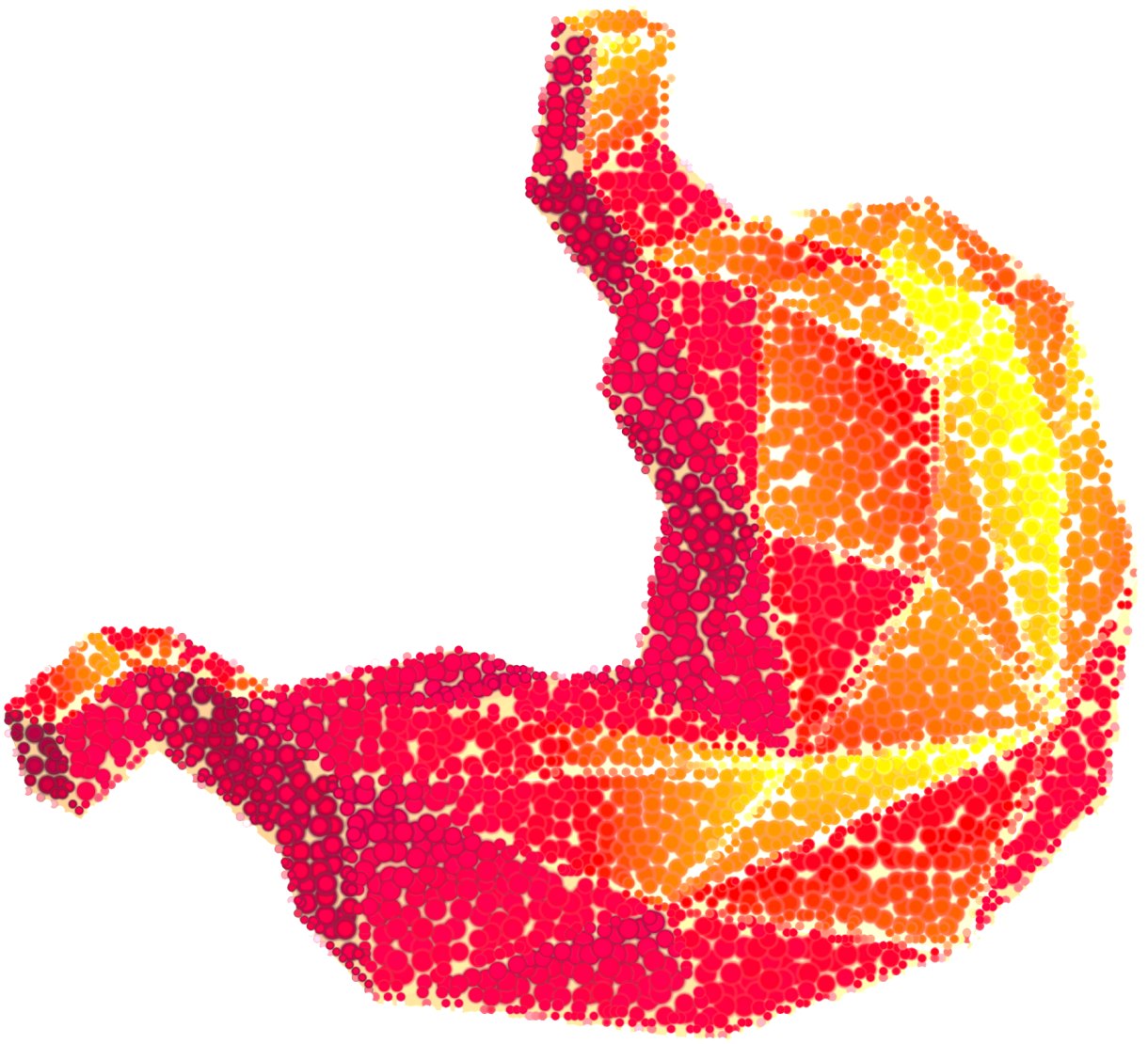
Optimal Staging and Surgical Treatment for Gastric Cancer



Emma C. Gertsen

Optimal Staging and Surgical Treatment for Gastric Cancer

Optimal staging and surgical treatment for gastric cancer
PhD thesis, Utrecht University, The Netherlands

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Optimal Staging and Surgical Treatment for Gastric Cancer

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(met een samenvatting in het Nederlands)

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Chapter 1

General introduction and thesis outline

GENERAL INTRODUCTION

Gastric cancer

Gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of cancer-related mortality worldwide, accounting for over one million new cases and approximately 768.000 deaths in 2020[1]. The worldwide prevalence of gastric cancer varies, with a high prevalence in Asian countries and a low prevalence in Western countries. Due to the high prevalence in Asian countries, their population is subject to screening for gastric cancer, and as a result Asian patients are often diagnosed with early stage disease, whereas advanced tumors are more common in Western countries[2]. Advanced tumors may expand through the stomach wall, and often involve lymph nodes. It is known that these characteristics are associated with peritoneal and distant metastases[3–5]. Of the 1200 newly diagnosed patients every year in the Netherlands, only some 500 patients undergo curative treatment. Most patients are not eligible for curative treatment due to advanced tumor stage, with metastatic or non-resectable disease, or due to patient-related reasons, such as comorbidities[6]. For those who undergo curative treatment, the 5-year overall survival in Western populations remains poor, approximately 40%, due to advanced tumor stage at diagnosis, which is associated with high risk of tumor recurrence[7,8].

Regardless of much research being done in the field of gastric cancer, some knowledge gaps remain. For example, it remains challenging to identify the best staging options and perioperative therapy, to determine the most beneficial surgical approach to reduce the number of complications, and to determine treatment in the case of metastatic disease.

Staging

The initial staging of gastric cancer consists of gastroscopy with biopsies and computed tomography (CT)[9]. The aim of staging is to determine the extent and associated prognosis of the disease in order to classify the disease according to the TNM classification system[10,11]. The purpose of restaging is to assess whether there is disease progression and upstaging following neoadjuvant treatment. One of the objectives of CT, both as a staging and re-staging modality, is to detect distant metastases, since the absence or presence of metastases decides on a curative or palliative pathway, respectively. The curative treatment of patients with gastric cancer

entails (sub)total gastrectomy and lymphadenectomy, combined with perioperative chemotherapy to improve survival[12–16]. If non-curable gastric cancer is diagnosed, the designated treatment is palliative chemotherapy[14]. Curative treatment – including surgery and perioperative chemotherapy – is accompanied by significant morbidity[17]. Therefore, it is undesirable to perform surgery or administer chemotherapy in patients who initially were thought to have curable disease, but eventually appear to be incurable. This overtreatment of patients is accompanied by a reduced quality of life[18] and increased health care costs[19]. To adequately make a distinction between potentially curable and non-curable disease, it is important to improve the accuracy of the staging and restaging process of gastric cancer. Because CT is not sensitive enough for detecting metastatic disease, the use of fluorodeoxyglucose positron emission tomography with CT (FDG-PET/CT) and staging laparoscopy have emerged in recent years[12]. FDG-PET/CT aims to detect distant metastases, whereas peritoneal metastases can be identified with staging laparoscopy by inspecting the interior of the abdomen and obtaining histological biopsies or peritoneal lavage cytology for pathological evaluation[19]. Solid evidence on the use and accuracy of re-staging CT, FDG-PET/CT and staging laparoscopy in Western populations with more advanced tumors is lacking. In addition, questions on whether FDG-PET/CT and staging laparoscopy provide additive value in detecting metastases in addition to CT are remaining, and it is unclear if both modalities are cost-effective by preventing futile surgery. Recently, FDG-PET/CT and staging laparoscopy have both been included in the Dutch national guidelines for gastric cancer, but information on their impact on clinical decision making is not yet available.

Surgical treatment

It is widely recognized that surgical resection is the cornerstone of curative treatment for any type of gastric cancer, but the surgical approach differs around the world. For surgical resection of the stomach, an open approach remains the preferred method by many surgeons[20], despite the advancement of minimally invasive surgery in recent years. In line with trials from Asia, the recently published Dutch LOGICA trial found a minimally invasive approach to be a safe alternative to open gastrectomy with regard to postoperative recovery, morbidity, short-term oncological outcomes and quality of life[21]. The question remains whether these results apply to all types of gastrectomy, in particular total gastrectomy. It is well known that total gastrectomy

is a more extensive and difficult procedure compared to distal gastrectomy[22–25]. In general, the high risk of postoperative complications after gastrectomy (up to 40%[26]) remains a concern and much research is performed to reduce this rate. However, it is unclear what the impact of complications on specific outcomes such as mortality, hospital stay and re-interventions are, and how to determine the clinically most relevant complications. With that knowledge, surgical quality improvement programs could focus on reducing these specific complications.

For different tumor subtypes and subgroups of patients, the optimal treatment approach may differ. For example, gastrointestinal stromal cell tumors are large, exophytically growing tumors, potentially complicating a minimally invasive surgical procedure. Moreover, most patients with adenocarcinomas profit from the administration of perioperative chemotherapy, which has been reported to provide survival benefit[8,27]. However, it is also suggested that neoadjuvant therapy may not always be profitable, especially not for microsatellite instable tumors or signet ring cell tumors[28,29]. Also, chemotherapy is often associated with severe toxicity (in up to 51%)[8,30–34] and as a result of this toxicity, some of the patients do not proceed to surgical resection. Besides the group of patients who do not proceed to gastrectomy due to chemotherapeutic side effects, there is also a group with potentially curative gastric cancer who refrain from surgical resection for which the reasons have not yet been identified[35–37]. Lastly, some patients with metastasized disease are treated with non-curable gastrectomy due to obstructive symptoms or bleeding from the tumor. It is largely unknown whether the risk of postoperative complications is higher in patients with metastatic disease undergoing surgical resection compared to patients who undergo curative gastrectomy. Some retrospective studies previously reported that surgical resection can potentially reduce symptoms and possibly improve quality of life[38–40]. If the risk of postoperative complications is found to be acceptable, non-curative gastrectomy may potentially be considered in patients with metastatic disease as well.

THESIS OUTLINE

The research presented in this thesis evaluates numerous aspects of the staging process and surgical treatment of gastric cancer, aiming for a more tailored treatment for patients with gastric cancer. In part I, several staging modalities are assessed in order to optimize clinical decision making and determine the preferred treatment. Part II evaluates different aspects of perioperative and surgical treatment with the intention of achieving the best postoperative outcomes.

RESEARCH OBJECTIVES PER CHAPTER

Part 1. Staging

Chapter 2 & 5 To evaluate the impact and cost-effectiveness of FDG-PET/CT and staging laparoscopy in addition to initial staging in patients with locally advanced gastric cancer.

Chapter 3 To establish the additive value of restaging-CT during neoadjuvant chemotherapy in guiding clinical decision making in gastric cancer.

Chapter 4 To evaluate the implementation of FDG-PET/CT and staging laparoscopy in the Netherlands.

Part 2. Surgical treatment

Chapter 6 To perform an update of a previous survey in order to identify any trends and regional differences that may exist in the surgical management of gastric cancer.

Chapter 7 To compare primary surgery with different perioperative treatments for diffuse type gastric cancer, with a focus on SRCC, to assess whether one of these approaches may result in survival gain.

Chapter 8 To describe patients who start preoperative chemotherapy, but do not proceed to surgical resection, and to provide insight in reasons why these patients did not proceed to surgical resection.

Chapter 9 To describe reasons for, and patient and tumor characteristics that are associated with refraining from surgical resection in patients with potentially curable gastric cancer.

Chapter 10 To evaluate the safety of the introduction of minimally invasive distal and total gastrectomy in the Netherlands.

Chapter 11 To assess the safety and feasibility of minimally invasive gastric resection of large gastrointestinal stromal tumors.

Chapter 12 To identify the clinically most relevant complications after gastrectomy, using the population attributable fraction.

Chapter 13 To investigate whether the postoperative outcomes differ between non-curative and curative gastrectomy.

REFERENCES

1. GLOBOCAN. The Global Cancer Observatory - All cancers. *Int Agent Res Cancer - WHO*. 2020;419:199-200.
2. Griffin SM. Gastric cancer in the East: Same disease, different patient. *Br J Surg*. 2005;92(9):1055-1056.
3. Thomassen I, Gestel YR Van, Ramshorst B Van, et al. Peritoneal carcinomatosis of gastric origin: A population-based study on incidence, survival and risk factors. *Int J Cancer*. 2014;628:622-628.
4. Koemans WJ, Lurvink RJ, Grootscholten C, Verhoeven RHA, de Hingh IH, van Sandick JW. Synchronous peritoneal metastases of gastric cancer origin: incidence, treatment and survival of a nationwide Dutch cohort. *Gastric cancer Off J Int Gastric Cancer Assoc Japanese Gastric Cancer Assoc*. Published online January 2021.
5. Koemans WJ, Luijten JCHBM, van der Kaaij RT, et al. The metastatic pattern of intestinal and diffuse type gastric carcinoma - A Dutch national cohort study. *Cancer Epidemiol*. 2020;69:101846.
6. Integraal Kankercentrum Nederland (IKNL). Cijfers over kanker. Maag. Overleving. https://www.iknl.nl/nkr-cijfers?fs%7Cepidemiologie_id=9&fs%7Ctumor_id=287&fs%7Coverlevingssoort_id=83&fs%7Cperiode_id=120%2C121%2C122%2C124%2C125&fs%7Cjaren_na_diagnose_id=18%2C19%2C20%2C21%2C22%2C23%2C24%2C25%2C26%2C27%2C28%2C29&cs%7Ctype=column&cs%7CxAx
7. Hartgrink HH, Van De Velde CJH, Putter H, et al. Extended lymph node dissection for gastric cancer: Who may benefit? Final results of the randomized Dutch Gastric Cancer Group Trial. *J Clin Oncol*. 2004;22(11):2069-2077.
8. Cunningham D, Allum WWH, Stenning SSP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355(1):11-20.
9. Integraal Kankercentrum Nederland. Richtlijn Diagnostiek, behandeling en follow-up van het maagcarcinoom 2009. Published online 2009.
10. International Union Against Cancer. *TNM: Classification of Malignant Tumors 7th Edition*.; 2009.
11. International Union Against Cancer. TNM: Classification of Malignant Tumors 8th edition. 2016;(December):1-16.
12. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27(August):v38-v49.
13. Cunningham D, Allum WH, Stenning SP, et al. Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. *N Engl J Med*. Published online 2007:11-20.
14. Integraal Kankercentrum Nederland. Diagnostiek, behandeling en follow-up van het maagcarcinoom 2016. Published 2016. http://www.oncoline.nl/uploaded/docs/Maagcarcinoom/Richtlijn maagcarcinoom.pdf
15. Bang Y-J, Kim Y-W, Yang H-K, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet*. 2012;379(9813):315-321.
16. Al-Batran S, Homann N, Schmalenberg H, et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO). *J Clin Oncol*. 2017;35(15_suppl):4004-4004.
17. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, et al. Early outcomes from the Dutch Upper Gastrointestinal Cancer Audit. *Br J Surg*. 2016;103(13):1855-1863.
18. Avery K, Hughes R, McNair A, Alderson D, Barham P, Blazeby J. Health-related quality of life and survival in the 2 years after surgery for gastric cancer. *Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol*. 2010;36(2):148-154.
19. Smyth E, Schöder H, Strong VE, et al. A prospective evaluation of the utility of 2-deoxy-2-[^{18} F]fluoro- <scp>D</scp> -glucose positron emission tomography and computed tomography in staging locally advanced gastric cancer. *Cancer*. 2012;118(22):5481-5488.
20. Brenkman HJF, Haverkamp L, Ruurda JP, Van Hillegersberg R. Worldwide practice in gastric cancer

surgery. *World J Gastroenterol*. 2016;22(15):4041-4048.
21. van der Veen A, Brenkman HJF, Seesing MFJ, et al. Laparoscopic Versus Open Gastrectomy for Gastric Cancer (LOGICA): A Multicenter Randomized Clinical Trial. *J Clin Oncol*. 0(0):JCO.20.01540.
22. Li Z, Ji G, Bai B, et al. Laparoscopy-assisted distal gastrectomy versus laparoscopy-assisted total gastrectomy with D2 lymph node dissection for middle-third advanced gastric cancer. *Surg Endosc Other Interv Tech*. 2017;0(0):1-8.
23. Chen K, Zhai S-T, Pan J-H, et al. Short-term outcomes of laparoscopic total gastrectomy for gastric cancer: a comparative study with laparoscopic distal gastrectomy at a high-volume center. *Minim Invasive Ther Allied Technol*. 2017;0(0):1-7.
24. Lee SE, Ryu KW, Nam BH, et al. Technical feasibility and safety of laparoscopy-assisted total gastrectomy in gastric cancer: a comparative study with laparoscopy-assisted distal gastrectomy. *J Surg Oncol*. 2009;100(5):392-395.
25. Kodera Y, Yoshida K, Kumamaru H, et al. Introducing laparoscopic total gastrectomy for gastric cancer in general practice: a retrospective cohort study based on a nationwide registry database in Japan. *Gastric Cancer*. Published online 2018.
26. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, et al. Early outcomes from the Dutch Upper Gastrointestinal Cancer Audit. *Br J Surg*. 2016;103(13):1855-1863.
27. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ra. *Lancet*. 2019;393(10184):1948-1957.
28. Messager M, Lefevre JH, Pichot-Delahaye V, Souadka A, Piessen G, Mariette C. The impact of perioperative chemotherapy on survival in patients with gastric signet ring cell adenocarcinoma: A multicenter comparative study. *Ann Surg*. 2011;254(5):684-693.
29. Pietrantonio F, Miceli R, Raimondi A, et al. Individual patient data meta-analysis of the value of microsatellite instability as a biomarker in gastric cancer. *J Clin Oncol*. 2019;37(35):3392-3400.
30. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: An FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol*. 2011;29(13):1715-1721.
31. Cunningham D, Starling N, Rao S, et al. Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer. *N Engl J Med*. 2008;358(1):36-46.
32. Al-Batran S-E, Hofheinz RD, Pauligk C, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO. *Lancet Oncol*. 2016;17(12):1697-1708.
33. Reynolds J V., Preston SR, O'Neill B, et al. ICORG 10-14: NEOadjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric junction International Study (Neo-AEGIS). *BMC Cancer*. 2017;17(1):1-10.
34. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19(5).
35. Claassen YHM, Dikken JL, Hartgrink HH, et al. North European comparison of treatment strategy and survival in older patients with resectable gastric cancer: A EURECCA upper gastrointestinal group analysis. *Eur J Surg Oncol*. 2018;44(12):1982-1989.
36. Van Putten M, Verhoeven RHA, Van Sandick JW, et al. Hospital of diagnosis and probability of having surgical treatment for resectable gastric cancer. *Br J Surg*. 2016;103(3):233-241.
37. National Oesophago-Gastric Cancer Audit N. An audit of the care received by people with Oesophago-gastric Cancer in England and Wales. 2018;(March).
38. Samarasam I, Chandran BS, Sitaram V, Perakath B, Nair A, Mathew G. Palliative gastrectomy in advanced gastric cancer: Is it worthwhile? *ANZ J Surg*. 2006;76(1-2):60-63.
39. Izuishi K, Mori H. Recent strategies for treating stage IV gastric cancer: Roles of palliative gastrectomy, chemotherapy, and radiotherapy. *J Gastrointest Liver Dis*. 2016;25(1):87-94.

40. Kahlke V, Bestmann B, Schmid A, Doniec JM, Küchler T, Kremer B. Palliation of Metastatic Gastric Cancer: Impact of Preoperative Symptoms and the Type of Operation on Survival and Quality of Life. *World J Surg*. 2004;28(4):369-375.

Part 1

Staging

Chapter 2

Evaluation of FDG-PET/CT and laparoscopy in staging advanced gastric cancer: a multicenter prospective study (PLASTIC-study)

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BMC Cancer 2018; 18(1):450-457

ABSTRACT

Background: Initial staging of gastric cancer consists of computed tomography (CT) and gastroscopy. In locally advanced (cT3–4) gastric cancer, fluorodeoxyglucose positron emission tomography with CT (FDG-PET/CT) and staging laparoscopy (SL) may have a role in staging, but evidence is scarce. The aim of this study is to evaluate the impact and cost-effectiveness of FDG-PET/CT and SL in addition to initial staging in patients with locally advanced gastric cancer.

Methods: This prospective observational cohort study will include all patients with a surgically resectable, advanced gastric adenocarcinoma (cT3–4b, N0–3, M0), that are scheduled for treatment with curative intent after initial staging with gastroscopy and CT. The modalities to be investigated in this study is the addition of FDG-PET/CT and SL. The primary outcome of this study is the proportion of patients in whom the FDG-PET/CT or SL lead to a change in treatment strategy. Secondary outcome parameters are: diagnostic performance, morbidity and mortality, quality of life, and cost-effectiveness of these additional diagnostic modalities. The study recently started in August 2017 with a duration of 36 months. At least 239 patients need to be included in this study to demonstrate that the diagnostic modalities are break-even. Based on the annual number of gastrectomies in the participating centers, it is estimated that approximately 543 patients are included in this study.

Discussion: In this study, it is hypothesized that performing FDG-PET/CT and SL for locally advanced gastric adenocarcinomas results in a change of treatment strategy in 27% of patients and an annual cost-reduction in the Netherlands of €916.438 in this patient group by reducing futile treatment. The results of this study may be applicable to all countries with comparable treatment algorithms and health care systems.

Trial registration: NCT03208621.

BACKGROUND

Gastric cancer is the fifth most common type of cancer worldwide[1]. In Western countries, curative treatment consists of gastrectomy with perioperative chemotherapy[2-4]. Unfortunately, the prognosis of patients who undergo curative treatment remains relatively poor, with a 5-year overall survival rate of 20–40%. The main cause for this poor prognosis is tumor recurrence[2,5]. The poor prognosis, treatment-related morbidity and mortality, and impairments in quality of life result in a high disease burden[6].

The standard diagnostic work-up of patients with gastric cancer includes a gastroscopy to assess tumor size and location and to obtain tissue to characterize the tumor. Furthermore, computed tomography (CT) of the thorax and abdomen is performed to detect metastases and evaluate local resectability. However, the accuracy of CT for detecting metastatic disease (M1) or local irresectability (T4b) is low: the sensitivity to detect peritoneal metastases is 22%–33%, to detect distant metastases is 14%–65% and to detect T4b disease is 5%–69%[7-10]. Consequently, two undesirable situations may occur in practice:

1. Unexpected intraoperative peritoneal metastases or local tumor irresectability are found at the onset of gastrectomy.
2. Undetected distant metastases presenting shortly after treatment with curative intent (neoadjuvant chemotherapy and/or surgery).

In both situations, patients undergo a futile treatment, probably leading to a reduced quality of life and an increase in health care costs.

A recent study from the United States investigated the additional staging capacities of fluorodeoxyglucose positron emission tomography with CT (FDG-PET/CT) and staging laparoscopy (SL) in gastric cancer. In this study, combination of FDG-PET/CT and SL identified additional metastases in

27% of patients: distant metastases by FDG-PET/CT in 10% of patients, and peritoneal metastases by SL in 19% of patients (with an overlap of 2%)[11]. To reduce the number of patients undergoing futile treatment, the new Dutch guidelines for the treatment of gastric cancer recently included

FDG-PET/CT and SL in the staging algorithm of locally advanced (cT3–4) tumors[12]. However, this guideline concludes that the evidence for both staging modalities is weak, and additional studies are needed to further investigate the cost-effectiveness and applicability of routinely adding FDG-PET/CT and SL to the staging of locally advanced gastric cancer.

AIM

The aim of this study is to evaluate the clinical impact and cost-effectiveness of FDG-PET/CT and SL in addition to initial staging by CT and gastroscopy in patients with locally advanced (cT3–4) gastric cancer.

METHODS

Objectives

The primary outcome of this study is the proportion of patients in whom FDG-PET/CT and SL lead to a change in treatment strategy. The accuracy of each modality will be analysed separately. Secondary outcome parameters are diagnostic performance (sensitivity, specificity, positive and negative predictive value), morbidity and mortality, quality of life, cost reduction and cost-effectiveness. The hypothesis of this study is that adding FDG-PET/CT and SL to additional staging in these patients will lead to a change of treatment strategy in 27% of patients, leading to an annual cost reduction in the Netherlands of €916.438 by reducing futile treatment.

Study design

The study design is a prospective observational cohort study. All patients with a locally advanced tumor who are candidates for gastrectomy with curative intent will be invited to participate in this study. A locally advanced tumor is defined as a transmural tumor invading the outer layer of the stomach (cT3–4 according to the 7th edition of the American Joint Committee on Cancer TNM staging system[12]), objectified on CT[13].

Study population

The study population consists of patients with a surgically resectable, advanced gastric adenocarcinoma (cT3–4b, N0–3, M0), who are scheduled for treatment with curative intent after initial staging with gastroscopy and CT. Patients' inclusion and exclusion criteria are defined as follows:

Inclusion criteria:

- Histologically proven adenocarcinoma of the stomach or esophagogastric junction (Siewert type III) as observed by gastroscopy.
- Underwent evaluation with CT of the abdomen and chest.
- Surgically resectable, advanced gastric cancer (cT3–4b, N0–3, M0), as determined by the multidisciplinary team (MDT).
- Intention to perform a potentially curative gastrectomy with or without perioperative treatment.

Exclusion criteria.

- Siewert type I-II esophagogastric junction tumor.
- Unfit or unwilling to undergo surgery.

Study protocol

Initial staging

Initial staging should be performed according to national guidelines, including at least gastroscopy with tumor biopsies and a CT of the thorax and abdomen. Endoscopic Ultrasonography (EUS) may be performed optionally. In case of a cT3–4 tumor (defined as a transmural tumor invading the outer layer of the stomach)[13], patients will be invited to participate in this study and thereby give permission to collect and analyze their data. Differentiation between cT2 and cT3 tumors is not always possible with initial staging. In case of considerable doubt whether a tumor is cT2 or cT3, patients will be included if deemed appropriate by the MDT. As part of a side study, an expert panel will review all CT-scans to reach consensus on the clinical T-stage.

Patient inclusion

If eligible for treatment with curative intent by the MDT, patients will be invited to participate in this study. Patients will be informed and included at the outpatient department of one of the

Dutch investigational centers or its associated hospitals. As this study does not allocate patients to study interventions other than usual care, as recommended by the new Dutch guidelines, this study does not fall within the Medical Research Involving Human Subjects Act (WMO). Patients will be asked to sign informed consent form to confirm that they know that their data will be anonymously used for research purposes, and approve to fill out quality of life questionnaires, making use of the previously reported infrastructure of POCOP[14].

