad Sci* 2013;1300:213-25
33. **van Rossum PSN**, van Hillegersberg R, Lever FM, Lips IM, van Lier ALHMW, Meijer GJ, van Leeuwen MS, van Vulpen M, Ruurda JP. Imaging strategies in the management of esophageal cancer: What's the role of MRI? *Eur Radiol* 2013;23:1753-65
34. van Esser S, Madsen EV, van Dalen T, Koelemij R, **van Rossum PSN**, Borel Rinkes IH, van Hillegersberg R, Witkamp AJ. Axillary staging in breast cancer patients with exclusive lymphoscintigraphic drainage to the internal mammary chain. *World J Surg* 2011;35:159-64



Curriculum Vitae Auctoris

Peter Sylvain Nicolas van Rossum was born on the 20th of July, 1989, in Rhenen, The Netherlands. After graduating from the Ichthus College Veenendaal in 2006, he attended Medical School at the University of Utrecht, The Netherlands. During his studies he was active as student researcher at the Department of Surgical Oncology, University Medical Center (UMC) Utrecht, The Netherlands, under supervision of Prof. dr. R. van Hillegersberg from 2009 to 2012. He was mainly active in breast and esophageal cancer research. In 2011, as part of his medical training he completed an elective clinical rotation at the Transplant and Trauma Surgery Unit of the Groote Schuur Hospital in Cape Town, South Africa, under supervision of Prof. D. Kahn. After he obtained his medical degree, he was given the opportunity to continue his research endeavors in esophageal oncology as a PhD candidate at the Departments of Radiation Oncology and Surgery of the UMC Utrecht, under supervision of Prof. dr. M. van Vulpen, Prof. dr. R. van Hillegersberg, Dr. J.P. Ruurda, and Dr. G.J. Meijer. In 2014 and 2015, during his PhD program he was appointed as research fellow at The University of Texas MD Anderson Cancer Center, Houston (Texas), under supervision of Dr. S.H. Lin. In 2015, he obtained a postgraduate Master of Science degree (*cum laude*) in Epidemiology at the University of Utrecht, specializing in Clinical Epidemiology and Medical Statistics. From June 2016, he is a resident in Radiation Oncology at the UMC Utrecht under supervision of Dr. J.L. Noteboom and Dr. I.E. van Dam.