Investigated modalities

The modalities to be investigated in this study are both FDG-PET/CT and SL in addition to the initial staging with gastroscopy and CT of patients with an advanced gastric cancer (cT3–4). Patients will undergo FDG-PET/CT and SL according to the recently revised Dutch guidelines[15]. All patients will first undergo a FDG-PET/CT, and if the FDG-PET/CT does not show evidence of distant metastases a SL will be performed (Figure 1). FDG-PET/CT or SL may be omitted if it is deemed appropriate by the MDT or if it appears that a patient is not able to undergo one of both modalities.

FDG-PET/CT

Preparation of patients for FDG-PET/CT, and scanning and image reconstruction will be performed according to the institutional protocols of the participating centers, preferably incorporating guidelines of the European Association of Nuclear Medicine (EANM) / EANM Research Ltd. (EARL) and/or Netherlands Association of Nuclear Medicine (NVNG)[16]. In general, patients should refrain from strenuous exercise, and fast for at least 4 to 6 h before the injection of FDG. Patients should be pre-hydrated by drinking approximately 1 L of water in the 2 h before injection. Fasting blood glucose should preferably be below 11 mmol/L. After the injection of FDG, patients will remain seated or lying, and silent for 1 h in a warm room. A full body FDG-PET/CT scan will be performed 60 min (range 55–75 min) after the injection of FDG, accompanied by a CT at the same scanning range. Scans are read, interpreted and reported by the nuclear medicine physicians of the respective participating centers. The report generally includes information regarding the FDG-avidity of the primary tumor and/or locoregional lymph nodes, and suspicion of distant metastases. For this study, the maximum standardized uptake values (SUVmax, corrected for body weight) of the primary tumor will also be registered.

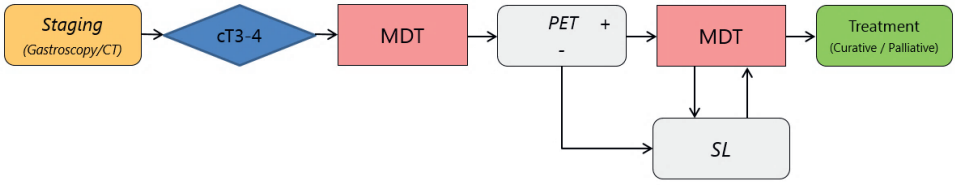

Figure 1. Study flowchart. cT3-4: advanced tumor with clinical T-stage 3 or 4; MDT: multidisciplinary team; PET: FDG-PET/CT; SL: staging laparoscopy

If the FDG-PET/CT identifies new lesions that are possible metastases, a histological of cytological biopsy and/or additional imaging of a lesion is advised to confirm or exclude metastases.

Staging laparoscopy

SL will be performed after the FDG-PET/CT, prior to the initiation of treatment, and should be performed by or under supervision of a gastrointestinal or oncological surgeon. During staging laparoscopy, the goals are to evaluate the resectability of the primary tumor (T-stage) and to evaluate the presence or absence of peritoneal metastases. To evaluate the resectability of the tumor, a thorough inspection of the region of the stomach and tumor along with surrounding organs will be performed. In case of a tumor localized at the posterior wall of the stomach, it is advised to open the omental bursa and inspect it accordingly. To evaluate the presence or absence of peritoneal metastases, all quadrants of the peritoneal cavity and Douglas' pouch will be inspected. In case of suspicious macroscopic lesions, biopsies will be taken and sent for histological review. When macroscopic lesions are present, all thirteen regions of the abdomen will be evaluated and the peritoneal cancer index (PCI) will be scored[17]. Cytology of the peritoneal cavity should be performed (500cm^3 dispersed throughout all quadrants and Douglas' pouch) as it is a promising prognostic factor with possible implications for treatment in the future[18,19].

MDT

Ideally, patients will be discussed in a first MDT after initial staging with gastroscopy and CT of the thorax and abdomen, and in a second MDT after additional staging with FDG-PET/CT and SL (Fig. 1). In practice, in some patients the first or second MDT will be skipped and patients will

proceed to additional staging or treatment without intervention of MDT's. An included patient should be discussed in at least one MDT. Occasionally, an additional diagnostic modality will be required and the patient is discussed during a third MDT.

Treatment

If the tumor is deemed to be resectable, patients will be scheduled for treatment. Treatment will not be initiated before completion of staging according to the Dutch guidelines, including FDG-PET/CT and SL[15]. There are no additional restrictions to the further treatment strategy, such as chemotherapy regimen or type/approach of resection.

Outcome measurements

The primary outcome of this study is the proportion of patients in whom FDG-PET/CT and/or SL leads to a change in treatment strategy. This includes the proportion of patients in whom surgery with curative intent is prevented, and the proportion of patients in whom the chemotherapy regimen is changed or omitted. Secondary outcome parameters include cost-effectiveness, modality-specific performances (diagnostic performance of both modalities, incidental findings on FDG-PET/CT), patients' extra burden of the diagnostic modalities (morbidity and mortality, diagnostic delay, number of extra MDT's held), and overall quality of life of patients (EORTC Quality of Life questionnaires).

Sample size calculation

Based on previous literature it is expected that 27% of patients will have a change in treatment strategy[11]. Taking a safety margin of 5% into account (thus at least 22% of patients will have a change in treatment strategy), an alpha of 0.05 and a power of 0.80, at least 239 patients need to be included in this study to demonstrate that performing a combination of both diagnostic modalities is cost-effective. Based on the yearly number of gastrectomies performed in the participating centers, approximately 543 patients are expected to be eligible for the study in 36 months.

Statistical analysis

The primary outcome measures, change in treatment strategy of FDG-PET/CT and SL, will be presented as a percentage. To evaluate the performance of FDG-PET/CT and SL, sensitivity and

specificity will be calculated. A separate analysis will be performed to assess whether both diagnostic modalities

are accurate for various subgroups, for instance tumor types (Lauren classification: diffuse, intestinal and mixed). The quality of life of patients in this study will be compared to previous data from literature and to a retrospective cohort of patients who did not undergo FDG-PET/CT and SL.

Differences are tested using linear mixed-effects modelling, taking relevant patient characteristics into account. Missing values will be imputed using multiple imputation techniques. Statistical significance is defined as $p<0.05$. Cost-effectiveness will be calculated, taking all relevant health-related costs into account, including costs arising from complications of medical treatment, and additional diagnostics arising from false-positive findings on FDG-PET/CT. A

model (Figure 2) will be developed to compare health care costs with only CT. A budget impact analysis (BIA) will be performed, adhering to the newest guidelines and applying the societal, health insurance/third party payer and health care perspectives. Analyses will be performed for the combination of FDG-PET/CT and SL and for both treatment modalities separately.

Time schedule

The study recently started on 01–08-2017, and will last for 36 months. After the start of the study, the first 30 months will consist of inclusion and follow-up of the patients. The last 6 months will consist of follow-up and analysis of results. The study will end at 01–08-2020.

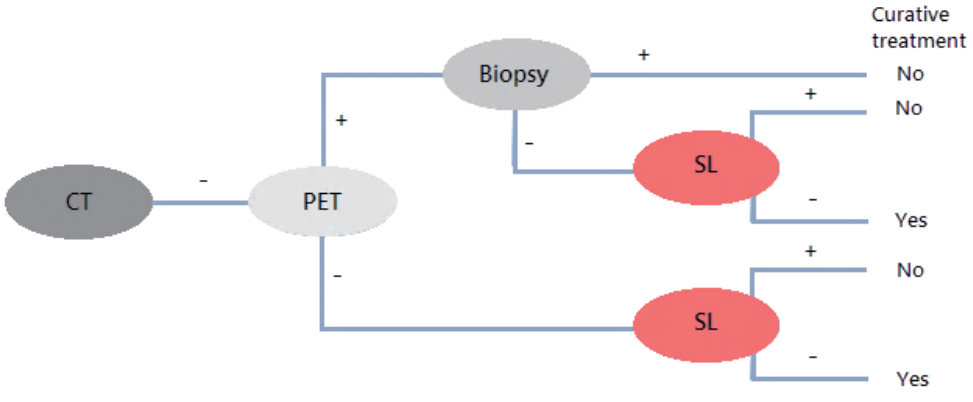

Figure 2. Decision tree for FDG-PET/CT and SL.

DISCUSSION

The PLASTIC-study is a prospective observational cohort study evaluating the impact and cost-effectiveness of FDG-PET/CT and SL in addition to initial staging by CTand gastroscopy in patients with locally advanced gastric cancer. The new Dutch guidelines recently included these staging modalities for staging locally advanced gastric cancer but recommended additional studies to be performed.

Until recently, the role of FDG-PET/CT in the staging of gastric cancer has been limited. Indeed, during initial staging of gastric cancer, the sensitivity and specificity of FDG-PET/CT are not better than that of CT for lymph node metastases, liver metastases and peritoneal metastases[7–9,15]. However, for patient with locally advanced tumors, FDG-PET/CT may be able to find additional distant metastases which were not detected during initial staging with CT. This was recently reported in a single study from the United States by Smyth et al., who prospectively evaluated the utility of FDG-PET/CT and SL in patients with locally advanced gastric cancer[11]. They found that FDG-PET/CT is able to detect additional distant metastases in 10% of patients, resulting in an estimated cost reduction of $13.000 per patient. Moreover, they concluded that FDG-PET/CT is most costeffective if performed prior to SL[11]. However, the cost-effectiveness analysis was performed retrospectively and might not be applicable to health care systems outside the US.

SL prior to gastrectomy has been broadly applied to diagnose peritoneal metastases. Studies evaluating the percentage of patients who benefit from SL are abundant, with percentages varying between 16 and 38% [10, 20–27]. Unfortunately, high quality evidence supporting cost-effectiveness is not available. The PLASTIC study will be the first study to prospectively investigate the cost-effectiveness of SL in combination with FDG-PET/CT. In this study, patients will first undergo a FDG-PET/CT, followed by a SL if FDG-PET/CT does not show distant metastases. If distant metastases found on FDG-PET/CT are confirmed by biopsy or additional imaging, SL will be omitted. This order was chosen as it is more applicable in clinical practice for the following reasons:

- FDG-PET/CT is non-invasive, whereas a SL is invasive and is accompanied by a higher risk of adverse events for the patients;
- Assessing the FDG-PET/CT after SL will be less reliable, due to uptake of FDG in postoperative inflammation;
- FDG-PET/CT scans can be scheduled more easily and probably results in less diagnostic delay;
- In a theoretical model from a previous study, first performing FDG-PET/CT resulted in more cost savings compared to a SL-first approach (difference $2168 per patient)[11].

This study aims to include patients with locally advanced (cT3–4) gastric cancer, but the accuracy of CT for determining T-stage is low[8]. This could result in the unintended inclusion of early stage (T2) tumors or failure to include truly advanced tumors. Nevertheless, these flaws reflect current practice. To reduce the impact of these current limitations, an expert panel will review all CT-scans to reach consensus on the clinical T-stage as a side study.

The current study is relevant, as the addition of FDG-PET/CT and SL may prevent futile gastrectomies, which are associated with considerable morbidity, mortality, reduction in quality of life and costs[28-30]. On the other hand, the number of prevented gastrectomies should exceed a certain level, as FDG-PET/CT and SL are accompanied by costs and possible risks for the patient (ionizing radiation, surgical complications) as well. The results of this study will be implemented in an updated version of the Dutch guidelines, but may also be applicable to all other Western countries with comparable treatment algorithms and health care systems.

By performing staging laparoscopy before starting treatment, a side effect of this study might be that more patients with peritoneal carcinomatosis will be detected. Recent studies have shown that there may be a role for hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery in these patients[31,32]. Patients with peritoneal carcinomatosis as detected in this study may therefore be included in HIPEC trials[33].

CONCLUSION

This prospective observational cohort study will evaluate the impact and cost-effectiveness of FDG-PET/CT and staging laparoscopy in addition to initial staging by CT and gastroscopy in patients with locally advanced gastric cancer. It is hypothesized that in 27% of patients a change in treatment strategy will occur, and that the annual cost reduction in the Netherlands will be approximately €916.438.

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(5):E359–86.
2. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11–20.
3. Brenkman HJ, Haverkamp L, Ruurda JP, et al. Worldwide practice in gastric cancer surgery. World J Gastroenterol. 2016;22(15):4041–8.
4. Al-Batran S, Homann N, Schmalenberg H, et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): a multicenter, randomized phase 3 trial. JCO. 2017;35(15):4004.
5. Dassen AE, Dikken JL, Bosscha K, et al. Gastric cancer: decreasing incidence but stable survival in the Netherlands. Acta Oncol. 2014;53(1):138–42.
6. Hoeymans N, Melse JM, Schoemaker CG: Gezondheid en determinanten. Deelrapport van de VTV 210 Van gezond naar beter. 2010, RIVM rapport 270061006: http://www.rivm.nl/bibliotheek/rapporten/270061006.pdf.
7. Choi JY, Shim KN, Kim SE, et al. The clinical value of 18Ffluorodeoxyglucose uptake on positron emission tomography/computed tomography for predicting regional lymph node metastasis and non-curative surgery in primary gastric carcinoma. Korean J Gastroenterol. 2014;64(6):340–7.
8. Seevaratnam R, Cardoso R, McGregor C, et al. How useful is preoperative imaging for tumor, node, metastasis (TNM) staging of gastric cancer? A meta-analysis. Gastric Cancer. 2012;15(Suppl 1):S3–18.
9. Wang Z, Chen JQ. Imaging in assessing hepatic and peritoneal metastases of gastric cancer: a systematic review. BMC Gastroenterol. 2011;11:19.
10. Hu YF, Deng ZW, Liu H, et al. Staging laparoscopy improves treatment decision-making for advanced gastric cancer. World J Gastroenterol. 2016;22(5):1859–68.
11. Smyth E, Schoder H, Strong VE, et al. A prospective evaluation of the utility of 2-deoxy-2-[(18) F]fluoro-D-glucose positron emission tomography and computed tomography in staging locally advanced gastric cancer. Cancer. 2012;118(22):5481–8.
12. Landelijke werkgroep Gastro-intestinale Tumoren. Richtlijn maagcarcinoom. 2016. Available at: http://www.oncoline.nl/maagcarcinoom.
13. Edge S, Byrd D, Compton C, et al. AJCC cancer staging manual. 7th edition ed. New York: Springer; 2010.
14. Kim JW, Shin SS, Heo SH, et al. Diagnostic performance of 64-section CT using CT gastrography in preoperative T staging of gastric cancer according to 7th edition of AJCC cancer staging manual. Eur Radiol. 2012;22(3):654–62.
15. Coebergh van den Braak RRJ, van Rijssen LB, van Kleef JJ, et al. Nationwide comprehensive gastro-intestinal cancer cohorts: the 3P initiative. Acta Oncol. 2018;57(2):195–202
16. Boellaard R, Delgado-Bolton R, Oyen WJ, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015;42(2):328–54.
17. Sugarbaker PH. Management of peritoneal surface malignancy using intraperitoneal chemotherapy and cytoreductive surgery: manual for physicians and nurses. 3rd ed. Grand Rapids: Ludann Company; 1998.
18. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer. 2011;14(2):101–12.
19. Jamel S, Markar SR, Malietzis G, et al. Prognostic significance of peritoneal lavage cytology in staging gastric cancer: systematic review and meta-analysis. Gastric Cancer. 2017;21:10–8.
20. Tourani SS, Cabalag C, Link E, et al. Laparoscopy and peritoneal cytology: important prognostic tools to guide treatment selection in gastric adenocarcinoma. ANZ J Surg. 2015;85(1–2):69–73.
21. Santa-Maria AF, Valadao M, Iglesias AC. The role of staging laparoscopy in treatment of locally advanced gastric cancer. Surg Laparosc Endosc Percutan Tech. 2014;24(5):434–9.

22. Huang H, Jin JJ, Long ZW, et al. Three-port laparoscopic exploration is not sufficient for patients with T4 gastric cancer. Asian Pac J Cancer Prev. 2014;15(19):8221–4.
23. Kapiev A, Rabin I, Lavy R, et al. The role of diagnostic laparoscopy in the management of patients with gastric cancer. Isr Med Assoc J. 2010;12(12):726–8.
24. Mahadevan D, Sudirman A, Kandasami P, et al. Laparoscopic staging in gastric cancer: an essential step in its management. J Minim Access Surg. 2010;6(4):111–3.
25. Muntean V, Mihailov A, Iancu C, et al. Staging laparoscopy in gastric cancer. Accuracy and impact on therapy. J Gastrointestin Liver Dis. 2009;18(2):189–95.
26. Shelat VG, Thong JF, Seah M, et al. Role of staging laparoscopy in gastric malignancies - our institutional experience. World J Gastrointest Surg. 2012; 4(9):214–9.
27. Ikoma N, Blum M, Chiang YJ, et al. Yield of staging laparoscopy and lavage cytology for radiologically occult peritoneal Carcinomatosis of gastric Cancer. Ann Surg Oncol. 2016;23:4332–7.
28. Brenkman HJ, Ruurda JP, Verhoeven RH, et al. Safety and feasibility of minimally invasive gastrectomy during the early introduction in the Netherlands: short-term oncological outcomes comparable to open gastrectomy. Gastric Cancer. 2017;20:853–60.
29. Busweiler LA, Wijnhoven BP, van Berge Henegouwen MI, et al. Early outcomes from the Dutch upper gastrointestinal Cancer audit. Br J Surg. 2016;103(13):1855–63.
30. Avery K, Hughes R, McNair A, et al. Healthrelated quality of life and survival in the 2 years after surgery for gastric cancer. Eur J Surg Oncol. 2010;36(2):148–54.
31. Glehen O, Gilly FN, Arvieux C, et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol. 2010;17(9):2370–7.
32. Desiderio J, Chao J, Melstrom L, et al. The 30-year experience-a meta-analysis of randomised and high-quality non-randomised studies of hyperthermic intraperitoneal chemotherapy in the treatment of gastric cancer. Eur J Cancer. 2017;79:1–14.
33. van der Kaaij RT, Braam HJ, Boot H, et al. Treatment of peritoneal dissemination in stomach Cancer patients with Cytoreductive surgery and Hyperthermic intraperitoneal chemotherapy (HIPEC): rationale and design of the PERISCOPE study. JMIR Res Protoc. 2017;6(7):e136.

Chapter 3

The additive value of restaging-CT during neoadjuvant chemotherapy for gastric cancer

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ABSTRACT

Background: Computed tomography (CT) is used for restaging of gastric cancer patients during neoadjuvant chemotherapy (NAC). The treatment strategy could be altered after detection of distant interval metastases, possibly leading to a reduction in unnecessary chemotherapy cycles, its related toxicity, and surgical procedures. The aim of this study was to evaluate the additive value of restaging-CT during NAC in guiding clinical decision making in gastric cancer.

Methods: This retrospective, multicenter cohort study identified all patients with surgically resectable gastric adenocarcinoma (cT1-4a-x, N0-3-x, M0-x), who started NAC with curative intent. Restaging-CT was performed after 2 out of 3 cycles of NAC. The primary outcome was treatment alterations made based on restaging-CT by a multidisciplinary tumor board. Confirmation of metastases was obtained by surgery or biopsy.

Results: Between 2007 and 2015, CT-restaging was performed in 122 out of 152 included patients and timed after 2 cycles (n=76) or after 3 cycles (n=46) of NAC. Restaging-CT revealed a metastasis in 1 out of 122 restaged patients (1%) after which surgical resection was omitted, whereas 4 patients (3%) with distant interval metastases were not identified by restaging-CT and underwent a futile laparotomy. In 5 out of 76 patients (7%) disease progression was detected while undergoing NAC, leading to omission of the 3rd cycle of chemotherapy.

Conclusion: The additive value of restaging-CT during NAC in gastric cancer is limited in guiding clinical decision making and therefore not recommended. Further studies may identify subgroups that may benefit of alternative diagnostic modalities.

BACKGROUND

Gastric cancer is the fourth most common cause of cancer related death worldwide[1]. The 5-year survival rate is 25-35% after radical gastrectomy with curative intent[2-4]. The main reason for failure of curative treatment is recurrence of disease, despite achieving R0-resection[3,5-7]. Numerous studies have shown that perioperative chemotherapy prolongs survival and is therefore recommended by Dutch national guidelines for gastric cancer[8-17]. In past years, perioperative chemotherapy was administered according to the MAGIC-trial regimen in most European countries, consisting of 3 neoadjuvant and 3 adjuvant cycles of epirubicin, cisplatin and 5-fluorouracil or capecitabine (ECF/ECX), or a comparable regimen[8-18].

Despite the benefits of neoadjuvant treatment, many patients experience severe chemotherapy-related toxic effects (22-51%) or death (1-3%) during treatment[8,16,18-22]. Furthermore, 16% of patients develop progression of disease while undergoing neoadjuvant ECF-/ECX-chemotherapy (NAC), which often consists of distant interval metastases[19]. Such cases may warrant an alteration of treatment strategy.

Patients with disease progression should be identified preoperatively in order to prevent any further delay to surgery if gastrectomy with curative intent is still feasible, or in order to avoid unnecessary surgery if curative treatment is no longer feasible. Hence, detection of disease progression and/or interval metastases by imaging guided restaging could be valuable. Therefore, restaging by computed tomography (CT) after two cycles of NAC may be performed and is part of the current policy of the participating centers. Due to logistic challenges, it was not always feasible to perform the scan after the second cycle, resulting in a restaging-CT after three cycles in a number of cases.

Few good-quality studies have investigated the accuracy of restaging-CT after NAC for gastric cancer[23-27]. However, the evidence for its ability to guide treatment decisions in clinical practice is scarce. Therefore, the aim of the current study was to evaluate the additive value of restaging-CT during NAC in guiding clinical decision making in gastric cancer.

METHODS

Study design

The Netherlands Cancer Registry (NCR) was used to retrospectively identify a cohort of gastric cancer patients between 2007 and 2015 in four hospitals in the Netherlands. The inclusion criteria consisted of: histologically proven gastric adenocarcinoma, surgically resectable tumor (cT1-4a-x, N0-3-x, M0-x) and initiation of NAC with curative intent. Institutional and NCR scientific review board approval were obtained and informed consent requirement was waived.

Staging, restaging and treatment

Primary staging was performed by upper endoscopy for obtaining tumor histology, frequently in combination with endoscopic ultrasound, and by CT of thorax and abdomen[17]. ^{18}Ffluorodeoxyglucose (FDG) positron emission tomography (PET)/CT and a staging laparoscopy were not routinely performed during the study period, as indications for these modalities (>T3 and/or N+ tumors) were only included in the revised Dutch guidelines in July 2016. Tumors were staged according to the 7th edition of the UICC/AJCC TNM-classification[28]. All individual treatment strategies were determined by the regional multidisciplinary tumor board.

Perioperative chemotherapy (3 neoadjuvant and adjuvant cycles) consisted of a triplet regimen of mostly ECX, EOX (containing oxaliplatin instead of cisplatin) or ECF. At day 1 of a 21-day cycle, intravenous epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) were administered, and capecitabine was given orally twice daily during 14 days (2000 mg/m^2/day) followed by 7 days of recovery (ECX). In case of EOX, cisplatin was replaced by oxaliplatin (130 mg/m^2) and capecitabine was given during all 21 days (1250 mg/m^2/day). In case of ECF, capecitabine was replaced by 5-fluorouracil (200 mg/m^2) via 21 days of continuous infusion. Adverse events were defined according to the Common Terminology Criteria for Adverse Events version 4.03[29].

By protocol, restaging-CT of thorax and abdomen was performed after 2 cycles of NAC in the portal venous phase after powered injection of iodinated intravenous contrast. Patients were prepared with oral contrast 30-60 min prior to scanning for improved gastric visualization by attaining distension. The restaging-CTwas assessed by a radiologist (not blinded) in the

participating center, specialized in abdominal imaging. At restaging-CT, disease progression was defined as evident visible tumor progression (upsizing/-staging) or evident visible progression of suspected lymph nodes or new lymph nodes with a short-axis diameter ≥10mm. Subsequently, the multidisciplinary tumor board re-evaluated the original treatment strategy.

Surgical resections and histopathological examination were performed according to the evidence based national guideline. Curative resection depended on tumor location and the extent of the primary tumor: an open/minimally invasive (sub)total gastrectomy including a modified D2-lymphadenectomy, 4-6 weeks after finishing the last NAC cycle[17]. If tumor regression was reported by the pathologist, the Mandard criteria were applied[30].

Outcomes

To evaluate the additive value of restaging-CT, the proportion of prevented unnecessary surgical procedures and ineffective cycles of NAC were calculated. Second, all treatment decisions made based on restaging-CT were re-evaluated. The diagnostic performance of restaging-CT, the toxicity of chemotherapy and surgical complications were analyzed.

Statistical analysis

The proportion of patients in which restaging-CT led to an alteration of the treatment strategy was classified as clinically relevant at ≥5% for prevented surgical procedures and >10% for omitted ineffective chemotherapy cycles. This ≥5% cut-off point was based on several previous studies, reporting 3-7% of patients not proceeding to surgery because of disease progression at CT-restaging[16,19,20,24,26]. There is no literature to substantiate the cut-off value of ≥10%, however this rate was considered to be clinically relevant based on previous literature[16,19,20,25,27].

Statistical analyses were processed by IBM SPSS Statistics version 21 for Windows (SPSS Inc. Chicago, USA).

RESULTS

Study population

Out of all 181 identified patients with gastric adenocarcinoma between 2007 and 2015, 152 patients met the inclusion criteria. Baseline characteristics are summarized in Table 1. Restaging-CT was not performed in 30 patients due to various reasons (Figure 1), remaining 122 eligible patients for analysis.

Chemotherapy

Of 152 patients in total, 112 (74%) completed all 3 cycles of NAC. Severe chemotherapy-related adverse events (grade 3-4) were experienced by 63 patients (41%), of whom 28 patients (18%) discontinued NAC. Toxicity (Table 2) predominantly consisted of gastrointestinal side-effects (63%), vascular thromboembolisms (27%) and febrile neutropenia (24%). In 4 patients (3%) an acute anaphylactic reaction induced by platinum-based chemotherapy occurred, with oxaliplatin (n=2) or cisplatin (n=2). A total of 5 patients (3%) died (grade 5) as a result of neutropenic sepsis following pneumonia (n=4) or spontaneous gastric perforation after 2 cycles of NAC (n=1).

Treatment alterations

Surgical treatment was altered in 1 out of 122 restaged patients (1%), for whom unnecessary gastrectomy was prevented due to detection of a solitary liver metastasis, leading to cancellation of both gastrectomy and the 3rd cycle of NAC. Regarding NAC, restaging-CT was performed after 2 cycles in 76 out of 122 patients (62%), whereas the remaining 46 patients (38%) were restaged after 3 cycles. Treatment regarding NAC was altered in 5 out of 76 patients with restaging-CT after 2 cycles of NAC (7%) because of disease progression, which reflects ineffective chemotherapy cycles. Of these patients, 4 had T- or N-upstaging but could still undergo resection with curative intent, except for the aforementioned patient with a solitary liver metastasis. Furthermore, in 2 out of 46 patients with restaging-CT after 3 cycles (4%) disease progression was also detected (N-upstaging), however NAC treatment could not be adjusted since all 3 cycles were already administered. Gastrectomy with curative intent was still considered feasible for all 46 patients.

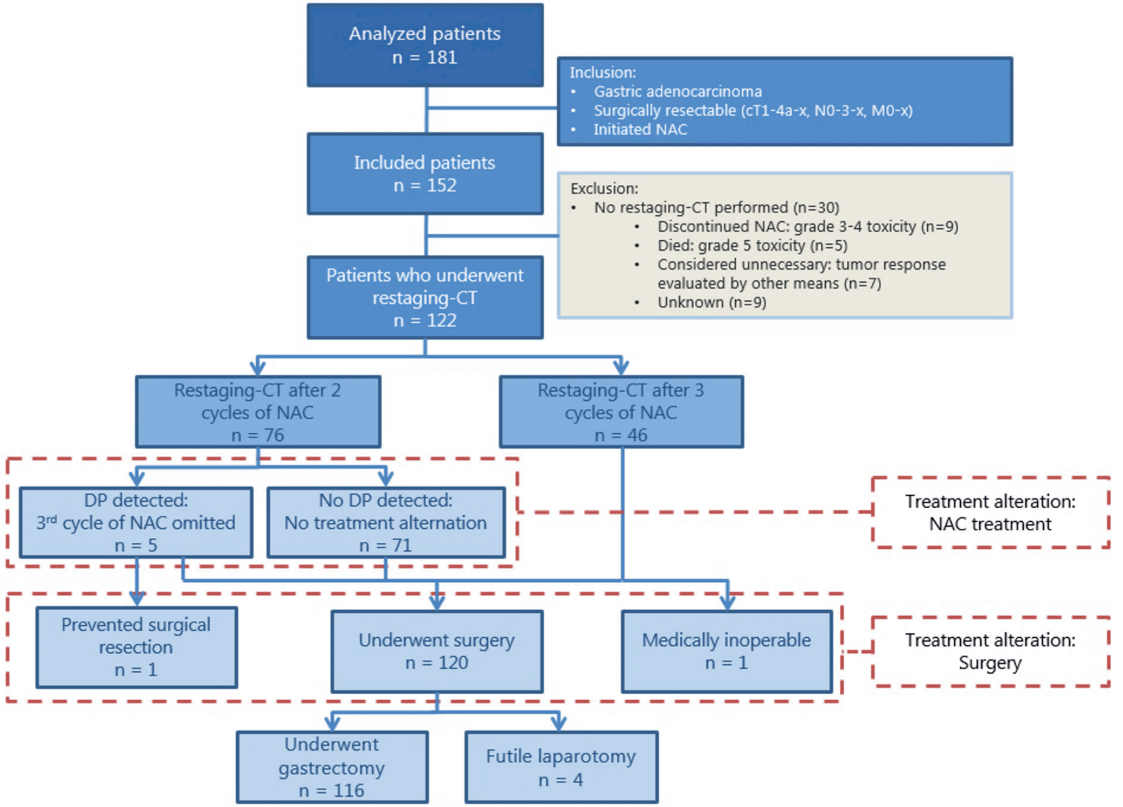

Figure 1. Study flowchart. NAC: neoadjuvant chemotherapy; CT: computed tomography; DP: disease progression

Table 1. Baseline characteristics of 152 patients who underwent restaging computed tomography after starting neoadjuvant chemotherapy for gastric cancer

	No. (%)	Missing values (%)
Age, years (median; in years) [IQR]	64 [54-70]	0 (0)
Gender (% male)	89 (59)	0 (0)
ECOG Performance score		0 (0)
0	100 (66)	
1	48 (32)	
2	4 (3)	
Previous malignancy (yes)	17 (11)	0 (0)
Tumor location		0 (0)
Proximal (Siewert III, fundus/corpus)	73 (48)	
Distal (antrum, pylorus)	59 (39)	
Diffuse	20 (13)	
Laurén classification		32 (21)
Intestinal	43 (36)	
Diffuse	68 (57)	
Mixed	9 (8)	
Tumor differentiation		25 (16)
Good/moderate	32 (25)	
Poor/ undifferentiated	95 (75)	
Signet ring cells (yes)	55 (36)	0 (0)
cT-stage		0 (0)
T1	0 (0)	
T2	29 (19)	
T3	42 (28)	
T4a	6 (4)	
Tx	75 (49)	
cN-stage		0 (0)
N0	86 (57)	
N1	34 (22)	
N2	25 (16)	
N3a	5 (3)	
N3b	1 (1)	
Nx	1 (1)	
Neoadjuvant treatment		0 (0)
ECX	119 (78)	
EOX	28 (18)	
ECF	3 (2)	
Other	2 (1)	

IQR: interquartile range; ECOG: Eastern Cooperative Oncology Group; ECX: Epirubicin, cisplatin and capecitabine; EOX: Epirubicin, oxaliplatin and capecitabine; ECF: Epirubicin, cisplatin and 5-fluorouracil. Percentages may not add up to or exceed 100% due to rounding.

Restaging-CT and surgery

Metastases were identified in 5 out of all 122 restaged patients (4%), either by restaging-CT (n=1) or intraoperatively (n=4). Since 1 patient did not proceed to surgery due to a detected liver metastasis at restaging-CT and 1 patient was medically inoperable, 120 patients (98%) remained for surgery. Gastrectomy was performed in 116 patients (97%), because in 4 patients peritoneal metastases were detected during surgery that were not identified at the previously performed staging laparoscopy (n=1) or restaging-CT, as shown in Figure 1.

Table 2. Grade 3-4 adverse events associated with neoadjuvant chemotherapy of 63 patients (41%) out of 152 patients in total.

	No. (%)
Gastro-intestinal complications	40 (63)
Mucositis	35 (56)
Ileus	3 (5)
Spontaneous perforation*	2 (3)
Thrombo-embolic complications	17 (27)
Pulmonary embolism	13 (21)
Arterial embolism	3 (5)
Deep venous thrombosis	1 (2)
Febrile neutropenia	15 (24)
Respiratory complications	6 (10)
Pneumonia#	6 (10)
Myelosuppresion	4 (6)
Anaphylaxis†	4 (6)
Cardiac complications	3 (5)
Myocardial infarction	2 (3)
Myocarditis	1 (2)
Peripheral sensory neuropathy	1 (2)

The total number of complications exceeds the amount of patients since several adverse events could be observed per patient. *1 patient died due to neutropenic sepsis following spontaneous gastric perforation. #4 patients died due to neutropenic sepsis following pneumonia. †Platinum-based chemotherapy induced anaphylaxis.

Confirmation of metastases was obtained by histopathological examination (97%) or was determined intraoperative after futile laparotomy (3%). Surgical and histopathological characteristics are listed in Table 3. Surgical complications resulted in death during hospital admission in 5 patients (4%) and 90-day postoperative mortality was 5% (n=6) (see Table 4).

During early follow-up, distant metastases were discovered in 6 out of 116 patients (5%) who underwent gastrectomy, within 3-6 months after the restaging-CT, including peritoneal (n=2), omental (n=1), hepatic (n=1), pleural (n=1) and distant lymph node (n=1) metastases.

DISCUSSION

The aim of the present study was to evaluate the additive value of restaging-CT during NAC for gastric cancer patients in guiding clinical decision making. All treatment decisions, made by the regional multidisciplinary tumor board based on restaging-CT, were re-evaluated. It was found that restaging-CT influences surgical treatment in only 1% and is reason to omit a 3rd cycle of NAC in 7% of patients due to detected disease progression or metastases. Our results indicate that restaging-CT during NAC is of limited additive value in guiding clinical decision

Table 3. Surgical and histopathological characteristics of 116 patients that underwent gastrectomy for gastric cancer

	No. (%)	Missing values (%)
Hospital stay (median; in years) [IQR]	10 [7 – 13]	0 (0)
Type of surgery		0 (0)
Total gastrectomy	65 (56)	
Subtotal gastrectomy	51 (44)	
Surgical approach (open)	76 (66)	0 (0)
Radicality		0 (0)
R0	98 (84)	
R1	16 (14)	
R2	2 (2)	
ypT-stage		0 (0)
T0	6 (5)	
T1	14 (12)	
T2	14 (12)	
T3	47 (41)	
T4a	29 (25)	
T4b	6 (5)	
ypN-stage		0 (0)
N0	49 (42)	
N1	28 (24)	
N2	22 (19)	
N3a	14 (12)	
N3b	3 (3)	
Lymph node yield (median) [IQR]	16 [10 – 25]	0 (0)
Histopathological TRG		36 (31)
Mandard 1	6 (8)	
Mandard 2	2 (3)	
Mandard 3	20 (26)	
Mandard 4	26 (33)	
Mandard 5	26 (33)	
Postoperative complications	33 (28)	0 (0)
In-hospital mortality	5 (4)	0 (0)
90-days postoperative mortality	6 (5)	0 (0)

IQR = interquartile range, TRG = tumor regression grading.

Table 4. Postoperative complications of 33 patients (28%) out of 116 patients in total who underwent gastrectomy for gastric cancer.

	No. (%)
Anastomotic leakage*	14 (12)
Pneumonia#	11 (9)
Spleen infarction	5 (4)
Pleural empyema	4 (3)
Ileus	4 (3)
Abscess	3 (3)
Pneumothorax	3 (3)
Pancreatitis	2 (2)
Perforation of colon	2 (2)
Ischemia of jejunum	1 (1)

*5 patients died due to sepsis following anastomotic leakage. #1 patient died as a result of pneumosepsis.

making in order to prevent unnecessary surgical procedures or ineffective chemotherapy cycles.

To assess clinical relevance, cut-off values were determined for treatment alterations regarding prevented unnecessary surgical procedures (≥5%) and chemotherapy cycles (≥10%), based on previous literature[16,19,20,24,26]. Both predefined cut-off values were not achieved, since our results showed 1% and 7%, respectively. Restaging-CT prevented unnecessary gastrectomy in only 1% (1 out of 122 patients) because a solitary liver metastasis was detected. Previous studies reported a slightly higher rate of 3-7% of patients not proceeding to surgery as a result of CT-restaging post-NAC[16,19,20,24,26]. This difference may be due to the earlier timing of restaging in our study, which was during NAC instead of after completing NAC. Furthermore, in 5 out of 76 patients (7%) who were restaged after 2 cycles, the 3rd cycle was cancelled due to detected disease progression while undergoing NAC, consequently reducing the time interval to surgery and possibly limiting further progression. No studies were found for comparison. Besides possibly limiting further progression, preventing such ineffective cycles of NAC is also important because of possible severe toxicity, illustrated by a chemotherapy related mortality of 3% in our study, which is comparable to literature[16,18-22]. Moreover, disease progression was detected in 2 out of 46 patients who were restaged after 3 cycles, however, potentially toxic NAC was already completed and thus could not be adjusted. Theoretically, disease progression may have also been detected if restaging-CT would have been performed after 2 cycles instead of 3, which should have led to treatment alterations.

Unfortunately, peritoneal metastases were diagnosed in 4 patients (3%) during surgery despite previously performed staging laparoscopy and restaging, indicating false-negative outcomes of restaging-CT and highlighting the inability of CT to detect peritoneal metastases. Therefore, these 4 patients underwent futile surgery. Several previous studies reported a slightly higher rate (7-15%) of false-negative outcomes[18,20,21,25,31]. It should be stressed that initial staging should be as accurate as possible in order to evaluate the value of restaging. In case of peritoneal metastases, it is well established that staging laparoscopy is the appropriate diagnostic tool[31-34] and that contrast-enhanced-CT lacks performance in detecting peritoneal carcinomatosis in gastric cancer and performs better in detecting liver metastases[35]. In recent years, both FDG-PET/CT and staging laparoscopy have gained popularity in the initial staging process, as it was reported that these modalities detect additional metastases in 27% of patients (10% and 19%,

respectively, with 2% overlap of both modalities in 1 patient) and it is hypothesized that this could decrease futile treatment[31]. In the Netherlands, the PLASTIC-study is currently researching the additive value of both FDG-PET/CT and staging laparoscopy, as both now are advised by the revised Dutch guidelines as of July 2016[17,36]. Furthermore, during early follow-up (<3-6 months after restaging) distant metastases were discovered in another 6 patients (5%) by CT. It could be argued that (micro-)metastases were possibly already present at the time of restaging and that gastrectomy for these patients was also unnecessary. These results emphasize the clinical importance of restaging, but also highlight the diagnostic limitations of restaging-CT during NAC in this study.

Due to the aforementioned deficits, restaging-CT during NAC demonstrated a lack of detecting metastases resulting from disease progression in this study. Previous studies also demonstrated inadequate detection, reporting sensitivity rates of 16-60% for detecting disease progression by means of CT-restaging post-NAC[16,19,20,25,26]. This wide range may be explained by the fact that none of those studies specified CT-criteria for disease progression, and because of small sample sizes. However, this indicates restaging-CT is not very effective. Currently, no consensus exists regarding the optimal approach for accurate restaging. CT is relatively low-cost and easily accessible, and is widely used for restaging in gastric cancer, but restaging-CT seems of limited additive value in guiding treatment decisions in the present and previous studies[26,27]. Further research is required to improve preoperative detection of distant metastases in order to decrease futile surgery, such as the PLASTIC-study[36]. Furthermore, introduction of FLOT-chemotherapy may alter the value of CT-restaging, as this regimen significantly increases histopathological tumor response compared to current regimens, and therefore less patients may possibly develop disease progression while undergoing FLOT[19].

A limitation of this study is its retrospective design, introducing heterogeneity in the timing of restaging, scanning protocols and chemotherapy regimens (97% ECX/EOX). Only 62% of patients were restaged according to study protocol, after 2 cycles of NAC, possibly leading to selection bias. Furthermore, ideally, subgroups of patients with disease progression for whom restaging-CT could be beneficial should be identified. In our study, the small amount of patients with disease progression (n=7) limited a reliable statistical comparison. Moreover, disease progression was not measured using RECIST (Response Evaluation Criteria In Solid Tumors)

because of inconsistent results in gastric tumors, the fact that a measurable lesion is required whereas gastric tumors are often inevaluable and due to the retrospective design[23,24,34,37]. Last, sensitivity and specificity rates of restaging-CT for detecting distant metastases during NAC were not reported due to the small amount of patients with interval metastases.

To our knowledge, this multicenter study is the first to evaluate treatment decisions made by a multidisciplinary tumor board based on restaging-CT during NAC for gastric cancer with primary outcomes focused on clinical decision making rather than the technical abilities of CT itself in restaging. Thus, the study period covering 7 years is illustrative for clinical practice.

CONCLUSION

The additive value of restaging-CT during NAC in gastric cancer is limited in guiding clinical decision making in order to avoid unnecessary surgical procedures or ineffective, potentially toxic chemotherapy cycles. Therefore, performing a restaging-CT is not recommended. Further research may focus on subgroup identification or alternative diagnostic modalities for improved detection of disease progression and distant interval metastases during NAC for gastric cancer.

REFERENCES

1. World Health Organization (WHO). Cancer. Feb 2018.
2. Agboola O. Adjuvant treatment in gastric cancer. Cancer Treat Rev. 1994;20(3):217-240.
3. Siewert JR, Böttcher K, Roder JD, et al. German Gastric Carcinoma Study Group. Prognostic relevance of systematic lymph node dissection in gastric carcinoma. Br J Surg. 1993;80(8):1015-1018.
4. Wanebo HJ, Kennedy BJ, Chmiel J, et al. Cancer of the stomach. A patient care study by the American College of Surgeons. Ann Surg. 1993;218(5):583-592.
5. Gee DW, Rattner DW. Management of gastroesophageal tumors. Oncologist. 2007;12(2):175-185.
6. D'Angelica M, Gonen M, Brennan MF, et al. Patterns of initial recurrence in completely resected gastric adenocarcinoma. Ann Surg. 2004;240(5):808-816.
7. Bonenkamp JJ, Hermans J, Sasako M, et al. Extended lymp-node dissection for gastric cancer. N Engl J Med. 1999;340(12):908-914.
8. Cunningham D, Allum WH, Stenning SP, et al. Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. N Engl J Med. 2006;355(1):11-20.
9. Diaz-Nieto R, Orti-Rodríguez R, Winslet M. Postsurgical chemotherapy vs. surgery alone for resectable gastric cancer. Cochrane Database Syst Rev. 2013;9:CD008415.
10. Xiong B-H, Cheng Y, Ma L, et al. An Updated Meta-Analysis of Randomized Controlled Trial Assessing the Effect of Neoadjuvant Chemotherapy in Advanced Gastric Cancer. Cancer Invest. 2014;32(6):272-284.
11. Li W, Qin J, Sun YH, et al. Neoadjuvant chemotherapy for advanced gastric cancer: A meta-analysis. World J Gastroenterol. 2010;16(44):5621-5628.
12. Mezhir JJ, Tang LH, Coit DG. Neoadjuvant therapy of locally advanced gastric cancer. J Surg Oncol. 2010;101(4):305-314.
13. Biondi A, Lirosi MC, D'Ugo D, et al. Neo-adjuvant chemo(radio)therapy in gastric cancer: Current status and future perspectives. World J Gastrointest Oncol. 2015;7(12):389-400.
14. Ronellenfitsch U, Schwarzbach M, Hofheinz R, et al. Perioperative chemo(radio)therapy versus primary surgery for resectable adenocarcinoma of the stomach, gastroesophageal junction, and lower esophagus. Cochrane Database Syst Rev. 2013;5:CD008107.
15. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, Pignon JP, et al. Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer. JAMA J Am Med Assoc. 2010;303(17):1729-1737.
16. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: An FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29(13):1715-1721.
17. Vereniging van Integrale Kankercentra. National Guidelines. Diagnostics, treatment and follow-up of gastric cancer. Version 2.2. last updated: 2017-03-01. http://oncoline.nl/maagcarcinoom.
18. Cunningham D, Starling N, Rao S, et al. Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer. N Engl J Med. 2008;358(1):36-46.
19. Al-Batran SE, Hofheinz RD, Pauligk C, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol. 2016;17(12):1697-1708.
20. Mongan AM, Kalachand R, King S, et al. Outcomes in gastric and junctional cancer using neoadjuvant and adjuvant chemotherapy (epirubicin, oxaliplatin, and capecitabine) and radical surgery. Ir J Med Sci. 2015;184(2):417-423.
21. Schulz C, Kullmann F, Kunzmann V, et al. NeoFLOT: Multicenter phase II study of perioperative chemotherapy in resectable adenocarcinoma of the gastroesophageal junction or gastric adenocarcinoma - Very good response predominantly in patients with intestinal type tumors. Int J Cancer. 2015;137(3):678-685.

22. Cats A, Jansen EPM, Grieken NCT Van, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19:616-628.
23. Kwee RM, Kwee TC. Role of imaging in predicting response to neoadjuvant chemotherapy in gastric cancer. World J Gastroenterol. 2014;20(7):1650-1656.
24. Achilli P, De Martini P, Ceresoli M, et al. Tumor response evaluation after neoadjuvant chemotherapy in locally advanced gastric adenocarcinoma: A prospective, multicenter cohort study. J Gastrointest Oncol. 2017;8(6):1018-1025.
25. Joo I, Kim SH, Ahn SJ, et al. Preoperative tumor restaging and resectability assessment of gastric cancers after chemotherapy: diagnostic accuracy of MDCT using new staging criteria. Abdom Radiol. 2017;42(12):2807-2815.
26. Yoshikawa T, Tanabe K, Nishikawa K, et al. Accuracy of CT staging of locally advanced gastric cancer after neoadjuvant chemotherapy: Cohort evaluation within a randomized phase II study. Ann Surg Oncol. 2014;21:S385-389.
27. Park SR, Lee JS, Kim CG, et al. Endoscopic ultrasound and computed tomography in restaging and predicting prognosis after neoadjuvant chemotherapy in patients with locally advanced gastric cancer. Cancer. 2008;112(11):2368-2376.
28. Washington K. 7th edition of the AJCC cancer staging manual: Stomach. Ann Surg Oncol. 2010;17(12):3077-3079.
29. National Cancer Institute (US). Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. NIH Publ. 2010;2009:0-71.
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(11):2680-2686.
31. Smyth E, Schöder H, Strong VE, et al. A prospective evaluation of the utility of 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography and computed tomography in staging locally advanced gastric cancer. Cancer. 2012;118(22):5481-5488.
32. Fukagawa T. Role of staging laparoscopy for gastric cancer patients. Ann Gastroenterol Surg. 2019;3(5):496-595. doi:10.1002/ags3.12283
33. Machairas N, Charalampoudis P, Molmenti EP, et al. The value of staging laparoscopy in gastric cancer. Ann Gastroenterol. 2017;30(3). doi:10.20524/aog2017.0133.
34. Ikoma N, Blum M, Chiang YJ, et al. Yield of staging laparoscopy and lavage cytology for radiologically occult peritoneal carcinomatosis of gastric cancer. Ann Surg Oncol. 2016;23(13):4332-7. doi: 10.1245/s10434-016-5409-7.
35. Wang Z, Chen J-Q. Imaging in assessing hepatic and peritoneal metastases of gastric cancer: a systematic review. BMC Gastroenterol. 2011;11(1):19. doi:10.1186/1471-230X-11-19
36. Brenkman HJF, Gertsen EC, Vegt E, et al. Evaluation of PET and laparoscopy in STagIng advanced gastric cancer: A multicenter prospective study (PLASTIC-study). BMC Cancer. 2018;18(1):450.
37. 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(2):228-247.

Chapter 4

Evaluation of the implementation of FDG-PET/CT and staging laparoscopy for gastric cancer

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ABSTRACT

Background: The role of ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) and staging laparoscopy (SL) has increased in the preoperative staging of gastric cancer. Dutch national guidelines have recommended the use of FDG-PET/CT and SL for patients with locally advanced tumors since July 2016. The aim of this study was to evaluate the implementation of FDG-PET/CT and SL in the Netherlands.

Methods: Between 2011–2018, all patients who underwent surgery for gastric cancer were included from the Dutch Upper GI Cancer Audit. The use of FDG-PET/CT and SL was evaluated before and after revision of the Dutch guidelines. Outcomes included the number of non-curative procedures (e.g. palliative and futile procedures), and the association of FDG-PET/CT and SL with waiting times from diagnosis to start of treatment.

Results: A total of 3310 patients were analyzed. After July 2016, the use of FDG-PET/CT (23% vs. 61%, $p<0.001$) and SL (21% vs. 58%, $p<0.001$) increased. FDG-PET/CT was associated with additional waiting time to neoadjuvant therapy (4 days) as well as primary surgical treatment (20 days). SL was associated with 8 additional days of waiting time to neoadjuvant therapy. Performing SL or both modalities consecutively in patients in whom it was indicated was not associated with the number of non-curative procedures.

Conclusion: During implementation of FDG-PET/CT and SL after revision of the guidelines, both have increasingly been used in the Netherlands. The addition of these staging methods was associated with increased waiting time to treatment. Number of non-curative procedures did not differ after performing none, solely one or both staging modalities.

BACKGROUND

For patients with locally advanced gastric cancer, the main curative treatment comprises perioperative chemotherapy and gastrectomy[1-3]. The standard initial staging of gastric cancer consists of gastroscopy and computed tomography (CT) of the thorax and abdomen[4]. However, these modalities frequently miss distant metastases or tumor invasion in adjacent structures[5-7], which are important characteristics that limit curative treatment. As a result, patients may undergo neoadjuvant chemotherapy and/or surgery without any evident survival benefit, but with the risk of additional morbidity and short-term mortality, due to surgery as well as chemotherapeutic toxicity.

There has been an increasing interest in the role of fluorodeoxyglucose positron emission tomography with CT (FDG-PET/CT) and staging laparoscopy (SL) in the pre-operative staging of gastric cancer. Compared to CT alone, FDG-PET/CT has been reported to detect additional distant metastases in 10% of patients with locally advanced gastric cancer, whereas SL detects peritoneal metastases in another 19% of patients[8]. If distant metastases are detected during the diagnostic process, a more tailored treatment can be offered, such as systemic treatment with palliative intent. In July 2016, the Dutch national guidelines for the diagnosis and treatment of gastric cancer have been revised and advise FDG-PET/CT and SL for patients with locally advanced tumors that are considered for treatment with curative intent[1]. However, the consequences of these new guidelines on patient outcomes are not yet clear. The main potential positive effect is reduction of non-curative procedures, whereas the main possible negative effect is delay of treatment, which is undesirable from a patient perspective. The aim of the current population-based study was to evaluate the implementation of FDG-PET/CT and SL in the Netherlands and its effect on non-curative resection rates and waiting time from diagnosis to treatment.

METHODS

Study design

This population-based observational study retrieved anonymous data from the Dutch Upper GI Cancer Audit (DUCA) database. DUCA is a national surgical registry of all patients who underwent

surgery for gastroesophageal cancer since 2011. Patients in whom no surgical procedure was performed, for example due to distant metastases detected by FDG-PET/CT, are not registered in the DUCA database. For Dutch hospitals performing gastroesophageal cancer surgery it is mandatory to provide patient-, tumor- and surgical treatment-related data to the DUCA every year, which is part of the Dutch Institute for Clinical Auditing. An in-depth quality investigation of this national audit has shown trustworthy and complete data registry[9]. The current study was approved by the scientific committee of DUCA, and no ethical approval or informed consent was required according to the Dutch law.

Study population

All patients who underwent any type of surgery for gastric adenocarcinoma between 2011 and 2018 in the Netherlands were included. Patients with inadequate staging (no diagnostic CT scan), or who underwent emergency, prophylactic or other resection than gastrectomy, or with missing data preventing the analysis of the study outcomes (e.g. time of diagnosis) were excluded.

Diagnosis and treatment

In the Netherlands, diagnosis, staging and treatment of gastric cancer is advised to be performed according to Dutch national guidelines and the 7th edition of the American Joint Committee on Cancer TNM staging system[1,4,10].

Centralization of gastric cancer surgery has been gradually introduced in the Netherlands during the study period. As of 2013, a minimum of 20 gastrectomies per center per year is required[11-13] and a center performing at least that number of resections in a year is defined as a high-volume center. The recommended staging process consists of gastroscopy with biopsies and CT scan of thorax and abdomen in all patients. If there is doubt about the depth of ingrowth, an endoscopic ultrasound (EUS) can be performed to make a better distinction between cT1-2 and cT3-4 or to decide on whether or not to perform an endoscopic mucosal resection (EMR)/endoscopic submucosal dissection (ESD). Since July 2016, FDG-PET/CT and SL with peritoneal lavage and cytology are advised by the Dutch national guidelines for patients with a locally advanced tumor detected on CT (FDG-PET/CT in patients with ≥cT3 and/or cN+ tumors and SL in patients with ≥cT3 tumors)[1]. If no metastases are diagnosed, the recommended curative treatment consists of surgical resection by (sub)total gastrectomy with lymphadenectomy according to the Japanese Gastric Cancer Treatment Guidelines[14]. All patients with resectable gastric cancer

(clinical stage > I) are treated with perioperative chemotherapy similar or comparable to the MAGIC or FLOT4 trial if deemed fit enough[2,3,15]. Palliative treatment consists of systemic chemotherapy and palliative resection or radiotherapy in patients with symptoms, such as obstruction or bleeding.

Outcomes

The study outcomes included adherence to the national guidelines before and after publication of the new update of the guidelines (July 1st, 2016), waiting time from diagnosis to start of treatment, and number of non-curative procedures. Treatment in adherence to the revised guidelines was defined as the proportion of patients that underwent FDG-PET/CT or SL who had an indication for these diagnostic modalities as stated earlier, and the proportion of patients not undergoing these modalities if there was no indication. To evaluate waiting time, the time of diagnosis was defined as the date of the pathology report of the endoscopic biopsies confirming presence of gastric cancer and time of treatment was defined as either the start date of neoadjuvant therapy or the date of surgery in case of primary surgery. Since staging laparoscopy in clinical practice was frequently performed during the same procedure as the planned gastrectomy, it was decided not to perform an analysis on waiting time after SL for the group that underwent primary surgery. Non-curative procedures consisted of palliative gastrectomy (which was intended curative before the start of the procedure), construction of a bypass (i.e. no resection), or a futile procedure. In order to analyze the effects of FDG-PET/CT and SL on the rate of non-curative procedures, a sub selection was made, including all patients with curative intent with at least a ≥cT3 and/or N+ tumor, as this is the indication for performing FDG-PET/CT (≥cT3 and/or N+) or SL (≥cT3) according to the current Dutch guidelines.

Statistical analysis

Patient, tumor and treatment-related characteristics were evaluated and described, as was the frequency of missing values per variable. Missing values in time points to evaluate waiting time were imputed using means of the total cohort and other known time points during diagnostic work-up and treatment. Baseline characteristics were compared between patients undergoing or not undergoing FDG-PET/CT or SL, using χ^2, Student's t-tests or Mann-Whitney U tests, depending on type and distribution of the variable. Waiting time from diagnosis to start of treatment was visually inspected and because of a non-normally distribution logarithmically

transformed before performing univariable and multivariable linear regression analyses. In order to determine the differences in the proportion of non-curative procedures with or without FDG-PET/CT or SL, cross tables with $\chi 2$ statistics were generated. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY). Statistical significance was set at $p<0.05$.

RESULTS

Study population

In the Netherlands, 3818 patients underwent surgery for gastric adenocarcinoma in the period 2011–2018. A total of 508 patients were excluded, due to an emergency setting (n=165), prophylactic (n=26) or other resection than gastrectomy (n=58), missing CT-scans (n=30), missing time points (n=100) or missing data (n=129). Of the remaining 3310 patients, 1912 patients did not undergo either FDG-PET/CT or laparoscopy, 643 patients underwent FDG-PET/CT only, 396 patients underwent solely SL and 359 patients underwent both diagnostic modalities (Figure 1). Baseline characteristics are presented in Table 1. Patients undergoing FDG-PET/CT had more comorbidities compared to the other groups. Patients undergoing SL were younger, had a marginally lower BMI and more favorable ASA classification. Patients undergoing the diagnostic modalities were more frequently referred to a high-volume center and had more advanced tumors.

The majority of patients underwent neoadjuvant chemotherapy (55%), 50 patients (2%) underwent neoadjuvant chemoradiotherapy, 3 patients (<1%) neoadjuvant radiotherapy and 44% of patients did not undergo neoadjuvant treatment. In total, 86% underwent curative surgery, 4% palliative surgery, and in 10% no resection was performed (a futile procedure in 7% and construction of a bypass in 3%). Total gastrectomy was performed in 1235 patients (37%), and subtotal gastrectomy in 1749 patients (53%).

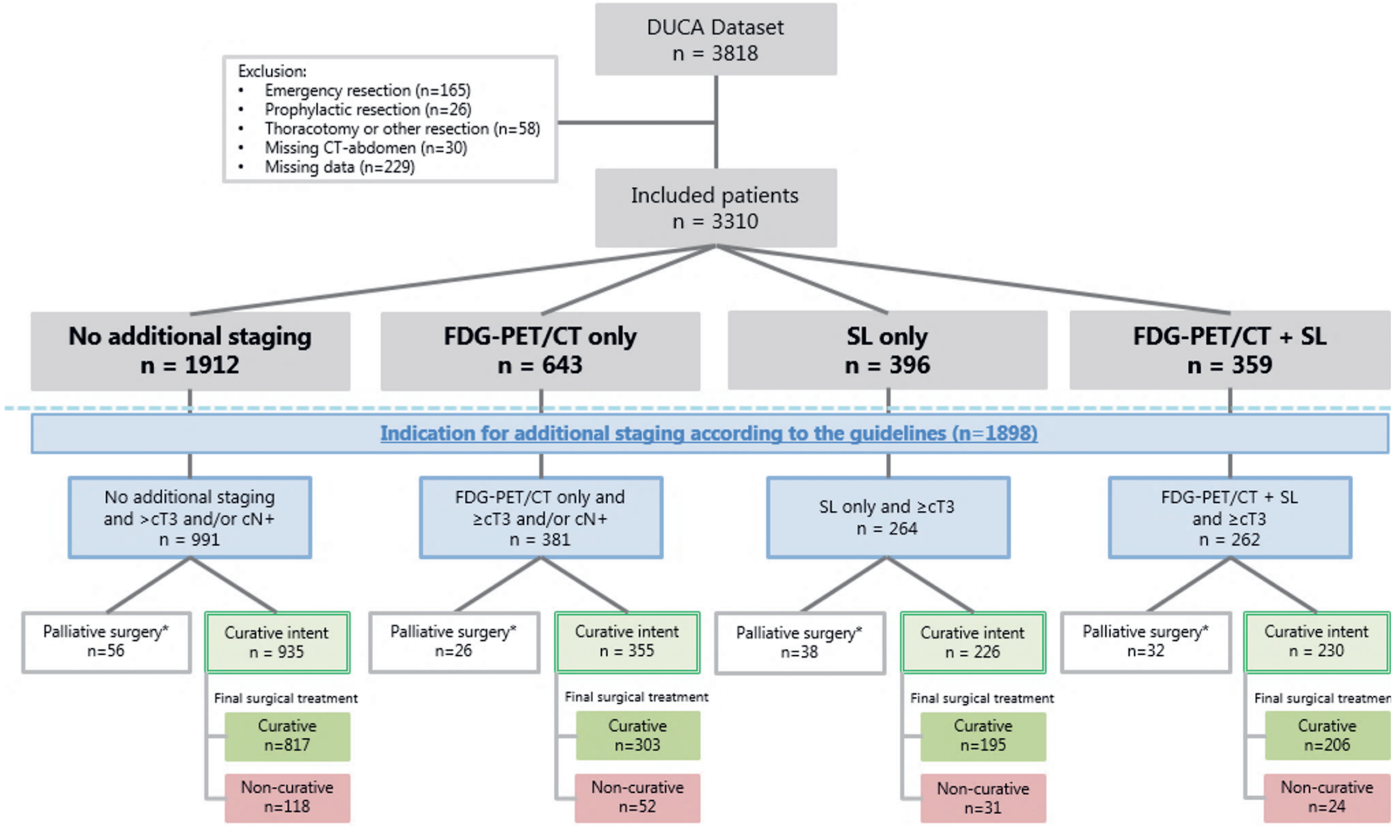

Figure 1. Study flowchart. *As determined prior to surgery. For the analysis on number of non-curative surgery, only patients with a curative intent of treatment, as was determined prior to surgery, were included (double outline). Final treatment represents the final treatment that has taken place, as was determined at the end of surgery.

Table 1. Baseline characteristics of 3310 patients who underwent surgery for gastric cancer

	No additional staging modalities n=1912	FDG-PET/CT n=643	Staging laparoscopy n=396	FDG-PET/CT and staging laparoscopy n=359	*p*-value	Missing values (%)
Patient characteristics						
Age, years (mean ± SD)	69.9 ± 11.7	69.7 ± 11.2	65.9 ± 11.7	66.8 ± 11.1	<0.001	0 (0)
BMI, kg/m^2 (mean ± SD)	25.4 ± 4.6	25.6 ± 4.3	24.7 ± 4.0	24.9 ± 4.4	0.003	63 (2)
Gender (%)					0.289	0 (0)
Male	1189 (62)	421 (66)	240 (61)	217 (60)		
Female	723 (38)	222 (35)	156 (39)	142 (40)		
ASA-classification					0.008	17 (1)
I-II	1270 (67)	418 (65)	296 (75)	251 (70)		
III-IV	629 (33)	221 (35)	100 (25)	108 (30)		
Comorbidities	1557 (81)	544 (85)	308 (78)	300 (84)	0.035	0 (0)
Cardiac[a]	609 (32)	232 (36)	85 (22)	103 (29)	<0.001	0 (0)
Vascular[b]	794 (42)	285 (44)	151 (38)	150 (42)	0.270	0 (0)
Diabetes mellitus	354 (19)	113 (18)	59 (15)	69 (19)	0.339	0 (0)
Pulmonary[c]	315 (17)	121 (19)	44 (11)	59 (16)	0.013	0 (0)
Malignancy[d]	302 (16)	147 (23)	61 (16)	67 (19)	0.001	65 (2)
Previous abdominal or thoracic surgery	770 (40)	280 (44)	150 (38)	142 (40)	0.292	5 (<1)
Tumor characteristics						
cT-stage					<0.001	0 (0)
<cT3	583 (42)	183 (38)	77 (23)	5818 (30)		
≥cT3[e]	810 (58)	303 (62)	264 (77)	262 (82)		
cTx	770 (23)	196 (20)	94 (13)	676 (27)		
cN-stage					<0.001	0 (0)
N0	1045 (63)	312 (56)	162 (45)	137 (40)		
N+	627 (38)	249 (44)	197 (55)	208 (60)		
Nx	373 (11)	96 (10)	51 (7)	322 (13)		
cM-stage					<0.001	0 (0)
M0	1790 (99)	594 (67)	347 (93)	317 (91)		
M1	22 (1)	20 (3)	28 (8)	32 (9)		
Mx	160 (5)	39 (4)	31 (4)	129 (5)		
Tumor location					<0.001	41 (1)
Fundus	104 (6)	78 (12)	29 (7)	38 (11)		
Corpus	577 (31)	213 (34)	148 (37)	128 (36)		
Antrum	858 (46)	226 (36)	139 (35)	127 (36)		
Pylorus	154 (8)	46 (7)	33 (8)	28 (8)		
Whole stomach	89 (5)	43 (7)	40 (10)	26 (7)		
Residual stomach	97 (5)	30 (5)	7 (2)	26 (7)		
Referral status					<0.001	280 (9)
Diagnosis in treatment hospital	635 (37)	168 (29)	108 (28)	69 (20)		
Diagnosis in other hospital	1075 (63)	420 (71)	274 (72)	281 (80)		
Hospital volume					<0.001	0 (0)
<20 gastrectomies	535 (28)	122 (19)	41 (10)	20 (6)		
20-40 gastrectomies	734 (38)	269 (42)	174 (44)	137 (38)		
>40 gastrectomies	643 (34)	252 (39)	181 (46)	202 (56)		

Percentages may not add up to 100% due to rounding. ASA: American Society of Anesthesiologists, BMI: Body Mass Index. a. Patients with a history of angina pectoris, myocardial infarction, congestive heart failure, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG), valve insufficiency or replacement, heart rhythm disorders, cardiomyopathy, status after heart transplant; b. Patients with hypertension of peripheral vascular disease; c. Patients with asthma or chronic obstructive pulmonary disease; d. Currently or previously treated malignancy other than gastric carcinoma; e. of which 1495 patients underwent curative treatment.

The mean (±SD) waiting time from diagnosis to start of treatment for all patients was 36 days (±18.9) for neoadjuvant treatment and 54 days (±31.7) for primary surgery.

FDG-PET/CT

Before implementation of the guidelines, FDG-PET/CT was performed in 323 out of 1389 patients (23%) for whom this would have been indicated according to the revised guidelines (≥cT3 and/or N+ tumors), whereas after implementation of the guidelines 354 out of 583 patients (61%) underwent FDG-PET/CT ($p<0.001$) (Figure 2). However, after implementation of the guidelines, the use of FDG-PET/CT also increased in patients in whom it was not recommended by these guidelines (17% versus 43%).

Concerning waiting times, multivariable linear regression analyses showed that FDG-PET/CT was associated with an additional waiting time of 4 days ($p<0.001$) in the patients who were treated with neoadjuvant chemotherapy. In the group of patients who underwent primary surgery, FDG-PET/CT was associated with 20 extra waiting days ($p<0.001$). These results are presented in Tables 2a and 2b.

Staging laparoscopy

Before implementation of the revised guidelines, SL was performed in 237 out of 1140 patients (21%) in whom this would have been indicated according to the revised guidelines (≥cT3 tumors). This percentage increased to 58% (289 out of 499, $p<0.001$) after implementation of the revised guidelines (Figure 2). Additionally, the use of SL also increased in patients in whom there was no indication according to the revised guidelines after its implementation (from 8% to 32%).

SL was associated with an additional waiting time of 8 days ($p<0.001$) to the start of neoadjuvant chemotherapy in the group of patients that received neoadjuvant chemotherapy (Table 2a).

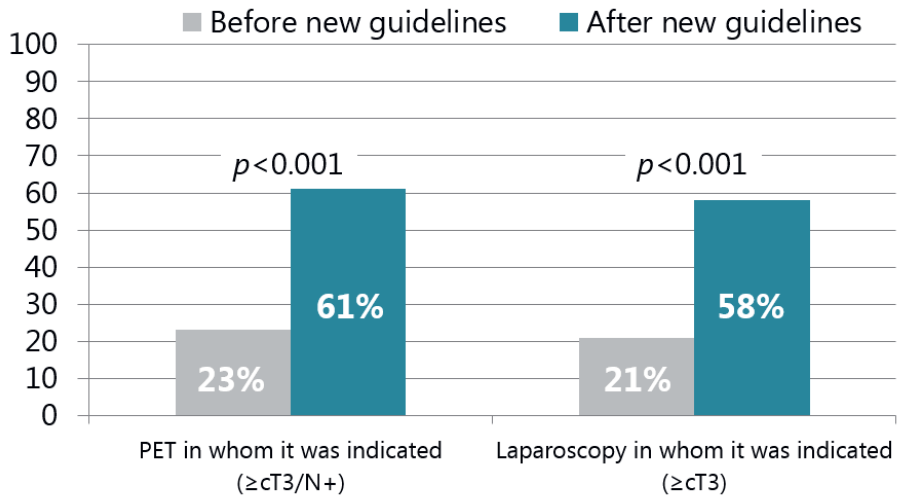

Figure 2. Use of FDG-PET/CT and SL before and after implementation of the revised national guidelines

Table 2a. Waiting time to neoadjuvant treatment. Multivariable linear regression analyses on the influence of patient, tumor and diagnostic characteristics on waiting time from diagnosis to start of neoadjuvant treatment (n=1808)

	Univariable **Mean waiting time (days, SD)**	Multivariable¥			
		B*	[95% CI]	Additional days	*p*-value
Modalities					
None	28.9 (± 15.9)	Ref	-	.	-
FDG-PET/CT	36.0 (± 18.5)	0.19	[0.07-0.31]	4	0.001
Staging laparoscopy	37.5 (±15.0)	0.34	[0.24-0.45]	8	<0.001
Both modalities	47.0 (± 23.9)	0.52	[0.41-0.62]	14	<0.001

*Intercept = 3.008 (20 days); ¥Adjusted for age, BMI, weight loss, comorbidities (overall, cardiac, pulmonary, previous malignancy, previous abdominal surgery), ASA, referral status, location of tumor, cT-stage, cN-stage, hospital volume.

Table 2b. Waiting time to surgical treatment. Multivariable linear regression analyses on the influence of patient, tumor and diagnostic characteristics on waiting time from diagnosis to primary surgical treatment with curative intent (n=1332)

	Univariable **Mean waiting time (days, SD)**	Multivariable¥			
		B*	[95% CI]	Additional days	*p*-value
FDG-PET/CT					
No	50.2 (± 28.3)	Ref	-	.	-
Yes	65.1 (±38.2)**	0.28	[0.20-0.36]	20	<0.001

*Intercept = 4.129 (62 days); ¥Adjusted for age, BMI, weight loss, comorbidities (overall, cardiac, pulmonary, previous malignancy, previous abdominal surgery), ASA, referral status, location of tumor, cT-stage, cN-stage, hospital volume. **Significantly different

In all patients who underwent either solely staging laparoscopy (n=396) or both modalities (n=359), staging laparoscopy identified metastases or irresectable disease in 76 patients (10%, numbers not shown in Figure 1) resulting in a preoperatively determined palliative intent in these patients. In the group of patients who have not undergone either FDG-PET/CT or staging laparoscopy (n=1912), a palliative intent of treatment was registered in 67 patients (4%), versus 36 patients (6%) in the group of patients who underwent solely FDG-PET/CT (n=643).

Non-curative surgery

For analyzing the effects of FDG-PET/CT and staging laparoscopy on the number of non-curative resections as determined at the end of the procedure, only those patients with at least a cT3 and/or N+ tumor and curative intent were selected. A total of 1746 patients with at least a cT3 and/or N+ tumor were treated with curative intent (Figure 1). Of these, 225 patients (13%) were eventually registered at the end of the surgical procedure as having undergone non-curative surgery, consisting of 51 patients in whom a palliative resection had been performed, 57 patients who received a bypass (i.e. no resection), and 117 patients who underwent a futile procedure. The incidence of intraoperatively determined non-curative surgery did not differ between the patient groups undergoing one or both of the staging modalities (13% after none; 15% after FDG-PET/CT; 14% after SL; 10% after both modalities, p=0.492).

DISCUSSION

In this population-based study, the implementation of FDG-PET/CT and SL for patients with gastric cancer in the Netherlands and their association with logistics and proportion of non-curative procedures were evaluated. After revision of the national guidelines in July 2016, which now recommends FDG-PET/CT and SL in patients with locally advanced tumors, significantly more FDG-PET/CTs and SLs were performed. Remarkably, the increase in PET/CT and SL was not only observed in patients with an indication for these modalities according to the guidelines, but also in patients without a predefined indication. This may be due to treating physicians becoming more aware of the possible value of FDG-PET/CT and SL, and therefore requesting these procedures also in other patients who they regard at increased risk for metastases. Referral to a high-volume center more frequently resulted in performing FDG-PET/CT and SL, which was

associated with a significantly longer waiting time from diagnosis to start of treatment. Performing SL or both modalities consecutively may not be associated with the incidence of non-curative surgery.

Although FDG-PET/CT and SL were more frequently performed for locally advanced gastric tumors, around 40% of the patients in whom this was indicated, still did not undergo FDG-PET/CT and SL in the current study. This might be explained by a lag time between publication of guidelines and their adoption in clinical practice[16]. Several general barriers for adoption of new guidelines have been identified and reported, such as lack of awareness, lack of agreement with the new guidelines, and lack of outcome expectancy[16]. Interventions to promote the implementation of research findings include educational outreach visits[17]. As part of the PLASTIC-study[18] – a prospective observational cohort study in the Netherlands that evaluates the impact and cost-effectiveness of FDG-PET/CT and SL in addition to initial staging (CT and gastroscopy) in patients with locally advanced gastric cancer –, these educational visits started in August 2017. Other factors that have been reported to contribute to slow implementation are qualities of the guidelines (such as compatibility with existing beliefs and values, or complexity), characteristics of the health care practice setting (including legal and financial aspects) and characteristics of the healthcare professional (e.g. age)[19]. Besides delayed adoption of the revised guidelines in clinical practice, there might be other factors contributing to not performing FDG-PET/CT or SL in appropriate patients. General reasons for refraining from SL may include older age (as older patients are more frail and have more comorbidities), tumors causing complications (e.g. obstruction, hemorrhage, perforation), and a history of prior upper abdominal surgery with severe adhesions[20,21].

In the current study, 32-43% of patients underwent FDG-PET/CT or SL although there was no indication according to current guidelines. In this context, it is important to note that clinical staging of gastric cancer is known to be inaccurate[5,6,22-24]. Several reasons to perform additional diagnostics in patients with lower tumor stages may exist, such as excessive weight loss or previous malignancy, which might increase the clinical suspicion of occult metastases. Nevertheless, considering additional diagnostics in patients for whom there is no accepted indication according to guidelines should be performed with care, as longer waiting times impair quality of life and might allow for tumor progression. Other possible disadvantages include

higher diagnostic health care costs, incidental findings which require further investigations, and possible morbidity due to SL. To slightly elaborate on the costs: a FDG-PET/CT costs €1200 on average [25] and a SL costs €900 on average, based on the minute price of the operating room (including operating room, nurses, surgeon, anesthesiologist, overhead)[26]. However, results of the PLASTIC-study have to be awaited in order to make statements on the economic aspects.

Although literature on whether or not high-volume centers follow directives more frequently is not available, the current study concluded that FDG-PET/CT and SL were more frequently performed in higher volume centers. It has been reported previously that centralization of gastric cancer care in high-volume centers in the Netherlands resulted in improved postoperative outcomes[11,27]. The results of the current study confirm that referral of patients to high-volume centers may result in better health care, by providing clinical care in accordance to the guidelines.

Baseline waiting times found in the current study fall within the indicated waiting times advised and aimed at by Dutch guidelines[28]. In addition, baseline waiting times were comparable to previously reported median waiting times of 4.6 weeks to start of neoadjuvant treatment and 6 weeks to primary surgery[29]. Performing FDG-PET/CT or SL was associated with a significantly prolonged waiting time from diagnosis to start of treatment, both for neoadjuvant treatment (although clinically less relevant) and primary surgical treatment. Patients undergoing primary surgery are usually older, have several comorbidities and are therefore not deemed fit enough for chemotherapy[30,31]. It is possible that in these patients, additional findings are more frequently detected on FDG-PET/CT or during SL, for which further diagnostics are required. Other confounding factors might also contribute to increasing waiting times. For example, generally increasing waiting times due to pressure on the health care system and centralization of gastric cancer treatment might play a role, as patients had to be referred to tertiary centers more often over the years. Regardless of potential causes, it is questionable what the clinical relevance of the reported extended waiting times is, since previous studies suggested that additional waiting time of some weeks does not lead to decreased long-term survival[29].

Smyth et al. conducted a study with 113 locally advanced gastric cancer patients (cT3-4) and reported a 10% reduction in the number of futile procedures after performing a FDG-PET/CT and a decrease of 19% after SL[8]. Findlay et al. performed a study with 279 gastric cancer patients

and reported unsuspected metastases found with FDG-PET/CT in 7%[32]. In a study from Bosch et al., additional metastases were detected in 16% of 105 patients[33]. These findings on FDG-PET/CT resulted in a treatment change from curative to palliative intent and prevention of futile surgery with accompanying morbidity in these patients. Unfortunately, as DUCA does not register patients in whom surgery was omitted based on findings on FDG-PET/CT, results of our study cannot confirm nor refute these results. Regarding the detection of metastatic or irresectable disease in case of SL, literature on the yield of SL varies from detection rates of 19-52% and the percentage found in this study (10%) does not completely support these previously published numbers[8,34-36]. An explanation for this might be that also peritoneal lavage is included in the aforementioned studies and scored as positive SL, whereas in the current dataset, neither information on whether peritoneal lavage has been performed nor outcomes of the SL are registered. In our study, no difference was found in the number of intraoperatively determined non-curative procedures when comparing the performance of no, solely one or both staging modalities. However, it should be noted that this has been analyzed during the implementation phase of the guideline.

Several other limitations apply to the current study. First, no data on outcomes of FDG-PET/CT are available and patients not undergoing surgery are not registered in DUCA, as this is a surgical registry, which could have resulted in an underestimation of the proportions reported in this study. Therefore, it is not possible to draw firm conclusions on treatment changes based on FDG-PET/CT findings. Second, the dataset used for this study does not contain histopathology data, while several studies report that FDG-PET/CT may specifically be useful in patients with specific tumor biology or characteristics, such as intestinal type or poorly differentiated adenocarcinomas[6,24]. For these reasons, results of the PLASTIC-study, evaluating also histopathology data, have to be awaited[18].

CONCLUSION

This population-based study demonstrates that FDG-PET/CT and SL have increasingly been used in patients with locally advanced gastric tumors in the Netherlands, mainly in high-volume centers, at the expense of prolonged waiting times from diagnosis to start of treatment. No difference in the proportion of non-curative procedures was found when performing SL or both modalities consecutively in the patients who had an indication. However, it should be noted that no firm conclusions can be made on solely performing FDG-PET/CT and therefore the results of the PLASTIC-study should be awaited. Future studies need focusing on patient selection for FDG-PET/CT and SL and potential consequences of prolonged waiting times.

REFERENCES

1. Integraal Kankercentrum Nederland. Diagnostiek, behandeling en follow-up van het maagcarcinoom 2016 2016:1–7. http://www.oncoline.nl/uploaded/docs/Maagcarcinoom/Richtlijn maagcarcinoom.pdf.
2. Cunningham D, Allum WH, Stenning SP, et al. Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. N Engl J Med 2007:11–20.
3. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ra. Lancet 2019;393:1948–57. https://doi.org/10.1016/S0140-6736(18)32557-1.
4. Integraal Kankercentrum Nederland. Richtlijn Diagnostiek, behandeling en follow-up van het maagcarcinoom 2009.
5. Choi JY, Shim K-N, Kim S-E, et al. The Clinical Value of 18F-Fluorodeoxyglucose Uptake on Positron Emission Tomography/Computed Tomography for Predicting Regional Lymph Node Metastasis and Non-curative Surgery in Primary Gastric Carcinoma 2014;64:340–7.
6. Seevaratnam R, Cardoso R, McGregor C, et al. How useful is preoperative imaging for tumor, node, metastasis (TNM) staging of gastric cancer? A meta-analysis. Gastric Cancer 2012;15.
7. Wang Z, Chen J-Q. Imaging in assessing hepatic and peritoneal metastases of gastric cancer: a systematic review. BMC Gastroenterol 2011;11:19. https://doi.org/10.1186/1471-230X-11-19.
8. Smyth E, Schöder H, Strong VE, et al. A prospective evaluation of the utility of 2-deoxy-2-[18F] fluoroglucose positron emission tomography and computed tomography in staging locally advanced gastric cancer. Cancer 2012;118:5481–8.
9. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, et al. Early outcomes from the Dutch Upper Gastrointestinal Cancer Audit. Br J Surg 2016;103:1855–63.
10. Washington K. 7th edition of the AJCC cancer staging manual: Stomach. Ann Surg Oncol 2010;17:3077–9.
11. Haverkamp L, Ruurda JP, van der Sluis PC, et al. Chirurgische behandeling van maagcarcinoom: Focus op centralisatie en laparoscopische resecties. Ned Tijdschr Geneeskd 2013;157:1–6.
12. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, Early outcomes from the Dutch Upper Gastrointestinal Cancer Audit. Br J Surg 2016;103:1855–63.
13. Nelen SD, Heuthorst L, Verhoeven RHA, et al. Impact of Centralizing Gastric Cancer Surgery on Treatment, Morbidity, and Mortality. J Gastrointest Surg 2017;21:2000–8.
14. Sano T, Kodera Y. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011;14:101–12.
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. Cabana MD, Rand CS, Powe NR, et al. Why Don ' t Physicians Follow A Framework for Improvement. Jama 1999;Vol 282:1458–65.
17. Bero LA, Grilli R, Grimshaw JM, et al. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. Br Med J 1998;317:462.
18. Brenkman HJF, Gertsen EC, Vegt E, van Hillegersberg R, van Berge Henegouwen MI, Gisbertz SS, et al. Evaluation of PET and laparoscopy in STagIng advanced gastric cancer: A multicenter prospective study (PLASTIC-study). BMC Cancer 2018;18:1–7.
19. Davis DA, Taylor-Vaisey A. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. CAN MED ASSOC J 1997;157:408–16.
20. Machairas N, Charalampoudis P, Molmenti EP, et al. The value of staging laparoscopy in gastric cancer. Ann Gastroenterol 2017;30.
21. Society of American Gastrointestinal and Endoscopic Surgeons. Guidelines for diagnostic laparoscopy. vol. 13. 1999.

22. Kwee RM, Kwee TC. Imaging in assessing lymph node status in gastric cancer. Gastric Cancer 2009;12:6–22.
23. Borggreve AS, Goense L, Brenkman HJF, Mook S, Meijer GJ, Wessels FJ, et al. Imaging strategies in the management of gastric cancer: Current role and future potential of MRI. Br J Radiol 2019;92.
24. Kwee RM, Kwee TC. Imaging in local staging of gastric cancer: A systematic review. J Clin Oncol 2007;25:2107–16.
25. Dutch Healthcare Authority (Nederlandse Zorgautoriteit). Performance and Tariffs Specialist Medical Care (Prestaties en tarieven medisch-specialistische zorg) 2017.
26. Bolkenstein HE, de Wit GA, Consten ECJ, et al. Cost-effectiveness analysis of a multicentre randomized clinical trial comparing surgery with conservative management for recurrent and ongoing diverticulitis (DIRECT trial). Br J Surg 2019;106:448–57.
27. Busweiler LAD, Dikken JL, Henneman D, et al. The influence of a composite hospital volume on outcomes for gastric cancer surgery: A Dutch population-based study. J Surg Oncol 2017;115:738–45.
28. Stichting Oncologische Samenwerking. Multidisciplinaire Normering Oncologische Zorg in Nederland. PodoPost 2017.
29. Brenkman HJF, Visser E, van Rossum PSN, Siesling S, van Hillegersberg R, Ruurda JP. Association Between Waiting Time from Diagnosis to Treatment and Survival in Patients with Curable Gastric Cancer: A Population-Based Study in the Netherlands. Ann Surg Oncol 2017;24:1761–9.
30. Sheng S, Chen Y, Li C. Outcomes of laparoscopic total gastrectomy for elderly gastric cancer patients. J Cancer 2018;9:4398–403.
31. Saif MW, Makrilia N, Zalonis A, et al. Gastric cancer in the elderly: An overview. Eur J Surg Oncol 2010.
32. Findlay JM, Antonowicz S, Segaran A, et al. Routinely staging gastric cancer with 18 F-FDG PET-CT detects additional metastases and predicts early recurrence and death after surgery. Eur Radiol 2019;29:2490–8.
33. Bosch KD, Chicklore S, Cook GJ, et al. Staging FDG PET-CT changes management in patients with gastric adenocarcinoma who are eligible for radical treatment. Eur J Nucl Med Mol Imaging 2019.
34. Ikoma N, Blum M, Chiang YJ, et al. Yield of Staging Laparoscopy and Lavage Cytology for Radiologically Occult Peritoneal Carcinomatosis of Gastric Cancer. Ann Surg Oncol 2016;23:4332–7.
35. Groh EM, Gupta S, Brown ZJ, Enewold L, Gamble LA, Hernandez JM, et al. Staging Laparoscopy is Underutilized in the Management of Gastric Adenocarcinoma. Ann Surg Oncol n.d.
36. Fukagawa T. Role of staging laparoscopy for gastric cancer patients. Ann Gastroenterol Surg 2019;3:496–505.

Chapter 5

FDG-PET/CT and laparoscopy for staging of locally advanced gastric cancer: a multicentre prospective Dutch cohort study (PLASTIC)

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ABSTRACT

Background: The optimal staging for gastric cancer remains a matter of debate. This multicentre prospective observational study evaluated the value of 18F-fludeoxyglucose–positron emission tomography with computed tomography (FDG-PET/CT) and staging laparoscopy (SL) in addition to initial staging by means of gastroscopy and CT in patients with locally advanced gastric cancer.

Methods: Patients with a locally advanced, clinically curable gastric adenocarcinoma (≥cT3 and/or N+, M0 based on CT) were prospectively included and underwent FDG-PET/CT and/or SL. The primary outcomewas the number of patients in whom the intent of treatment changed based on the results of these 2 investigations. Secondary outcomes included diagnostic performance, number of incidental findings on FDG-PET/CT, morbidity and mortality after SL, and diagnostic delay.

Results: Of the 394 patients included, 256 (65%) were men and mean (SD) age was 67.6 (10.7) years. A total of 382 patients underwent FDG-PET/CT and 357 underwent SL. Treatment intent changed from curative to palliative in 65 patients (16%) based on the additional FDG-PET/CT and SL findings. FDG-PET/CT detected distant metastases in 12 patients (3%), and SL detected peritoneal or locally nonresectable disease in 73 patients (19%), with an overlap of 7 patients (2%). FDG-PET/CT had a sensitivity of 33% (95%CI, 17%-53%) and specificity of 97% (95%CI, 94%-99%) in detecting distant metastases. Secondary findings on FDG/PET were found in 83 of 382 patients (22%), which led to additional examinations in 65 of 394 patients (16%). Staging laparoscopy resulted in a complication requiring reintervention in 3 patients (0.8%) without postoperative mortality. The mean (SD) diagnostic delay was 19 (14) days.

Conclusion: This study's findings suggest an apparently limited additional value of FDG-PET/CT; however, SL added considerably to the staging process of locally advanced gastric cancer by detection of peritoneal and nonresectable disease. Therefore, it may be useful to include SL in guidelines for staging advanced gastric cancer, but not FDG-PET/CT.

BACKGROUND

Gastric cancer is the third leading cause of cancer related death worldwide and accounted for more than 1 million patients with newly diagnosed gastric cancer in 2018[1]. In Western countries, the recommended treatment with curative intent is subtotal or total gastrectomy with lymphadenectomy, with perioperative chemotherapy in case of locally advanced tumors[2,3]. Prognosis mainly depends on tumor stage; recurrences occur in up to 60% of patients after Surgery[4], with the peritoneum most frequently involved[5,6]. For detecting non-curable disease, the accuracy of staging using gastroscopy and computed tomography (CT) of the thorax and abdomen is limited[7,8]. As a result, some patients incorrectly undergo treatment with curative intent, exposing them to the risk of complications of surgery and perioperative chemotherapy. If non-curable disease could be detected accurately before initiation of treatment, more tailored and less toxic palliative treatment can be offered[9-11].

To accurately detect non-curable gastric cancer, the role of other preoperative staging modalities, such as ^{18}F-fludeoxyglucose-positron emission tomography with CT (FDG-PET/CT) and staging laparoscopy (SL) has increased over the years. A study in patients with locally advanced gastric cancer reported that FDG-PET/CT detected additional distant metastases in 10% of patients, whereas SL detected peritoneal metastases in 19%, preventing futile treatment and improving quality of life of patients and cost-effectiveness[12]. As a result, several international guidelines now advise to perform FDG-PET/CT and SL in patients with locally advanced gastric cancer in addition to initial staging with CT and gastroscopy[2,3,13]. Although the evidence for performing SL is strong in Asian populations, the evidence for both SL and FDG-PET/CT in Western populations is limited. Therefore, the aim of the present study (Evaluation of FDG-PET/CT and Laparoscopy in Staging Advanced Gastric Cancer [PLASTIC], a Dutch multicenter prospective study) was to evaluate the value of FDG-PET/CT and SL in addition to initial staging in patients with locally advanced gastric cancer.

METHODS

Study design

The protocol of this multicenter prospective, observational cohort study has been published[13]. Inclusion criteria consisted of patients with a histologically proven adenocarcinoma of the stomach or gastroesophageal junction (Siewert type III); patients having undergone a CT scan of the thorax/abdomen; patients with locally advanced gastric cancer, defined either as transmural and invading the outer layer of the stomach or involving at least 1 lymph node, as reported on CT (≥cT3 and/or N+, M0 category according to the seventh edition of the American Joint Committee on Cancer TNM staging system)[13,14]; surgically resectable gastric cancer (<cT4b); and patients considered fit for treatment with curative intent (surgery with or without chemotherapy), as determined by the multidisciplinary team (MDT). In all centers in the Netherlands with patients included in the study, MDTs are composed of upper gastrointestinal surgeons, radiologists/nuclear medicine physicians, medical oncologists, gastroenterologists, radiation oncologists, and pathologists. Patients in whom it was not possible to make a clear distinction between cT2 and cT3 cancer based on CT scan or endoscopic ultrasonographic findings were also included. Data on race and ethnicity were not included in the electronic case report forms.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki of 1964 and later versions[15]. Because this study does not allocate patients to interventions other than standard of care according to national guidelines, this study does not fall within the Medical Research Involving Human Subjects Act (WMO). A non-WMO declaration (METC 16-633/C) has been obtained from the Medical Ethical Review Board of the University Medical Center Utrecht, Utrecht, the Netherlands. In addition, the trial was approved by the institutional review board in each of 18 participating centers (eAppendix in Supplement 1). Because questionnaires and financial hospital data were required for a side study, written informed consent was obtained. Patients did not receive financial compensation.

Patients who met the inclusion criteria as determined by the MDT were invited to participate in the study in 1 of the 18 Dutch centers. All 18 centers participated in a regional MDT including at least 1 surgical high-volume center (>20 procedures). Surgical procedures were performed in 13

high-volume centers. In the Netherlands, centralization of gastric cancer treatment was initiated in 2013, meaning that only hospitals in which at least 20 gastrectomies are performed annually are considered sufficiently competent to perform this type of surgery.

Procedures

After written informed consent was obtained, patients were enrolled in the study and underwent FDG-PET/CT and/or SL as standard of care according to Dutch national guidelines. Ideally, FDG-PET/CT was performed first, followed by SL if no distant metastases were found on FDG-PET/CT. Staging laparoscopy was performed as a separate procedure in patients scheduled for neoadjuvant chemotherapy or otherwise at the onset of gastrectomy. The protocol for performing FDG-PET/CT and SL is summarized in the eMethods in Supplement 1 and was previously published[13]. The FDG avidity of the primary tumor and lymph nodes and the presence of distant metastases were scored as yes, equivocal, or no, and distant metastases were scored as suspicious, equivocal, or no at the discretion of the nuclear medicine physician. Staging laparoscopy reported the location and extent of peritoneal metastases and local resectability, and it was recommended to perform peritoneal lavage with cytologic testing. Based on the results of both investigations, the final treatment strategy was determined at the subsequent MDT meeting.

Outcomes

The primary outcome of the study was the number of patients in whom the treatment intent was changed from curative to palliative based on the results of the FDG-PET/CT or SL. Secondary outcomes were the diagnostic performance (sensitivity and specificity) of both modalities, number of incidental findings on FDG-PET/CT, morbidity of SL, diagnostic delay, quality of life, and cost-effectiveness. All patient data were prospectively registered using electronic case report forms[13].

Statistical analysis

Factors associated with FDG avidity were evaluated using the χ^2 test or Fisher exact test when appropriate. For modality-specific performance, sensitivity and specificity with 95% CIs were calculated. By means of cross tabulation of the index test results against those of the reference standard, the sensitivity and specificity of the index test were estimated[16,17]. A priori–determined

subgroup analyses for specific patient and tumor characteristics were performed as described in the study protocol[13]. For FDG-PET/CT, the reference standard for positivity was biopsy or additional imaging, and for negativity, clinical follow-up of 6 months. For SL, biopsy findings from macroscopically suspicious lesions were the reference standard for positivity, and false-negative findings were defined as peritoneal metastases found at the onset of gastrectomy or within 6 months after an initially negative SL result. Members of the study team were not blinded to the results. All statistical analyses were performed using SPSS, version 25.0 (IBM Corp), and a 2-sided, unpaired *p*-value <0.05 was considered statistically significant.

RESULTS

Study population

Between August 1, 2017, and February 1, 2020, a total of 407 patients with locally advanced gastric cancer were included in 18 centers in the Netherlands. Two centers included more than 40 patients, 6 centers included 20 to 40 patients, and the remaining centers included fewer than 20 patients. In total, 13 patients were excluded: 9 patients were registered twice (in the referring and tertiary hospitals), a palliative intent was already decided for 2 patients during the first MDT meeting, and 2 patients were excluded because neither FDG-PET/CT nor SL was performed (Figure). Of the 394 included patients, 256 (65%) were men and 138 (35%) were women; mean (SD) age was 67.6 (10.7) years; other patient characteristics are presented in Table 1.

FDG-PET/CT scan

Of the 394 patients, 382 patients underwent FDG-PET/CT, revealing an FDG-avid primary tumor in 302 patients (79%). A more frequent association was noted between FDG avidity and male sex, positive lymph nodes on CT imaging, gastroesophageal junction tumor location, and intestinal type tumor (Table 2).

FDG-PET/CT results were suspicious for distant metastases in 16 patients (4%) and equivocal in 22 patients (6%). Metastatic disease was confirmed in 12 patients (3%); findings were suspicious on FDG-PET/CT in 10 patients and equivocal in 2 patients. These metastases were located in distant lymph nodes (n=4), liver (n=3), peritoneum (n=3), uterus (n=1), and bone (n=1). Of

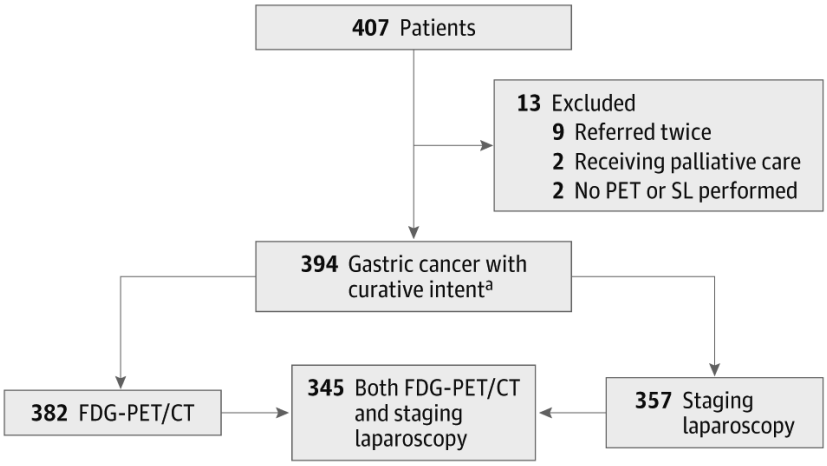


Figure Flowchart of inclusion and exclusion criteria.

these 12 patients with confirmed M1 category, 11 also had clinically positive locoregional lymph nodes and 2 patients had a cT4 tumor

The sensitivity of FDG-PET/CT for detection of distant metastases was 33% (95% CI, 17%-53%), and for specificity, 97% (95% CI, 94%-99%) (eTable, A in Supplement 1). In the subgroup of patients with an FDG-avid primary tumor, sensitivity was 31% (95% CI, 14%-55%), and for specificity, 98% (95% CI, 95%-99%) (eTable, B in Supplement 1). In subgroup analyses for patients with peritoneal metastases, cT4 tumors or cN+ status, the diagnostic accuracy of FDG-PET/CT did not improve (eTables, C-E in Supplement 1).

Of the total cohort of 382 patients, a clinically relevant lesion was found in 83 (22%) of 132 patients with suspected relevant secondary findings, resulting in additional investigations in 60 patients (Table 3). In 7 of 83 patients (8%) a second primary tumor was confirmed (3 colon, 2 lung, and 2 prostate cancers), but in most of these 83 patients, follow-up was not reported.

Table 1. Baseline characteristics of 394 included patients

	No. (%)	Missing values (%)
Patient characteristics		
Age, years (mean ± SD)	67.6 ± 10.7	0 (0)
Gender (male, %)	256 (65)	0 (0)
Diagnostics		
Gastroscopy (yes)	394 (100)	0 (0)
CT-thorax/abdomen (yes)	394 (100)	0 (0)
EUS (yes)	70 (18)	1 (<1)
Tumour characteristics		
cT-stage		0 (0)
T1	0 (0)	
T2	28 (7)	
T3	301 (76)	
T4	56 (14)	
Tx	9 (2)	
cN-stage		0 (0)
N0	177 (45)	
N1	126 (32)	
N2	72 (18)	
N3	13 (3)	
Nx	6 (2)	
Tumour location		6 (2)
Cardia	94 (24)	
Corpus	110 (28)	
Antrum	125 (32)	
Pylorus	33 (8)	
Diffuse	26 (7)	
Lauren classification		0 (0)
Intestinal	118 (30)	
Diffuse	135 (34)	
Mixed	19 (5)	
Unknown	122 (31)	
Tumour differentiation		176 (45)
Well	15 (4)	
Moderate	92 (23)	
Poorly	108 (27)	
Undifferentiated	3 (1)	
ERBB2 status*		261 (66)
Positive	18 (5)	
Negative	115 (29)	

Percentages may not total 100% owing to rounding. CT computed tomography; EUS endoscopic ultrasound; SD standard deviation. *Formerly *HER2/*neu

Staging laparoscopy

Of the 394 patients, 357 underwent SL and 264 (74%) also underwent peritoneal lavage for cytologic testing. Staging laparoscopy identified suspicious peritoneal lesions in 62 patients (17%), with metastatic disease confirmed in 44 of 357 patients (12%) patients: in 31 by histologic testing, 2 by cytologic testing, and 11 by both tests. Of 295 patients with no or low clinical suspicion during SL, biopsies were performed in 54 patients (18%) and peritoneal lavage was

performed in 223 patients (76%). Metastatic disease was still found in 25 patients: in 6 by histologic characteristics of biopsy samples that were not expected by the surgeon to be metastases, 17 by cytologic examination, and in 2 by both tests. Of all 357 patients who underwent SL, a nonresectable tumor was identified in 13 patients: 4 patients solely because of a T4b tumor and 9 patients who also had peritoneal metastases. Altogether, SL findings were positive in 73 patients (19%). Positive SL findings were significantly associated with cT4 tumor category (39% vs 17% cT3 tumors; p=0.001) and diffuse-type tumors (21% vs 14% intestinal types; p=0.006).

Staging laparoscopy results were false-negative in 11 patients. Hence, the sensitivity of SL for detection of macroscopically peritoneal metastases was 82% (95% CI, 70%-91%) and specificity was 78% (95% CI, 73%-83%) (eTable, F in Supplement 1).

Table 2. FDG-PET/CT avidity of primary tumour and tumour characteristics

	FDG-avidity primary tumour			
Variable	Yes	Equivocal	No	*p*-value
Sex (n=381)				0.001
Male	206 (83)	33 (13)	9 (4)	
Female	96 (72)	18 (14)	19 (14)	
Site (n=375)				<0.001
Gastroesophageal junction	90 (97)	3 (3)	0 (0)	
Corpus	75 (71)	17 (16)	14 (13)	
Antrum	96 (81)	15 (13)	8 (7)	
Pylorus	23 (74)	7 (23)	1 (3)	
Diffuse	16 (62)	6 (23)	4 (15)	
cT category (n=373)				0.422
cT2	20 (71)	5 (18)	3 (11)	
cT3	232 (79)	39 (13)	21 (7)	
cT4	47 (89)	4 (8)	2 (4)	
cN category (n=376)				0.029
cN0	122 (72)	31 (18)	16 (9)	
cN1	98 (80)	17 (14)	8 (7)	
cN2	67 (94)	1 (1)	3 (4)	
cN3	11 (85)	2 (15)	0 (0)	
Lauren classification (n=261)				<0.001
Intestinal	106 (91)	6 (5)	4 (3)	
Diffuse	81 (63)	28 (22)	19 (15)	
Mixed	14 (82)	1 (6)	2 (12)	
Differentiation (n=212)				0.017
Well	12 (86)	2 (14)	0 (0)	
Moderate	84 (92)	4 (4)	3 (3)	
Poorly	75 (72)	17 (16)	12 (12)	
Undifferentiated	3 (100)	0 (0)	0 (0)	

For this analysis, only patients in whom the designated tumor characteristics were registered were taken into account. Percentages may not total 100% owing to rounding. FDG-PET/CT ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography.

Table 3. FDG-PET/CT results in 382 patients with advanced (≥cT3 and/or N+) gastric adenocarcinoma with curative intent

	No. (%)	Missing values (%)
FDG-avidity of primary tumour		1 (<1)
No	28 (7)	
Equivocal	51 (13)	
Yes	302 (79)	
Maximum SUV, median (SD)	10.5 ± 8.0	270 (68)
Lymph nodes avid		5 (1)
No	225 (60)	
Equivocal	20 (5)	
Yes, location:	132 (35)	
Lesser curvature	98 (26)	
Greater curvature	13 (3)	
Paracardial	12 (3)	
Locoregional NOS	45 (12)	
Suspicion of metastatic disease		0 (0)
No	344 (90)	
Equivocal	22 (6)	
Yes, location:	16 (4)	
Liver	8 (2)	
Lung	8 (2)	
Bone	4 (1)	
Peritoneum	4 (1)	
Distant lymph nodes	15 (4)	
Corpus uteri	1 (<1)	
cM1 category confirmed (n=38)		0 (0)
No	26 (7)	
Yes	12 (3)	
Secondary findings		1 (<1)
No	249 (65)	
Yes, clinically irrelevant*	49 (13)	
Yes, clinically relevant, location:	83 (22)	
Pulmonary	8 (2)	
Gastrointestinal	38 (10)	
ENT	5 (1)	
Thyroid	10 (3)	
Soft tissue	4 (1)	
Adrenal	1 (2)	
Prostate	3 (1)	
HPB	5 (1)	
Other	9 (2)	
Additional examination# (yes)	60 (16)	

Percentages may not total 100% owing to rounding. *Clinically irrelevant secondary findings such as hepatic cysts or adrenal adenomas. #Excluding 2 patients with clinically irrelevant secondary findings in whom additional examination was conducted. cM1 clinically M-stage; ENT ear, nose, and throat; FDG-PET/CT ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography; HPB hepato-pancreato-biliary; NOS not otherwise specified; SUV standardized uptake value

Staging laparoscopy resulted in postoperative complications in 3 patients (0.8%): luxation of a simultaneously placed feeding jejunostomy, a wound hematoma and bilateral adrenal bleeding, and a trocar incisional hernia with obstruction of the small intestine. All complications required surgical reintervention. No perioperative mortality was observed (Table 4).

Treatment changes

The combination of FDG-PET/CT and SL detected metastatic disease in 78 of 394 patients (20%), metastases in 12 patients (3%) were detected by FDG-PET/CT, metastases in 73 patients (19%) were detected by SL, and metastases in 7 patients (2%) were identified by both examinations. Theoretically, this finding should have resulted in a change of treatment intent in all these patients. All confirmed positive FDG-PET/CT findings (12 of 394 [3%]) resulted in a change from curative to palliative treatment intent. After positive SL findings, intent of treatment was changed to palliative in 60 of 73 patients (60 of 394 [15%]). Of the remaining 13 patients, 3 did not undergo resection owing to death during or shortly after neoadjuvant chemotherapy (n=2) or progression of disease (n=1). The other 10 patients had limited peritoneal metastases (n=3) or only positive cytologic test results (n=7) and underwent perioperative chemotherapy or chemoradiotherapy and surgical resection. Overall, the number of patients in whom treatment strategy changed from a curative to palliative intent was 65 of 394 (16%).

Diagnostic delay

Performing only FDG-PET/CT resulted in a mean (SD) of 17 (20) additional days, and performing only SL resulted in 17 (8) additional days until the second MDT meeting. When the investigations were performed consecutively, the delay was 19 (14) days if FDG-PET/CT had been initially performed and 18 (12) days if SL was performed first.

Table 4. Staging laparoscopy results of 357 patients who were diagnosed with advanced (≥cT3 and/or N+) gastric adenocarcinoma with curative intent

	No. (%)	Missing values (%)
Performed by		47 (12)
Surgeon	215 (60)	
Resident in presence of surgeon	97 (27)	
Resident	37 (10)	
Operation time (mean ± SD)	34.6 ± 25.8	4 (1)
All quadrants scored		87 (24)
No	14 (4)	
Yes	256 (72)	
Ascites		90 (25)
No	237 (66)	
Yes	30 (8)	
Adhesions		71 (20)
No	230 (64)	
Yes	56 (16)	
Bursa opened		83 (23)
No	202 (57)	
Yes	72 (20)	
Suspicion of peritoneal metastases		2 (1)
No	293 (82)	
Yes	62 (17)	
PCI score (median, IQR)	3 [1-8]	5 (1)
Histologic examination performed		6 (2)
No	237 (66)	
Yes	115 (32)	
Positive	**50 (14)**	5 (1)
Peritoneal washing performed		5 (1)
No	88 (25)	
Yes	264 (74)	
Positive	**32 (9)**	5 (1)
Locally resectable		13 (4)
No (cT4b)	**13 (4)**	
Yes	331 (93)	
Positive SL*		1 (<1)
No	284 (80)	
Yes	73 (20)	
SL performed		0 (0)
As separate procedure	342 (96)	
At the onset of gastrectomy	15 (4)	
Complicated postoperative course		29 (8)
No	325 (91)	
Yes	3 (1)#	
Surgical intervention	3 (1)	
Hospital stay, median (IQR)¥	0 [0-1]	79 (22)

Percentages may not total 100% owing to rounding. IQR interquartile range; PCI peritoneal cancer index; SD standard deviation; SL staging laparoscopy. *Positive SL is defined as positive cytology test findings, positive histologic test findings, or non-resectable disease. #In 1 patient, peritoneal as well as non-resectable disease was found. In this patients, the procedure was interrupted and no resection was performed. ¥In a patient with a wound hematoma and bilateral adrenal bleedings, the hospital stay was prolonged to 30 days.

DISCUSSION

This multicenter prospective, observational cohort study evaluated the outcomes associated with adding FDG-PET/CT and SL to the staging process of locally advanced gastric cancer. We found that FDG-PET/CT identified distant metastatic disease in 12 of 394 patients (3%) and SL identified noncurable disease in 73 patients (19%). In all 12 patients with positive FDG-PET/CT results, the finding of metastatic disease resulted in a change of treatment strategy from curative to palliative intent. In the 73 patients with positive SL findings, treatment strategy was changed to palliative intent in 60 patients (15%), with an overlap of 7 patients (2%) who also had a positive FDG-PET/CT. These results suggest a limited additional role of FDG-PET/CT and what appears to be a considerable benefit of SL on the staging process of gastric cancer.

Retrospective studies reported a possible additional role of FDG-PET/CT in the identification of distant metastatic disease in gastric cancer being positive in 6% to 16% of patients[18-22], but limited additional value in detecting other noncurable disease[18,19,21,23-28]. The present study found a much lower detection rate of 3% for distant metastases. Moreover, in 7 of 12 patients with positive FDG-PET/CT findings, metastatic disease was detected by SL, resulting in a negligible value of FDG-PET/CT. A possible reason for this difference may be that some patients with positive FDG-PET/CT results may not have been included in this study because regional centers may not have referred them to a participating center. To reduce this risk of this bias, multidisciplinary consultation lists were checked, and centers were asked to discuss all FDG-PET/CTs in the MDT meeting. In addition, the study by Smyth et al[12] applied the sixth edition of the TNM classification system, whereas our staging was based on the seventh and, when available, the eighth edition. The T3 and T4 tumors according to TNM-6, included by Smyth et al, correspond to category T4a and T4b tumors according to TNM-7 and TNM-8. Therefore, we included lower T-category tumors (T3, T4a, and T4b) than Smyth et al. However, the accuracy of PET/CT did not increase in subgroup analyses with T4 tumors. In our study, 79% of tumors were FDG avid, which is comparable to other studies[8,12,24,29,30], but less than has been reported in other types of cancer, such as esophageal cancer[18]. FDG avidity of the primary gastric tumor has previously been reported to be associated with male sex, intestinal type tumors, gastroesophageal junction tumors, and larger tumor size and depth[12,18,19,21,23-25,30-32]. Determining FDG avidity of diffuse-type gastric cancer is challenging in clinical practice, because it may be

interpreted as physiological uptake. Moreover, because FDG avidity of this type of tumor is generally lower, FDG-PET/CT will also be less sensitive for metastases of these tumors[18,19,23,33].

The limited number of metastases detected by FDG-PET/CT alone, the additional waiting time of at least 17 days, and the high number of incidental findings leading to additional investigations raise questions regarding the routine use of FDG-PET/CT in patients with gastric cancer. Cost-effectiveness and quality-of-life analyses of our data will be performed after additional follow-up and may identify a subset of patients (eg, those with gastroesophageal junction or intestinal type tumors) that benefits from additional staging by FDG-PET/CT. In addition, patients with high FDG avidity of the primary tumor may have an increased risk of distant metastasis. Models to estimate the probability of this outcome, based on histopathological and other tumor characteristics, have been developed, such as the model reported by Kaneko et al[34]. However, this model has limited predictive value and may benefit from further optimization.

By detecting noncurable disease in 19% of patients, SL was found to have a significant and clinically relevant added value in the staging of locally advanced gastric cancer. This finding supports the results of previous, mostly retrospective studies, reporting a yield of SL of 8% to 53%[35]. Treatment was not changed to a palliative approach in all 73 patients in the present study with a positive SL outcome; instead, some patients with limited peritoneal metastases and positive cytologic test findings were treated with curative intent. In line with previous studies[36-38], the present study detected positive cytologic characteristics in 9% of the patients. Although positive cytologic findings are regarded as metastatic disease by the American Joint Committee on Cancer TNM-8 classification system[39] and some international guidelines[2,40], no instructions exist on how to treat the patients with only positive cytologic findings. Some studies have reported a survival benefit when patients in whom a repeat SL showed a change from positive to negative cytologic findings following neoadjuvant chemotherapy undergo gastrectomy (hazard ratio, 0.42; 95% CI, 0.31-0.57; $p<0.001$)[38,41,42]. Adjuvant chemotherapy could also be considered in these patients, as other studies reported a survival gain in patients with positive cytologic test results who receive postoperative chemotherapy after a surgical resection compared with no chemotherapy (hazard ratio, 4.17; 95% CI, 3.01-5.78; $p=0.01$)[43]. Moreover,

some studies have evaluated hyperthermic intraperitoneal chemotherapy in patients with positive cytologic findings, but no high-level evidence is yet available[44,45]. The PERISCOPE-II trial is evaluating a possible survival benefit of hyperthermic intraperitoneal chemotherapy and cytoreductive surgery after systemic chemotherapy, including both patients with limited peritoneal disease and those with solely positive cytologic test results of peritoneal fluid or peritoneal washing[46].

Regarding the risks of SL, research has suggested that the morbidity of SL does not outweigh the benefits[29]. The present study noted metastatic disease in 19% of the patients, with a postoperative morbidity rate of 0.8%. This morbidity rate of less than 1% is in line with previously reported rates of 0% to 3%[35], and, in our opinion, supports the additional value of SL. Despite these advantages of adding SL to the staging process, there is room for an improvement of the logistics because SL resulted in extra time in the diagnostic process.

Diagnostic delay

A limitation of this study is that the sensitivity and specificity of both FDG-PET/CT and SL could not be completely adequately assessed. Because follow-up of most patients who underwent FDG-PET/CT was lacking, the number of metastases detected at 6 months' follow-up is most likely underreported, resulting in an underestimation of sensitivity and specificity. Regarding sensitivity and specificity of SL, positive cytologic test results were not included in this analysis because peritoneal lavage was not repeated at the beginning of the gastrectomy and its clinical relevance is unclear, thereby precluding the adequate identification of true- and false-negative findings. Therefore, the sensitivity and specificity values reported herein should be interpreted with caution. In addition, no data on histopathological assessment of the resected specimens were collected, preventing examination of findings on FDG-PET/CT associated with tumor stage, nodal involvement, and metastatic status. Nevertheless, to our knowledge, the present study is the largest prospective study on the outcome of FDG-PET/CT and SL in patients with locally advanced gastric cancer in Western countries. The secondary outcomes (quality of life and cost-effectiveness) will be reported after the required 1-year follow-up for these end points has been reached.

CONCLUSION

In this study, FDG-PET/CT had limited value for detecting metastatic disease in patients with locally advanced gastric cancer. In contrast, SL detected metastatic or nonresectable disease in a considerable proportion of patients, resulting in a treatment change from curative to palliative intent. These findings suggest that it may be beneficial to include SL in guidelines for staging advanced gastric cancer, but not FDG-PET/CT.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. Published online 2018:394-424.
2. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(August):v38-v49.
3. Integraal Kankercentrum Nederland. Diagnostiek, behandeling en follow-up van het maagcarcinoom 2016. Published 2016. http://www.oncoline.nl/uploaded/docs/Maagcarcinoom/Richtlijn maagcarcinoom.pdf
4. Whiting J, Sano T, Saka M, Fukagawa T, Katai H, Sasako M. Follow-up of gastric cancer: A review. Gastric Cancer. 2006;9(2):74-81.
5. Koemans WJ, Luijten JCHBM, van der Kaaij RT, et al. The metastatic pattern of intestinal and diffuse type gastric carcinoma - A Dutch national cohort study. Cancer Epidemiol. 2020;69:101846.
6. Riihimäki M, Hemminki A, Sundquist K, Sundquist J, Hemminki K. Metastatic spread in patients with gastric cancer. Oncotarget. 2016;7(32):52307-52316.
7. Kwee RM, Kwee TC. Modern imaging techniques for preoperative detection of distant metastases in gastric cancer. World J Gastroenterol. 2015;21(37):10502-10509.
8. Seevaratnam R, Cardoso R, McGregor C, et al. How useful is preoperative imaging for tumor, node, metastasis (TNM) staging of gastric cancer? A meta-analysis. Gastric Cancer. 2012;15(SUPPL.1).
9. Veer E Ter, Mohammad NH, Van Valkenhoef G, et al. The Efficacy and Safety of First-line Chemotherapy in Advanced Esophagogastric Cancer: A Network Meta-analysis. J Natl Cancer Inst. 2016;108(10):1-13.
10. Dijksterhuis WPM, Verhoeven RHA, Slingerland M, et al. Heterogeneity of first-line palliative systemic treatment in synchronous metastatic esophagogastric cancer patients: A real-world evidence study. Int J Cancer. 2020;146(7):1889-1901.
11. Bang Y-J, 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 (London, England). 2010;376(9742):687-697.
12. Smyth E, Schöder H, Strong VE, et al. A prospective evaluation of the utility of 2-deoxy-2-[18 F]fluoro-deoxyglucose positron emission tomography and computed tomography in staging locally advanced gastric cancer. Cancer. 2012;118(22):5481-5488.
13. Brenkman HJF, Gertsen EC, Vegt E, et al. Evaluation of PET and laparoscopy in STagIng advanced gastric cancer: A multicenter prospective study (PLASTIC-study). BMC Cancer. 2018;18(1):1-7.
14. Washington K. 7th edition of the AJCC cancer staging manual: Stomach. Ann Surg Oncol. 2010;17(12):3077-3079.
15. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-2194.
16. Initiative S. STROBE statement—checklist of items that should be included in reports of observational studies (STROBE initiative). Int J Public Health. 2008;53(1):3-4.
17. Equator Network. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. September 9, 2021. Accessed July 10, 2021.
18. Smyth EC, Shah MA. Role of 18F 2-fluoro-2-deoxyglucose positron emission tomography in upper gastrointestinal malignancies. World J Gastroenterol. 2011;17(46):5059-5074.
19. Bosch KD, Chicklore S, Cook GJ, et al. Staging FDG PET-CT changes management in patients with gastric adenocarcinoma who are eligible for radical treatment. Eur J Nucl Med Mol Imaging. Published online 2019.
20. Findlay JM, Antonowicz S, Segaran A, et al. Routinely staging gastric cancer with 18F-FDG PET-CT detects additional metastases and predicts early recurrence and death after surgery. Eur Radiol. 2019;29(5):2490-2498.
21. Chen J, Cheong JH, Yun MJ, et al. Improvement in preoperative staging of gastric adenocarcinoma with positron emission tomography. Cancer. 2005;103(11):2383-2390.

22. Serrano OK, Love C, Goldman I, et al. The value of FDG-PET in the staging of gastric adenocarcinoma: a single institution retrospective review. J Surg Oncol. 2016;113(6):640-646
23. Kitajima K, Nakajo M, Kaida H, et al. Present and future roles of FDG-PET/CT imaging in the management of gastrointestinal cancer: an update. Nagoya J Med Sci. 2017;79(4):527-543.
24. Mukai K, Ishida Y, Okajima K, Isozaki H, Morimoto T, Nishiyama S. Usefulness of preoperative FDG-PET for detection of gastric cancer. Gastric Cancer. 2006;9(3):192-196.
25. Mochiki E, Kuwano H, Katoh H, Asao T, Oriuchi N, Endo K. Evaluation of 18F-2-deoxy-2-fluoro-D-glucose Positron Emission Tomography for Gastric Cancer. World J Surg. 2004;28(3):247-253.
26. Yun M, Lim JS, Noh SH, Hyung WJ, Cheong JH. Lymph Node Staging of Gastric Cancer Using 18F-FDG PET: A Comparison Study with CT. October. 2005;46(10):1582-1588.
27. Yoshioka T, Yamaguchi K, Kubota K, et al. Evaluation of 18F-FDG PET in patients with advanced, metastatic, or recurrent gastric cancer. J Nucl Med. 2003;44(5):690-699.
28. Lim JS, Kim MJ, Yun MJ, et al. Comparison of CT and 18F-FDG pet for detecting peritoneal metastasis on the preoperative evaluation for gastric carcinoma. Korean J Radiol. 2006;7(4):249-256.
29. Dassen AE, Lips DJ, Hoekstra CJ, Pruijt JFM, Bosscha K. FDG-PET has no definite role in preoperative imaging in gastric cancer. Eur J Surg Oncol. 2009;35(5):449-455.
30. Stahl A, Ott K, Weber WA, et al. FDG PET imaging of locally advanced gastric carcinomas: Correlation with endoscopic and histopathological findings. Eur J Nucl Med Mol Imaging. 2003;30(2):288-295.
31. Yamada A, Oguchi K, Fukushima M, Imai Y, Kadoya M. Evaluation of 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography in gastric carcinoma: Relation to histological subtypes, depth of tumor invasion, and glucose transporter-1 expression. Ann Nucl Med. 2006;20(9):597-604.
32. Wu CX, Zhu ZH. Diagnosis and evaluation of gastric cancer by positron emission tomography. World J Gastroenterol. 2014;20(16):4574-4585.
33. Donswijk ML, Hess S, Mulders T, Lam MGEH. [18F]fluorodeoxyglucose PET/computed tomography in gastrointestinal malignancies. PET Clin. 2014;9(4):421-441.
34. Kaneko Y, Murray WK, Link E, Hicks RJ, Duong C. Improving Patient Selection for 18F-FDG PET Scanning in the Staging of Gastric Cancer. J Nucl Med. 2015;56(4):523-529.
35. Fukagawa T. Role of staging laparoscopy for gastric cancer patients. Ann Gastroenterol Surg. 2019;3(5):496-505.
36. Groh EM, Gupta S, Brown ZJ, et al. Staging Laparoscopy is Underutilized in the Management of Gastric Adenocarcinoma. Ann Surg Oncol.
37. Ikoma N, Blum M, Chiang YJ, et al. Yield of Staging Laparoscopy and Lavage Cytology for Radiologically Occult Peritoneal Carcinomatosis of Gastric Cancer. Ann Surg Oncol. 2016;23(13):4332-4337.
38. Jamel S, Markar SR, Malietzis G, Acharya A, Athanasiou T, Hanna GB. Prognostic significance of peritoneal lavage cytology in staging gastric cancer: systematic review and meta-analysis. Gastric Cancer. 2017;21(1):10-18.
39. Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. Springer; 2017.
40. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer. 2017;20(1):1-19.
41. Badgwell B, Cormier JN, Krishnan S, et al. Does neoadjuvant treatment for gastric cancer patients with positive peritoneal cytology at staging laparoscopy improve survival? Ann Surg Oncol. 2008;15(10):2684-2691.
42. Yamamoto M, Kawano H, Yamaguchi S, et al. Comparison of Neoadjuvant Chemotherapy to Surgery Followed by Adjuvant Chemotherapy in Japanese Patients with Peritoneal Lavage Cytology Positive for Gastric Carcinoma. Anticancer Res. 2015;35(9):4859-4863.
43. Yamaguchi T, Takashima A, Nagashima K, et al. Efficacy of Postoperative Chemotherapy After Resection that Leaves No Macroscopically Visible Disease of Gastric Cancer with Positive Peritoneal Lavage Cytology (CY1) or Localized Peritoneum Metastasis (P1a): A Multicenter Retrospective Study. Ann Surg Oncol. 2020;27(1):284-292.

44. Ishigami H, Yamaguchi H, Yamashita H. Surgery after intraperitoneal and systemic chemotherapy for gastric cancer with peritoneal metastasis or positive peritoneal cytology findings. Gastric Cancer. 2017;20(s1):128-134.
45. Badgwell B, Blum M, Das P, et al. Phase II Trial of Laparoscopic Hyperthermic Intraperitoneal Chemoperfusion for Peritoneal Carcinomatosis or Positive Peritoneal Cytology in Patients with Gastric Adenocarcinoma. Ann Surg Oncol. 2017;24(11):3338-3344.
46. Koemans WJ, Van Der Kaaij RT, Boot H, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy versus palliative systemic chemotherapy in stomach cancer patients with peritoneal dissemination, the study protocol of a multicentre randomised controlled trial (PERISCOPE II). BMC Cancer. 2019;19(1):1-8.

SUPPLEMENTARY FILES

eTable 1a. FDG-PET/CT sensitivity and specificity, all patients

	Distant metastatic cancer confirmed			Positive Predictive Value
	Yes	No	Total	
FDG-PET/CT-positive	10	6	16	
FDG-PET/CT-negative	20	201	221	63% (95%CI: 40-81%)
Total	30	207	237	
Sensitivity and specificity	33% (95%CI: 17-53%)	97% (95%CI: 94-99%)		

In a total of 237 patients recurrent disease was scored during 6 months follow-up, data of 1 patient were missing. For this analysis, only those with high suspicion of metastatic disease (n=15) were regarded as FDG-PET/CT-positive; patients with equivocal FDG-PET/CT results were regarded as FDG-PET/CT -negative.

eTable 1b. FDG-PET/CT sensitivity and specificity, patients with FDG-avid primary tumour

	Distant metastatic cancer confirmed			Positive Predictive Value
	Yes	No	Total	
FDG-PET/CT-positive	7	4	11	
FDG-PET/CT-negative	15	199	214	64% (95%CI: 36-85%)
Total	22	203	225	
Sensitivity and specificity	31% (95%CI: 14-55%)	98% (95%CI: 95-99%)		

In a total of 225 patients recurrent disease was scored during 6 months follow-up. For this analysis, only those with high suspicion of metastatic disease (n=11) were regarded as FDG-PET/CT -positive; patients with equivocal FDG-PET/CT results were regarded as FDG-PET/CT -negative.

eTable 1c. FDG-PET/CT sensitivity and specificity for peritoneal disease

	Peritoneal disease confirmed			Positive Predictive Value
	Yes	No	Total	
FDG-PET/CT-positive	3	0	3	
FDG-PET/CT-negative	42	300	342	100% (95%CI: 31-100%)
Total	45	300	345	
Sensitivity and specificity	7% (95%CI: 2-19%)	100% (95%CI: 98-100%)		

A total of 345 patients underwent both FDG-PET/CT and SL. For this analysis, only those with high suspicion of peritoneal metastatic disease (n=3) were regarded as FDG-PET/CT -positive; patients with equivocal FDG-PET/CT results were regarded as FDG-PET/CT -negative.

eTable 1d. FDG-PET/CT sensitivity and specificity for patients with cT4 tumours

	Distant metastatic cancer confirmed			Positive Predictive Value
	Yes	No	Total	
FDG-PET/CT-positive	2	2	4	
FDG-PET/CT-negative	3	17	20	50% (95%CI: 16-84%)
Total	5	19	24	
Sensitivity and specificity	40% (95%CI: 5-85%)	89% (95%CI: 67-99%)		

A total of 24 patients had a cT4 tumour and available follow-up data. For this analysis, only those with high suspicion of metastatic disease (n=4) were regarded as FDG-PET/CT -positive; patients with equivocal FDG-PET/CT results were regarded as FDG-PET/CT -negative.

eTable 1e. FDG-PET/CT sensitivity and specificity for patients with cN+ tumours

	Distant metastatic cancer confirmed			Positive Predictive Value
	Yes	No	Total	
FDG-PET/CT-positive	8	5	13	
FDG-PET/CT-negative	14	103	117	62% (95%CI: 37-82%)
Total	22	108	130	
Sensitivity and specificity	36% (95%CI: 17-59%)	95% (95%CI: 90-98%)		

A total of 130 patients had a cN+ tumour and available follow-up data. For this analysis, only those with high suspicion of peritoneal metastatic disease (n=13) were regarded as FDG-PET/CT -positive; patients with equivocal FDG-PET/CT results were regarded as FDG-PET/CT -negative.

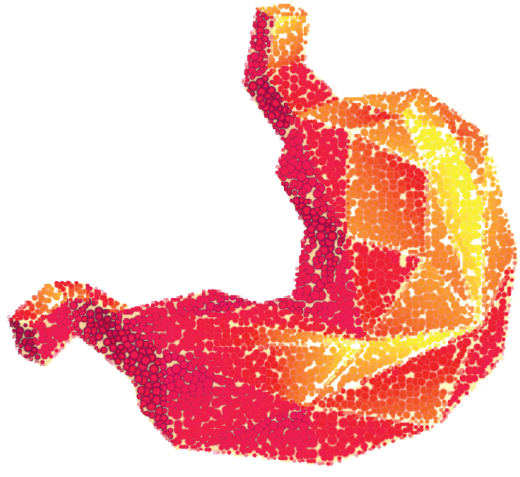
eTable 1f. SL sensitivity and specificity for detecting macroscopic peritoneal disease, all patients

	Metastatic cancer confirmed			Positive Predictive Value
	Yes	No	Total	
Macroscopic lesion (≥1)	50	65	115	
No macroscopic lesion	11	231	242	43% (95%CI: 38-50%)
Total	61	296	357	
Sensitivity and specificity	82% (95%CI: 70-91%)	78% (95%CI: 73-83%)		

Macroscopic lesion (≥1) includes all patients in whom biopsies were taken, also those in whom there was no or low suspicion of metastatic disease. For this analysis, patients with positive cytology only were not regarded as *Macroscopic lesion (≥1)* or confirmed metastatic cancer, as the outcome of peritoneal lavage cannot be determined in advance.

Part 2

Surgical treatment



Chapter 6

Worldwide practice in gastric cancer surgery: a 6-year update

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ABSTRACT

Background: To evaluate the current status of gastric cancer surgery worldwide and update the changes compared to a previous survey in 2014.

Methods: A cross-sectional survey was sent to surgical members of the International Gastric Cancer Association, pilot centers of the World Organization for Specialized Studies on Diseases of the Esophagus and the Australian and New Zealand Gastric and Oesophageal Surgeons Association in addition to participants of the 2019 International Gastric Cancer and European Society for Diseases of the Esophagus congresses. Topics addressed included hospital volume, staging, perioperative treatment, surgical approach, anastomotic techniques, lymphadenectomy and palliative management.

Results: Between June 2019 – January 2020 165 respondents from 44 countries completed the survey. In total, 80% worked in a hospital performing >20 gastrectomies annually. Staging laparoscopy and FDG-PET/CT were preferred by 68% and 26% for advanced cancer and 90% offered perioperative chemo(radio)therapy to patients. For early cancer, a minimally invasive surgical approach was preferred by 65% for distal and by 50% for total gastrectomy. For advanced cancer, this was preferred by 39% for distal and by 33% for total gastrectomy. 84% favored a stapled anastomosis, and 14% created a jejunal pouch as reconstruction during a total gastrectomy. A D2 lymphadenectomy was preferred for distal as well as for total gastrectomy, in both early (62% and 71%) and advanced (84% and 89%) cancer.

Conclusion: This international survey demonstrates that perioperative chemotherapy and a D2 lymphadenectomy have now become the preferred treatment for gastric cancer. A minimally invasive surgical approach has gained popularity.

BACKGROUND

In 2018, over a million patients were diagnosed with gastric cancer and it was the third leading cause for cancer-related death, accounting for 782.685 deaths[1]. Several aspects of the diagnostic work-up and treatment for gastric cancer are under debate. For example, various national guidelines differ about performing ^{18}F-fluorodeoxyglucose positron-emission tomography with computed tomography (FDG-PET/CT), staging laparoscopy and the use of perioperative treatment[2–4]. In addition, there is an ongoing debate on the value of minimally invasive surgery which was demonstrated to be associated with less postoperative morbidity, faster recovery and less pain, without impairing long-term outcomes[5–8]. Nevertheless, open surgery remains the treatment of choice for many surgeons[9].

In 2014, our study group conducted an international cross-sectional survey on the surgical treatment of gastric cancer[9]. The aim of the current study was to perform an update of our previous survey in order to identify any trends and regional differences that may exist in the surgical management of gastric cancer. Compared to the previous survey, additional information was also sought regarding preoperative staging and the palliative management of gastric cancer.

METHODS

All surgical members of the International Gastric Cancer Association (IGCA) and the Australian and New Zealand Gastric and Oesophageal Surgeons Association (ANZGOSA) as well as the heads of the Pilot Centers involved in the World Organization for Specialized Studies on Diseases of the Esophagus (OESO)-Stanford Platform were sent an electronic invitation for this international cross-sectional survey. In addition, surgical attendees of the 2019 International Gastric Cancer Congress in Prague and the European Society for Diseases of the Esophagus congress in Athens were also invited to participate, through a QR-code that was made available during the conference which provided a direct link to the online survey. The survey has been included in Supplementary File 1.

The topics that were assessed included: hospital volume, preoperative staging, perioperative chemotherapy, surgical approach, extent of resection, anastomotic and reconstructive

techniques and palliative management. The survey was conducted over an eight-month period from June 2019 until January 2020. Current data was then compared to data from a previous study conducted by our group in 2014[9]. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY) and the chi-square test was used to make comparisons between continents. A p-value <0.05 was considered statistically significant.

RESULTS

Demographics

The survey was sent to all IGCA (n=910) and ANZGOSA (n=220) members, as well as to the heads of the OESO Pilot Centers (n=21). In total, the survey was sent to 1151 surgeons, of which 179 completed the survey (16%). Duplicate respondents (n=14) were subsequently excluded, resulting in a specific response rate of 14%. Figure 1 shows the origins of the respondents and their relative contribution to the survey. Of the total 165 respondents, originating from 44 different countries, 2% represented low-income countries, 32% middle-income countries and 67% high-income countries. The distribution of respondents by continent was as follows: 65 (39%) originated from Europe, 34 (21%) from Asia, 27 (16%) from Oceania, 23 (14%) from South America and 16 (10%) from North America.

Volume

Most of the respondents (46%) worked in hospitals performing 21-50 gastrectomies per year, whereas 20% worked in hospitals performing ≤20 yearly and 35% in hospitals performing >50 gastrectomies per year. Figure 2 presents the distribution of hospital volumes per continent. The majority of the respondents (67%) worked in a university hospital.

Staging

The majority of the respondents routinely performed a staging laparoscopy (68%) for advanced gastric cancer, whereas only a minority (26%) routinely performed a FDG-PET/CT. Figure 3 presents the variations in the use of both modalities per continent. Compared to regional hospitals, staging laparoscopy was more frequently performed in university hospitals (73% versus 56%, p=0.018).

Perioperative treatment

Perioperative chemotherapy, defined as pre- and postoperative chemotherapy with epirubicin, cisplatin, and infused fluorouracil according to the MAGIC trial regimen [10], or a similar protocol, was favored by 84% of surgeons. Of the remainder, 6% preferred chemoradiotherapy whilst 10% preferred no perioperative treatment. This was found to differ significantly between continents ($p<0.001$). In Western countries, the majority used perioperative treatment, whereas in Asia, 27% preferred no perioperative treatment (see Table 1).

Surgical approach

When performing a distal gastrectomy for early gastric cancer, 64% of the surgeons preferred a minimally invasive approach. However, for locally advanced gastric cancer, only 39% of respondents preferred a minimally invasive approach. When performing a total gastrectomy, 50% of the surgeons performed a minimally invasive approach for early gastric cancer and only 33% performed a minimally invasive approach in the setting of advanced cancer. Some minor differences were seen across continents (Figure 4).

Extent of dissection

A D2 resection was favored by 62% of respondents for distal and by 71% for total gastrectomies performed for early cancers. For advanced cancers, this increased to 84% for a distal gastrectomy and 89% for a total gastrectomy. For early cancers, a D2 resection was favored most frequently by respondents from South America and Europe (Table 2). Few surgeons from Europe and Asia performed a D3 lymphadenectomy. The majority of surgeons also favored to resect the greater omentum in the setting of of advanced cancer (89%).

Anastomoses

The majority of the respondents preferred a mechanical circular stapler when constructing the esophago-jejunal anastomosis after total gastrectomy (61%), compared to 23% who preferred a mechanical linear stapler and 16% a hand-sewn anastomosis, which differed between continents ($p=0.016$, Table 3). The results of the survey revealed that 86% of the surgeons favored a direct reconstruction, whereas merely 14% favored a jejunal pouch for reconstruction following total gastrectomy.

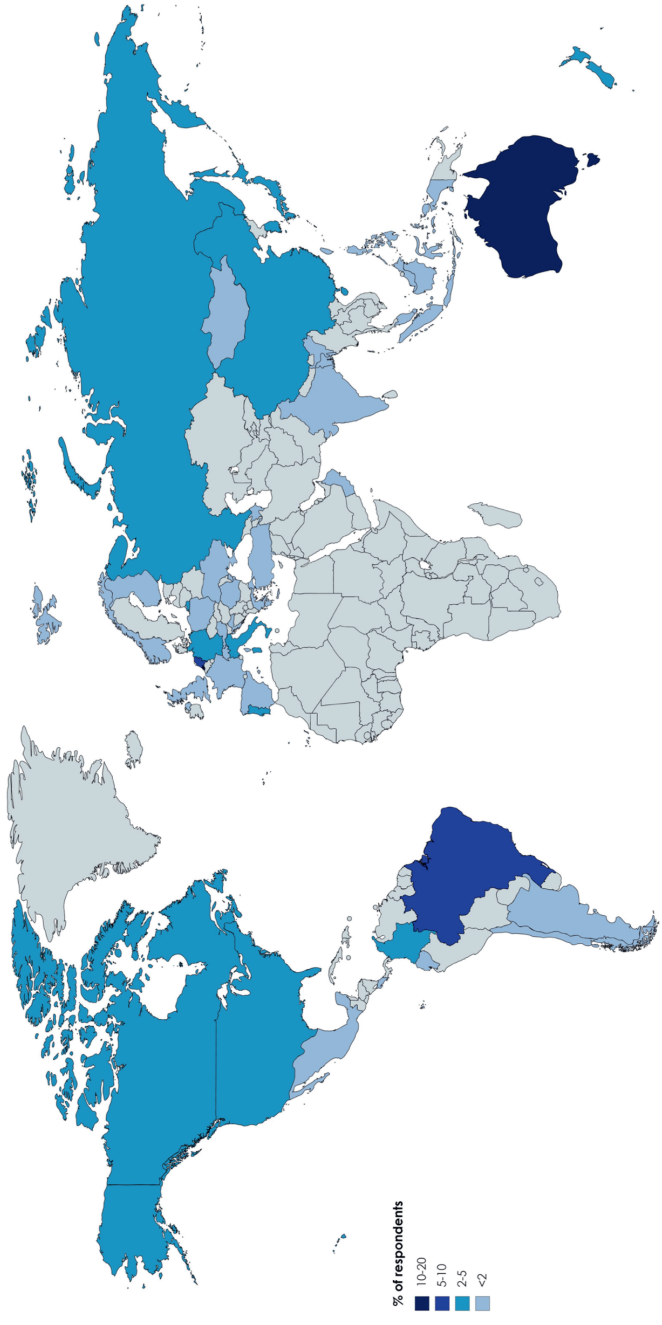

Figure 1. Number of respondents per participating country.

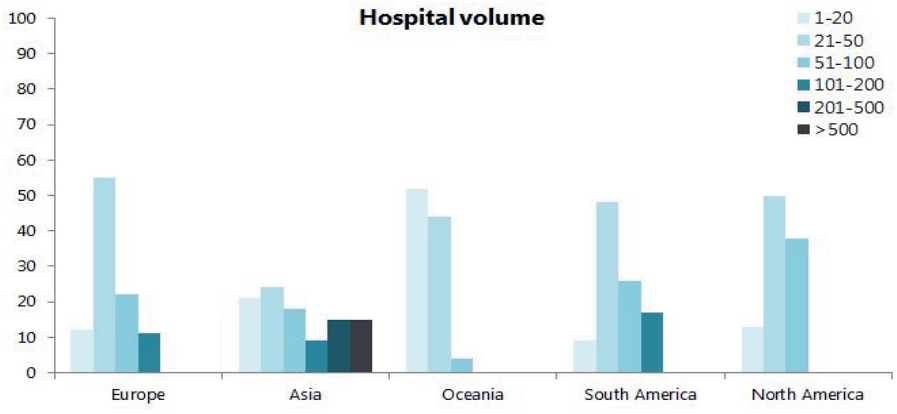

Figure 2. Annual number of gastrectomies per hospital

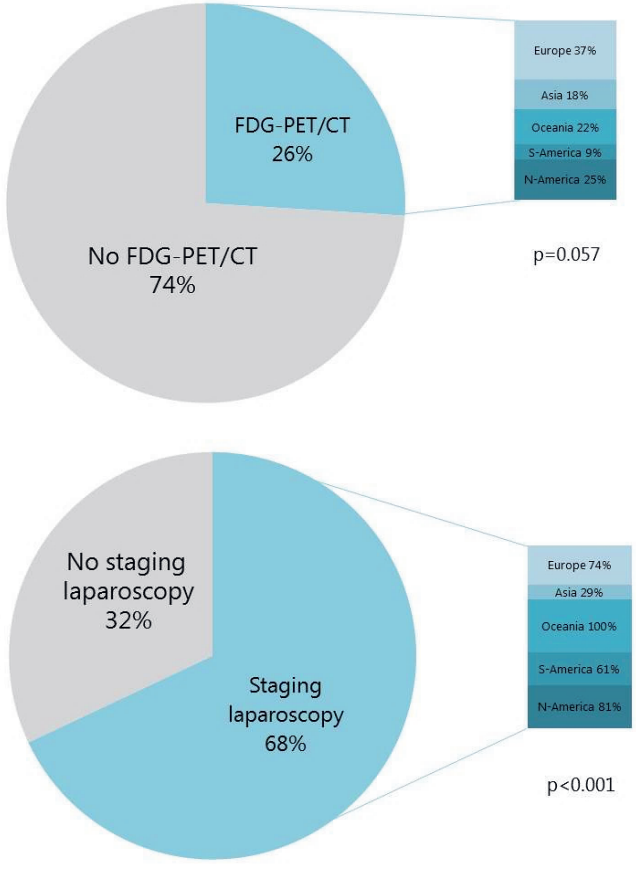

Figure 3. Global usage of FDG-PET/CT and SL in advanced gastric cancer and percentages per continent

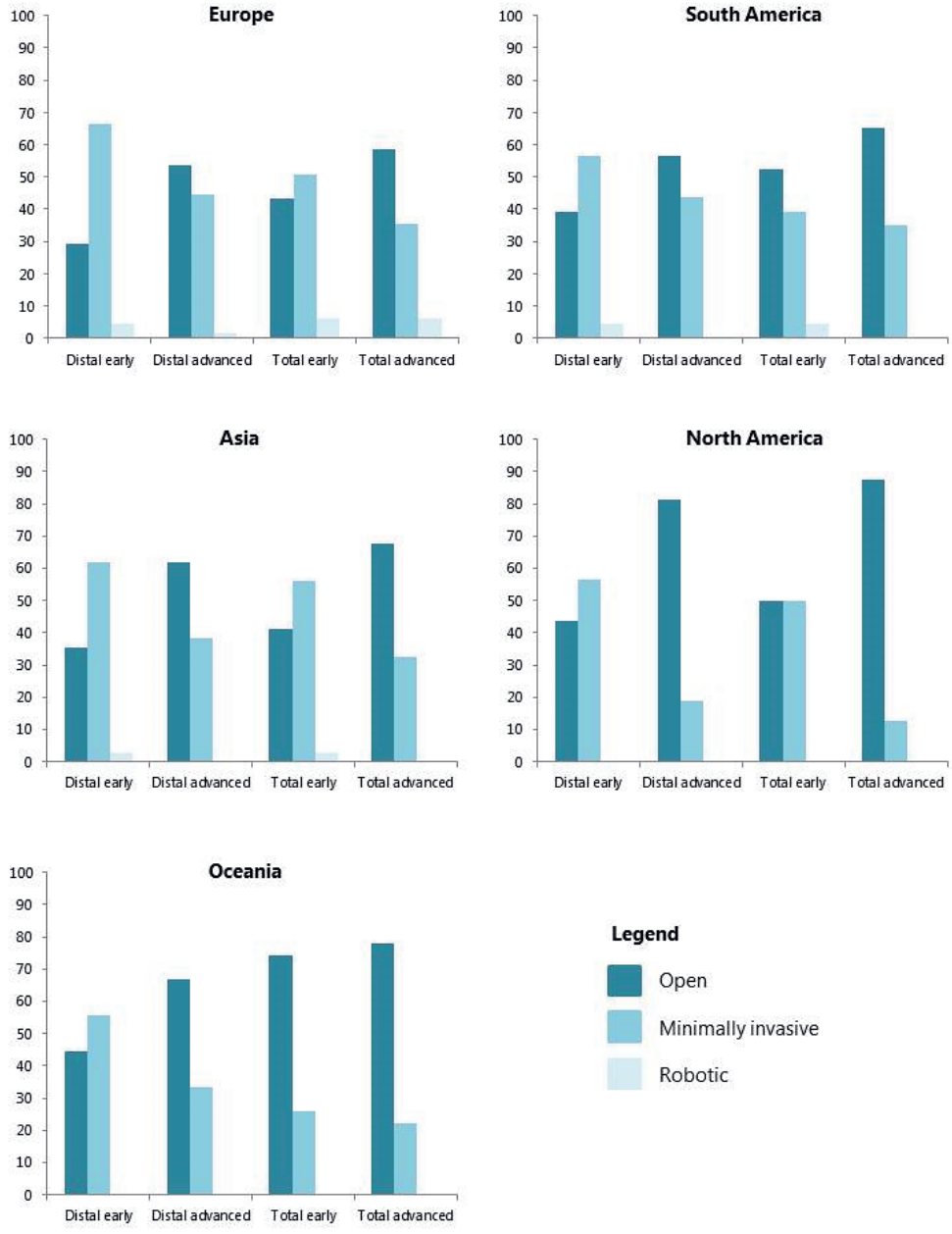

Figure 4. Surgical approach across continents for early and advanced gastric cancer

Table 1. Preferred types of perioperative treatment

	Europe	Asia	Oceania	South America	North America
Chemotherapy	89%	67%	100%	65%	94%
Chemoradiotherapy	3%	6%	0%	22%	6%
None	8%	27%	0%	13%	0%

Percentages may not add up to 100, due to rounding

Table 2. Percentage of at least a D2-lymphadenectomy, divided per tumor stage and type of procedure

	Europe	Asia	Oceania	South America	North America	*p*-value
Distal gastrectomy for early cancer	71%	53%	52%	74%	50%	0.330
Distal gastrectomy for advanced cancer	89%*	94%	67%	87%	94%	0.008
Total gastrectomy for early cancer	85%**	62%	48%	87%	53%	0.015
Total gastrectomy for advanced cancer	94%***	97%****	74%	87%	100%	0.030

*including 8% D3 resections; **including 3% D3 resections; ***including 5% D3 resections; ****including 3% D3 resections

Table 3. Type of anastomosis

	Europe	Asia	Oceania	South America	North America
Hand-sewn	15%	3%	30%	4%	38%
Mechanical, circular stapler	63%	65%	59%	61%	44%
Mechanical, linear stapler	22%	32%	11%	35%	22%

Percentages may not add up to 100, due to rounding

Metastatic disease

In the case of peritoneal metastases, 26% of respondents would offer hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery provided the Peritoneal Cancer Index (PCI) was ≤6. For a PCI of 7-12, only 9% of respondents would offer such treatment. In Europe, HIPEC is considered most often: 45% versus 4-25% in other continents, $p<0.001$. In case of distant metastases, 87% of respondents would perform a palliative gastrectomy in selected cases, which did not differ between continents.

Comparison to the 2014 survey

Table 4 shows the data of the present study in comparison to the data from the survey conducted in 2014. The percentage of high-volume centers, which is defined as a volume of ≥20 gastrectomies yearly, remained the same. The use of perioperative chemotherapy increased to 84%, whereas the use of chemoradiotherapy decreased. Moreover, the use of minimally invasive surgery for advanced cancers increased, with a more than 4-fold increase for distal (9 vs. 39%) and a 5.5-fold increase for total gastrectomy (6 vs. 33%). Regarding the

Table 4. Comparison of the current data with that of the previous survey

	2014	2020
No. respondents	227	165
High-volume centers	79%	80%
Perioperative therapy		
Chemotherapy	73%	84%
Chemoradiotherapy	12%	6%
None	16%	10%
Surgical approach, % minimally invasive		
Distal gastrectomy for early cancer	65%	64%×
Distal gastrectomy for advanced cancer	9%	39%××
Total gastrectomy for early cancer	49%	50%×××
Total gastrectomy for advanced cancer	6%	33%××××
Anastomosis		
Mechanical stapler	92%	84%
Hand-sewn	8%	16%
Jejunal pouch	17%	14%
Extent of dissection		
D2 in distal gastrectomy for early cancer	42%	62%
D2 in distal gastrectomy for advanced cancer	92%	84%*
D2 in total gastrectomy for early cancer	41%	71%**
D2 in total gastrectomy for advanced cancer	93%	89%***
Greater omentum	89%	89%
No. respondents	227	165

×including 3% robot-assisted; ××including 1% robot-assisted;×××including 4% robot-assisted; ××××including 2% robot-assisted. *not accounting 3% D3 resections; **not accounting 1% D3 resections; ***not accounting 2% D3 resections

anastomotic technique, the percentage of surgeons favoring a hand-sewn anastomosis doubled (8% to 16%). Lastly, an increase in D2 lymphadenectomy for early cancers was observed.

DISCUSSION

This study evaluated the current worldwide trends in surgical treatment for gastric cancer, by conducting a survey which was sent to upper gastrointestinal surgeons globally. The results show that the majority of surgeons worked in a high-volume hospital (81%), and offered patients perioperative chemo(radio)therapy (90%). For early gastric cancer, a minimally invasive approach is favored by the majority (50-64%), whereas in the case of advanced cancer, a minimally invasive approach was favored by only 33-39%. Regarding preoperative staging, anastomotic technique, extent of dissection and treatment in the setting of metastatic disease, some differences between continents were identified.

Regarding the use of FDG-PET/CT in advanced gastric cancer, no differences across continents were found. However, staging laparoscopy was found to be performed much less frequently in Asian compared to Western countries. This is most likely reflective of the differences in guideline recommendations between the countries. However, it may also be influenced by the fact that patients from Western countries typically present with more advanced tumours and, therefore, tend to have a higher chance of having peritoneal metastases[4,11,12].

In line with the previous survey[9], respondents from Europe favored perioperative chemotherapy more often than in Asia. These findings correspond to the recommendations from regional guidelines, which have remained relatively consistent across the study period. In Europe, perioperative chemotherapy remains the standard of care. Conversely, in Asia, surgery is performed up front, followed by adjuvant chemotherapy for advanced cancers[6]. Interestingly, the use of perioperative chemotherapy even appears to have increased in Europe. This increase is most likely related to the encouraging results from the FLOT-4 trial, which revealed an improved survival for patients receiving FLOT (fluorouracil plus leucovorin, oxaliplatin and docetaxel) compared with ECF/ECX (epirubicin, cisplatin plus either fluorouracil or capecitabine)[13]. To date, no solid data is available to support the use of neoadjuvant chemoradiotherapy as a standard of care and this may explain the decrease in use when compared to the previous survey. Although some studies reported on possible benefits of (adding) neoadjuvant chemoradiotherapy, such as improved pathological complete response and R0 rates[14], results of randomized controlled trials are to be awaited[15,16].

When comparing the current results with the survey of 2014, it was found that surgeons favor a minimally invasive approach more often, especially in Europe where a gradual change from open to minimally invasive gastrectomy was observed in early cancers. This is probably explained by an increasing amount of literature on the benefits of minimally invasive surgery. In this context, several Asian randomized controlled trials researched these topics and reported that laparoscopic gastrectomy is safe for early cancers[5,8,17], and may result in less postoperative morbidity and faster recovery after distal gastrectomy for advanced cancer[6,7]. In this enumeration, level 1 evidence reporting on laparoscopic total gastrectomy for advanced cancer is lacking. However, a Dutch multicenter randomized controlled trial (LOGICA trial [NCT02248519]) recently reported laparoscopic total gastrectomy for patients with

predominantly advanced cancer to be safe and feasible. In addition, no differences regarding postoperative morbidity, short-term oncological outcomes and quality of life were reported, although laparoscopic gastrectomy was associated with less blood loss[18].
Over the past 6 years, the percentage of surgeons using a jejunal pouch remained relatively constant, whereas the percentage of surgeons creating a hand-sewn anastomosis doubled to 16%. Nevertheless, mechanical staplers remained the favored approach reported by the majority of respondents. It was previously described that stapling methods embrace benefits such as shorter operating time, shortened hospitalization, faster functional postoperative recovery and reduced anastomotic leakage[19]. Despite these possible benefits of mechanical staplers, there are no clear international guidelines regarding this topic.

Whereas the results of the previous survey showed that a D1+ lymphadenectomy was preferred by most of the surgeons in case of early cancer, the current results reveal that the majority performs at least a D2 lymphadenectomy in both early and advanced cancer. This is in line with current Western guidelines recommending a D2 lymphadenectomy routinely, and although not yet recommended by Eastern guidelines, a meta-analysis including also Asian trials, reported that D2 lymphadenectomy with spleen and pancreas preservation increases long-term survival[4,20.]

Another topic that is not yet established in most national guidelines is the treatment with cytoreductive surgery and HIPEC for patients with positive cytology and/or peritoneal metastases. The first studies investigating this originated from Asia and reported a possible survival gain after 1- and 3-years in patients with limited peritoneal disease[21,22]. Due to significant differences between Eastern and Western populations[12], similar trials have been established in the West. These include the European GASTRIPEC trial, which is assessing the added effect of cytoreductive surgery alone or in combination with HIPEC and the PERISCOPE-II trial, which is evaluating the role of gastrectomy in combination with both cytoreductive surgery and HIPEC versus palliative management alone[23,24]. The fact that both of these studies are being conducted in Europe may provide a possible explanation for the uptake of cytoreductive surgery and HIPEC across European respondents. Based on results from these studies, indicating that HIPEC can be performed safely and may even prevent peritoneal recurrence and prolong survival, there may also be a future role for prophylactic HIPEC[25]. In the case of distant metastases, a controversial

topic that is currently under debate, 87% of surgeons indicated that they would perform a palliative resection in selected cases, for example in the case of fit, symptomatic patients. Although the Asian REGATTA-trial demonstrated no survival benefit, several cohort studies suggest the opposite[26–28]. For now, the results of the Dutch COSTA and the German RENAISSANCE trial, both evaluating potential benefits of palliative gastrectomy, should be awaited[29].

One of the key limitations of this study is that statistical analyses comparing the current results with those of the previous survey could not be performed. This is due to a low number of respondents and methodological differences in how the surveys were conducted. This resulted in different cohorts of respondents between the surveys with different geographical distributions. In addition, when assessing the response rate, no rate for QR-code respondents could be determined and it was assumed that respondents were a member of solely one association. This resulted in a relatively low response rate, which is probably an underestimation. Due to the low number of respondents from low-income countries, it was decided not to perform an analysis evaluating this subdivision, although it would have been interesting to learn how under-represented regions manage gastric cancer. Nonetheless, due to its international design, we believe the results to be a representative of expert surgeons' opinions, as the majority of the respondents worked in a high-volume hospital (defined as ≥20 gastrectomies annually according to literature), providing both a useful and current update on the varying expert opinions and practices that exist around the world.

CONCLUSION

This 6-year update of the previous survey from 2014 reflects worldwide trends in gastric cancer surgery and reveals that surgeons favor a minimally invasive approach more often, especially for early cancers, combined with a D2 lymph node dissection, and that respondents are increasingly adopting perioperative therapy.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries 2018:394–424.
2. Integraal Kankercentrum Nederland. Diagnostiek, behandeling en follow-up van het maagcarcinoom 2016 2016:1–7. http://www.oncoline.nl/uploaded/docs/Maagcarcinoom/Richtlijn maagcarcinoom.pdf.
3. Sano T, Kodera Y. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011;14:113–23.
4. Waddell T, Verheij M, Allum W, et al. Gastric cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24:vi57–63.
5. Kim HH, Han SU, Kim MC, et al. Effect of Laparoscopic Distal Gastrectomy vs Open Distal Gastrectomy on Long-term Survival among Patients with Stage i Gastric Cancer: The KLASS-01 Randomized Clinical Trial. JAMA Oncol 2019;5:506–13.
6. Lee HJ, Hyung WJ, Yang HK, et al. Short-term outcomes of a multicenter randomized controlled trial comparing laparoscopic distal gastrectomy with D2 lymphadenectomy to open distal gastrectomy for locally advanced gastric cancer (KLASS-02-RCT). Ann Surg 2019;270:983–91.
7. Yu J, Huang C, Sun Y, et al. Effect of Laparoscopic vs Open Distal Gastrectomy on 3-Year Disease-Free Survival in Patients with Locally Advanced Gastric Cancer: The CLASS-01 Randomized Clinical Trial. JAMA - J Am Med Assoc 2019;321:1983–92.
8. Hyung WJ, Yang HK, Han SU, et al. A feasibility study of laparoscopic total gastrectomy for clinical stage I gastric cancer: a prospective multi-center phase II clinical trial, KLASS 03. Gastric Cancer 2019;22:214–22.
9. Brenkman HJF, Haverkamp L, Ruurda JP, Van Hillegersberg R. Worldwide practice in gastric cancer surgery. World J Gastroenterol 2016;22:4041–8.
10. Cunningham D, Allum WWH, Stenning SSP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11–20.
11. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v38–49.
12. Griffin SM. Gastric cancer in the East: Same disease, different patient. Br J Surg 2005;92:1055–6.
13. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ra. Lancet 2019;393:1948–57.
14. Trip AK, Stiekema J, Visser O, et al. Recent trends and predictors of multimodality treatment for oesophageal, oesophagogastric junction, and gastric cancer: A Dutch cohort-study. Acta Oncol (Madr) 2015;54:1754–62.
15. Leong T, Smithers BM, Haustermans K, et al. TOPGEAR: A Randomized, Phase III Trial of Perioperative ECF Chemotherapy with or Without Preoperative Chemoradiation for Resectable Gastric Cancer: Interim Results from an International, Intergroup Trial of the AGITG, TROG, EORTC and CCTG. Ann Surg Oncol 2017;24:2252–8.
16. Slagter AE, Jansen EPM, van Laarhoven HWM, et al. CRITICS-II: A multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery versus neo-adjuvant chemotherapy and subsequent chemoradiotherapy followed by surgery versus neo-adjuvant chemoradiotherapy followed by surgery in resecta. BMC Cancer 2018;18.
17. Katai H, Mizusawa J, Katayama H, et al. Short-term surgical outcomes from a phase III study of laparoscopy-assisted versus open distal gastrectomy with nodal dissection for clinical stage IA/IB gastric cancer: Japan Clinical Oncology Group Study JCOG0912. Gastric Cancer 2017;20:699–708.
18. Veen A van der, Brenkman HJ, Seesing MF, et al. Laparoscopic versus open gastrectomy for gastric cancer (LOGICA-trial). Accepted by Journal of Clinial Oncology
19. Liu B wei, Liu Y, Liu J ru, Feng Z xu. Comparison of hand-sewn and stapled anastomoses in surgeries of gastrointestinal tumors based on clinical practice of China. World J Surg Oncol 2014;12:1–6.

20. Jiang L, Yang KH, Guan QL, et al. Survival and recurrence free benefits with different lymphadenectomy for resectable gastric cancer: A meta-analysis. J Surg Oncol 2013;107:807–14.
21. Desiderio J, Chao J, Melstrom L, et al. The 30-year experience—A meta-analysis of randomised and high-quality non-randomised studies of hyperthermic intraperitoneal chemotherapy in the treatment of gastric cancer. Eur J Cancer 2017;79:1–14.
22. Coccolini F, Cotte E, Glehen O, et al. Intraperitoneal chemotherapy in advanced gastric cancer . Meta-analysis of randomized trials. Eur J Surg Oncol 2014;40:12–26.
23. Rau B, Loeffler M, Rau H-G, et al. Perioperative chemotherapy and cytoreductive surgery with versus without HIPEC in gastric cancer with limited peritoneal metastases: A randomized phase III study (GASTRIPEC). J Clin Oncol 2017;33.
24. Koemans WJ, Van Der Kaaij RT, Boot H, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy versus palliative systemic chemotherapy in stomach cancer patients with peritoneal dissemination, the study protocol of a multicentre randomised controlled trial (PERISCOPE II). BMC Cancer 2019;19:1–8.
25. Brenkman HJF, Päeva M, Hillegersberg R Van, et al. Prophylactic Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Gastric Cancer — A Systematic Review 2019.
26. Fujitani K, Yang HK, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): A phase 3, randomised controlled trial. Lancet Oncol 2016;17:309–18.
27. Hartgrink HH, Putter H, Klein Kranenbarg E, et al. Value of palliative resection in gastric cancer. Br J Surg 2002;89:1438–43.
28. Bonenkamp JJ, Sasako M, Hermans J, van de Velde CJH. Tumor load and surgical palliation in gastric cancer. Hepatogastroenterology 2001;48:1219–21.
29. Al-Batran SE, Goetze TO, Mueller DW, et al. The RENAISSANCE (AIO-FLOT5) trial: Effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III tri. BMC Cancer 2017;17:1–7.

Chapter 7

Multimodal therapy versus primary surgery for gastric and gastroesophageal junction diffuse type carcinoma, with a focus on signet ring cell carcinoma: a nationwide study

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ABSTRACT

Background: Diffuse type adenocarcinoma and, more specifically, signet ring cell carcinoma (SRCC) of the stomach and gastroesophageal junction (GEJ) have a poor prognosis and the value of neoadjuvant chemo(radio)therapy (nCRT) is unclear.

Methods: All patients who underwent surgery for diffuse type gastric and GEJ carcinoma between 2004 and 2015 were retrospectively included from the Netherlands Cancer Registry. The primary outcome was overall survival after surgery. Kaplan Meier curves were plotted. Furthermore, multivariable Poisson and Cox regressions were performed, correcting for confounders. To comply with the Cox regression proportional hazard assumption, gastric cancer survival was split in <90 days and >90 days postoperative by adding an interaction variable.

Results: Analyses included 2046 patients with diffuse type cancer: 1728 gastric (50% SRCC) and 318 GEJ cancer (39% SRCC). In the gastric cancer group, 49% received nCT and 51% primary surgery (PS). All-cause mortality within 90 days postoperatively was lower after nCT (HR=0.29; 95%CI [0.20-0.44], $p<0.001$). Also after 90 days, mortality was lower in the nCT group (HR for the interaction variable 2.84; 95%CI [1.87-4.30], $p<0.001$; Total HR=0.29*2.84=0.84). In the GEJ group, 38% received nCT, 22% nCRT and 39% PS. All-cause mortality was lower after nCT (HR=0.63 [95%CI 0.43-0.93], $p=0.020$), compared to PS. The nCRT group was removed from the Cox regression analysis, since the Kaplan Meier curves of nCRT and PS intersected. The results for gastric and GEJ were similar between the SRCC and non-SRCC subgroups.

Conclusion: For gastric and GEJ diffuse type cancer, including SRCC, nCT was associated with increased survival.

BACKGROUND

The Laurén classification system categorizes gastric adenocarcinomas into intestinal type, diffuse type and mixed type. Intestinal type carcinomas form glands, whereas diffuse type carcinomas consist of poorly cohesive cells[1]. In diffuse type adenocarcinomas often signet ring cells are found, and if the tumor predominantly consists of signet ring cells (>50%), the tumor is defined as a signet ring cell carcinoma (SRCC) according to the World Health Organization[2]. Generally, gastric adenocarcinomas are known for a poor prognosis, with a 5-year survival in stage I-III disease less than 40%[3–5]. Survival in diffuse types is suggested to be worse when compared to other types[6-8], with reported survival rates as low as 15%[9].

Curative treatment for gastric adenocarcinoma in general consists of surgical resection with lymphadenectomy, if possible combined with perioperative chemotherapy[5,10]. The poor prognosis of diffuse type gastric cancer is caused by unfavorable characteristics, such as deeper infiltrating tumors causing a higher rate of incomplete resections, a higher prevalence of lymph node and peritoneal metastases, resulting in a reduced disease-free survival[6,11]. Moreover, it is suggested that diffuse type adenocarcinomas exhibit a lower response to neoadjuvant chemo(radio)therapy compared to intestinal type adenocarcinomas[12]. A large French population-based study reported a significantly worse survival for diffuse types with perioperative chemotherapy compared to surgery alone, specifically for SRCC. In that study, perioperative chemotherapy did not result in tumor or nodal down-staging, and thus lacked cytostatic effect[13]. It was therefore suggested to consider primary surgery as standard of care for these tumors. Since other large studies are lacking, several national and international guidelines still state that it is too early to omit (neo)adjuvant chemo(radio)therapy in diffuse type adenocarcinoma[14,15]. In the Netherlands, neoadjuvant chemotherapy is started with the intent to also give adjuvant chemotherapy (perioperative therapy)[5,10]. In the current study, it was decided to only analyze neoadjuvant treatment, to reduce selection and immortal time bias. The aim of the current study was to compare neoadjuvant treatment combined with surgery to primary surgery for diffuse type gastric and gastroesophageal junction (GEJ) adenocarcinomas.

METHODS

Study design

This population-based retrospective study retrieved anonymous data from the Netherlands Cancer Registry (NCR). Each newly diagnosed cancer patient in the Netherlands is reported to the NCR by the National Automated Pathology Archive (PALGA). The NCR subsequently registers patient, tumor and treatment-related characteristics of each patient. The patient's vital status is annually updated through a linkage with the municipal personal records database. Data collection from hospital records is performed by trained data managers using the NCR's manual for registration and coding. The Privacy Review Board of the NCR and the scientific committee of the Dutch Upper-GI Cancer Group (DUCG) approved this study.

Study population and study outcomes

All patients who underwent a surgical resection for diffuse type gastric adenocarcinoma or a SRCC of the stomach or GEJ between 2004 and 2015 in the Netherlands were included. The definition of SRCCs varied over the years, according to the World Health Organization (WHO), depending on the percentage of signet ring cells in the tumor (varying from >50% to 90%)[16-18]. Patients with metastatic disease (cM1) and non-resectable disease (cT4b) were excluded. Based on tumor location, patients were subdivided into: gastric or GEJ, with GEJ mostly consisting of Siewert type II and III tumors, as type I was usually registered as distal esophageal cancer. The following treatment groups were distinguished: i. primary surgery group (PS; defined as surgery without (neo)adjuvant chemo(radio)therapy, ii. neoadjuvant chemotherapy group (nCT; defined as patients treated with neoadjuvant chemotherapy and surgery, with the intention to also administer adjuvant chemotherapy according to national guidelines) and iii. neoadjuvant chemoradiotherapy group (nCRT; only for GEJ cancer, defined as patients with GEJ cancer treated with nCRT and surgery).

The primary outcome was overall survival. Furthermore, patient, tumor and treatment-related characteristics and short-term oncological outcomes were described, including the frequency of missing values per variable. Finally, resection radicality was evaluated and defined according to the College of American Pathologists[19].

Diagnosis and treatment

Diagnosis, staging and treatment of gastric cancer in the Netherlands are advised to be performed according to the national guidelines and the at that time applicable edition of the Union for International Cancer Control TNM staging system[20-22]. The recommended staging process consists of endoscopy with biopsies and computed tomography (CT) scan of thorax and abdomen. If indicated, an endoscopic ultrasound (EUS), fluorodeoxyglucose positron emission tomography with CT (FDG-PET/CT) and/or staging laparoscopy with peritoneal lavage are performed[22]. Following publication of the MAGIC trial in 2006, the recommended curative treatment for gastric adenocarcinoma consists of perioperative chemotherapy (epirubicin, cisplatin, and capecitabin according to the MAGIC regimen, or similar) combined with (sub)total gastrectomy and lymphadenectomy[5]. Since 2006, the recommended curative treatment for GEJ tumors consisted of perioperative chemotherapy similar to the MAGIC regimen combined with surgery. As of 2010, this was changed to either perioperative chemotherapy or nCRT according to the CROSS regimen[23] (based on the advice of the local multidisciplinary tumor board), combined with surgery. Surgery consists of total gastrectomy, transhiatal esophagectomy or transthoracic esophagectomy and, regardless of the procedure, combined with lymphadenectomy[23]. Annual hospital volume of surgery for patients with gastric or GEJ cancer undergoing gastrectomy was based on the hospital gastrectomy volume and for patients with GEJ cancer undergoing esophagectomy it was based on esophagectomy volume. Low volume was defined as performing <20 procedures annually, mid as 20-40 and high as >40.

Statistical analysis

The chi-squared test or Fisher's exact test was used to compare categorical data between groups. The Mann-Whitney-Wilcoxon test with interquartile ranges (IQR) was used to compare non-Gaussian distributed continuous data between groups. Overall survival (OS) analyses were performed separately for the gastric cancer diffuse type group (regardless whether signet ring cells were present), the gastric cancer SRCC subgroup, the GEJ cancer diffuse type group, and the GEJ SRCC subgroup. The 90-day mortality was compared between treatment groups and Kaplan Meier curves were plotted for each treatment group, displaying overall survival up to 5 years, or in case of sufficient numbers at risk, up to 10 years. Survival time was calculated from date of surgery until death or end of follow-up. Differences in survival between treatment groups were compared by log-rank tests and univariable and multivariable Cox regression. Hazard ratios

(HRs) were provided for all-cause mortality with 95% confidence intervals (CIs). The proportional hazard assumption was assessed by visually checking the Kaplan Meier curves and performing Schoenfeld's global test (see Supplementary Files 1-2 for additional details). To comply with the proportional hazard assumption, for gastric cancer, additional regression analyses with an interaction variable "nCT[yes/no]*>90 days postoperatively[yes/no]" were performed[24,25]. It was decided to split the HR at 90 days postoperatively, since this allows for easy interpretation of the HRs by clinicians reading the current paper and since 90 day mortality is commonly regarded a parameter for surgery-related mortality[26-28]. For the GEJ nCRT group, a split was not possible due to low numbers, hence the GEJ nCRT group was removed from the Cox regression analyses (Supplementary Files 1-2). The multivariable Cox regression were adjusted for relevant patient, tumor and treatment-related characteristics that could influence clinical decision making (i.e. characteristics that are known preoperatively): age, sex, previous malignancy, cTNM stage, year of diagnosis, hospital annual volume and surgical treatment. Due to the small sample size of the GEJ SRCC subgroup to prevent over-fitting, only patient, tumor and treatment-related characteristics with $p<0.200$ in univariable Cox regression analysis were added to the multivariable analysis[29,30]. Furthermore, in the GEJ SRCC subgroup, the variable "year of surgery" was further aggregated (2004-2009/2010-2015) due to limited numbers in the categories. Possible collinearity was assessed between the variables neoadjuvant therapy, year of surgery and hospital volume. Lastly, additional analyses were performed to assess the association between annual hospital volume with R+ resection rate. The binary outcome R+ resection rate was analyzed by multivariable Poisson regression with robust error variances according to the methods by Zou et al., providing relative risks (RR)[31,32]. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY) and R statistical computing version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). $P<0.05$ was considered statistically significant.

RESULTS

Study population

In the Netherlands, 2233 patients underwent a surgical resection with curative intent for diffuse type gastric or GEJ adenocarcinoma between 2004 – 2015. Patients with gastric cancer who underwent neoadjuvant radiotherapy (n=1) or nCRT (n=10) were excluded, as this was not

standard of care. Likewise, patients who underwent surgery within 7 days after diagnosis were regarded as emergency surgery and were also excluded (n=26). A total of 123 patients were excluded due to metastatic (cM1) disease and 27 due to non-resectable disease (cT4b) (Figure 1). Baseline characteristics are presented in Table 1.

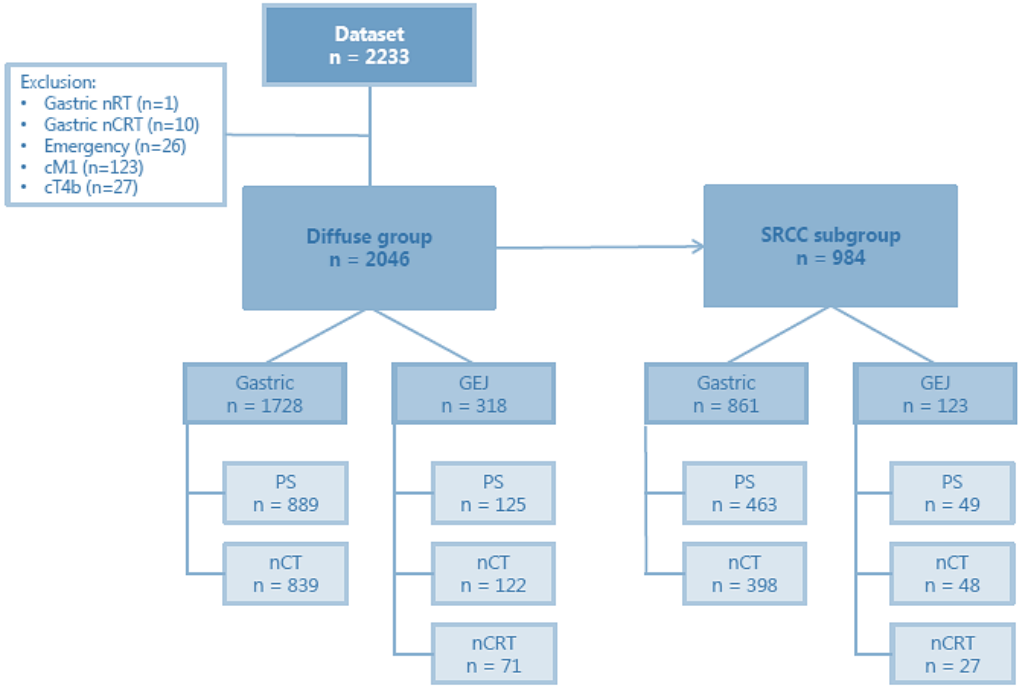


Figure 1. Study flowchart. GEJ: gastroesophageal junction tumor; nCRT: neoadjuvant chemoradiotherapy; nCT: neoadjuvant chemotherapy; nRT: neoadjuvant radiotherapy; PS: primary surgery; SRCC: signet ring cell carcinoma

Treatment and histopathological outcomes

In the diffuse type gastric cancer group, 49% of patients were treated with nCT, and 51% underwent primary surgery. In the diffuse type GEJ group, 38% were treated with nCT, 22% with nCRT, whereas 39% underwent primary surgery (Table 2). For the gastric and GEJ SRCC subgroups, these percentages largely corresponded to the diffuse type group (Supplementary File 3).

Histopathological parameters for diffuse type tumors are presented in Table 3.

Table 1 Baseline characteristics of 2046 patients who were diagnosed with a diffuse type gastroesophageal adenocarcinoma and underwent surgical resection

	Gastric (n=1728)		GEJ (n=318)	
	No. (%)	Missing values (%)	No. (%)	Missing values (%)
Patient characteristics				
Age, years (mean ± SD)	65.5 ± 12.6	0 (0)	63.3 ± 11.0	0 (0)
Gender (male, %)	953 (55)	0 (0)	252 (79)	0 (0)
Malignancy*	193 (11)	0 (0)	32 (10)	0 (0)
Tumor characteristics				
cT-stage		918 (52)		79 (25)
T1	74 (9)		2 (1)	
T2	428 (53)		83 (35)	
T3	230 (28)		142 (59)	
T4	78 (10)		12 (5)	
cN-stage		293 (17)		28 (9)
N0	1020 (71)		125 (43)	
N1	337 (24)		133 (46)	
N2	72 (5)		30 (10)	
N3	6 (<1)		2 (1)	
cM-stage (M0)	1640 (100)	88 (5)	303 (100)	15 (5)
Tumor location#		52 (3)		59 (10)
Proximal	51 (3)		318 (100)	
Mid	461 (28)		n.a.	
Distal	776 (46)		n.a.	
Overlapping	388 (23)		n.a.	
Tumor differentiation		539 (31)		91 (29)
Well/moderate	67 (6)		25 (11)	
Poorly/undifferentiated	1122 (94)		202 (89)	
Signet ring cell carcinoma (%)	861 (50)		123 (39)	
Hospital volume		0 (0)		0 (0)
<20 resections	1356 (79)		158 (50)	
20-40 resections	300 (17)		93 (29)	
>40 resections	72 (4)		67 (21)	
Year of surgery		0 (0)		0 (0)
2004 – 2008	451 (26)		101 (32)	
2008 – 2012	643 (37)		125 (39)	
2012 – 2015	634 (37)		92 (29)	

Percentages may not add up to 100% due to rounding. BMI: Body Mass Index. *Currently or previously treated malignancy other than gastroesophageal carcinoma. #Gastric: proximal included fundus (n=51); mid included corpus (n=356), lesser (n=81) and greater (n=24) curvature; distal included antrum (n=624) and pylorus (n=152).

Survival

Follow-up and proportional hazards

Median follow-up time of survivors in the entire cohort was 72 months [range: 11-156 months, interquartile range: 34-144 months]. The assessment of the proportional hazard assumptions is described in the method section and Supplementary Files 1-2.

Table 2 Treatment characteristics of 2046 patients who were diagnosed with a diffuse type carcinoma, divided per location

	Gastric (n=1728)		GEJ (n=318)	
	No. (%)	Missing values (%)	No. (%)	Missing values (%)
Neoadjuvant treatment		0 (0)		0 (0)
Chemotherapy	839 (49)		122 (38)[#]	
Chemoradiotherapy	0 (0)		71 (22)[#]	
Radiotherapy only	0 (0)		0 (0)	
None	889 (51)		125 (39)[#]	
Surgical treatment		0 (0)		0 (0)
Subtotal gastrectomy	969 (61)		n.a.	
Total gastrectomy	621 (39)		69 (20)	
Transthoracic esophagectomy	n.a.		56 (18)	
Transhiatal esophagectomy	n.a.		59 (18)	
Esophagectomy, unknown type	n.a.		124 (39)	
Unknown type of resection	138 (8)		10 (3)	
Adjuvant treatment		0 (0)		0 (0)
Chemotherapy*	459 (27)		556 (18)	
Chemoradiotherapy[$]	72 (4)		5 (2)	
Radiotherapy only	3 (<1)		0 (0)	
None	1194 (69)		257 (81)	

Percentages may not add up to 100% due to rounding. *442 patients in the gastric and 55 patients in the GEJ group underwent aCT in the context of nCT. Of these patients, 72 in the gastric and 10 in the GEJ group underwent additional radiotherapy. 17 patients in the gastric and 1 patient in the GEJ group did not undergo nCT. $53 patients in the gastric and 3 patients in the GEJ group underwent nCT followed by aCRT (instead of perioperative chemotherapy) within the context of the CRITICS trial (Cats et al., 2018). #For GEJ, the treatment combinations were: gastrectomy as PS (n=22), gastrectomy + nCT (n=45), gastrectomy + nCRT (n=2), esophagectomy as PS (n=96), esophagectomy + nCT (n=74), esophagectomy + nCRT (n=69), unknown resection as PS (n=6), unknown resection + nCT (n=4).

Table 3 Histopathological outcomes of 2046 patients who were diagnosed with a diffuse type carcinoma, divided per location

	Gastric (n=1728)		GEJ (n=318)	
	No. (%)	Missing values (%)	No. (%)	Missing values (%)
Tumor stage				
pT-stage		10 (1)		5 (2)
T0	45 (3)		20 (6)	
T1	270 (16)		19 (6)	
T2	450 (26)		112 (36)	
T3	660 (38)		148 (47)	
T4	293 (17)		14 (5)	
pN-stage		33 (2)		3 (1)
N0	684 (40)		113 (36)	
N1	447 (26)		100 (32)	
N2	291 (17)		64 (20)	
N3	273 (16)		38 (12)	
pM-stage		77 (5)		13 (4)
M0	1571 (91)		298 (98)	
M1	80 (5)		7 (2)	
Radicality of the resection (R0, %)	1285 (74)	88 (5)	236 (74)	14 (4)
Lymph node yield (median, IQR)	15 [9-23]	3 (<1)	16 [10-22]	0 (0)
Total positive lymph nodes (median, IQR)	1 [0-6]	34 (2)	2 [0-7]	1 (<1)

Gastric diffuse type cancer

For gastric diffuse type cancer, 90-day postoperative mortality in the PS and nCT groups was 13.2% and 3.7%, respectively (p<0.001). Median survival was 21.2 months and 34.1 months, respectively (p<0.001, Figure 2). In multivariable Cox regression, a total of 1190 events (deaths) were observed. The HR for "nCT[yes/no]" was 0.29 (95%CI [0.20-0.44], p<0.001) and the HR for the interaction variable "nCT[yes/no]*>90 days postoperatively[yes/no]" was 2.84 (95%CI [1.87-4.30], p<0.001). Thus, patients treated with nCT had a significantly reduced all-cause mortality within 90 days postoperatively (HR=0.29) and after 90 days (HR=0.29*2.84=0.84), compared to patients treated with PS (Table 4a).

Gastric SRCC subgroup

In the gastric SRCC subgroup, 90-day postoperative mortality in the PS and nCT groups was 11.2% and 3.5%, respectively (p<0.001). Median survival was 22.8 months and 34.0 months, respectively (p=0.002, Figure 2). In multivariable Cox regression, the HR for "nCT[yes/no]" was 0.33 (95%CI [0.18-0.61], p<0.001) and the HR for the interaction variable "nCT[yes/no]*>90 days postoperatively[yes/no]" was 2.61 (95%CI [1.41-4.83], p<0.001). Thus, patients treated with nCT had a significantly reduced all-cause mortality within 90 days (HR=0.33) and after 90 days (HR=0.33*2.61=0.87), compared to patients treated with PS (Table 4a).

GEJ diffuse type cancer

For GEJ diffuse type cancer, 90-day postoperative mortality in the PS, nCT and nCRT groups was 9.6%, 3.3% and 7.0%, respectively (p=0.133). Median survival was 19.3 months, 31.5 months and 20.6 months, respectively (p=0.01, Figure 3). Due to non-compliance with the proportional hazard assumption, the nCRT group was excluded from the multivariable Cox regression and a total of 189 events (deaths) were observed. Patients treated with nCT had a significantly reduced all-cause mortality (HR 0.63 [95%CI 0.43-0.93], p=0.020), compared to patients treated with PS (Table 4b).

GEJ SRCC subgroup

In the GEJ SRCC subgroup, 90-day postoperative mortality in the PS, nCT and nCRT groups was 12.2%, 6.4% and 3.7%, respectively (p=0.366). Median survival was 17.3 months, 32.8 months and 15.6 months, respectively (p=0.08, Figure 3). Due to non-compliance with the proportional

hazard assumption, the nCRT group was excluded from the multivariable Cox regression. Patients treated with nCT had a significantly reduced all-cause mortality (HR 0.53 [95%CI 0.31-0.92], *p*=0.024), compared to patients treated with PS (Table 4b).

Annual hospital volume

For patients with gastric diffuse type cancer, surgery in a mid or high volume hospital was not associated with R+ resection rate or reduced all-cause mortality in multivariable analyses, as compared to surgery in a low volume hospital (Table 4a, Supplementary Files 4 and 6).

For patients with GEJ diffuse type cancer, to analyze the effect of hospital volume, the nCRT group was not excluded. Surgery in a mid or high volume hospital was associated with a lower R+ resection rate compared to a low volume hospital in multivariable analyses (20-40 resections: RR 0.67 [95%CI 0.38-1.18], *p*=0.167; >40 resections: RR 0.47 [95%CI 0.25-0.91], *p*=0.025)(Supplementary File 5). In addition, surgery in a mid of high volume hospital was associated with lower all-cause mortality compared to a low volume hospital (20-40 resections, HR 0.69 [95%CI 0.47-1.02], *p*=0.060; >40 resections, HR 0.60 [95%CI 0.41-0.89], *p*=0.010)(Supplementary Files 6 and 7).

Assessment of collinearity

For gastric diffuse type cancer, both PS and nCT patients were included in most years of surgery as well as in low, mid and high hospital volumes (Supplementary File 8 Table A). Hence collinearity presumably did not affect the comparison of PS versus nCT.

For GEJ diffuse type cancer, there was a partial overlap between hospital volume, neoadjuvant therapy and year of surgery, indicating possible collinearity (Supplementary File 8 Tables B and D). Nevertheless, upon removal of the variable hospital volume from the Cox Regression and Poisson regression analyses, the neoadjuvant treatment and year of surgery HRs and RRs remained largely unchanged (Supplementary Files 5 and 7). Hence, collinearity was not an issue.

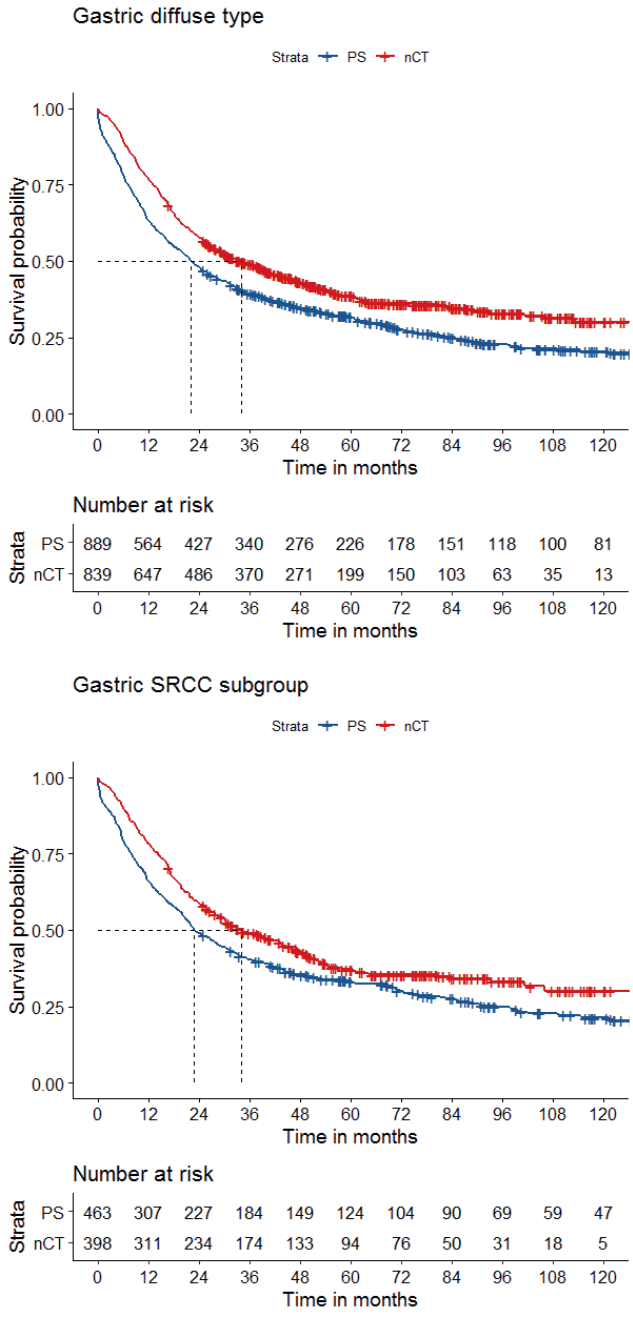


Figure 2 Overall 10-year survival for gastric diffuse type carcinoma (top) and the gastric SRCC subgroup (bottom). Kaplan-Meier plots and number of patients at risk are displayed. Median survival times are shown by interrupted lines. Censoring of patients is shown by a "+" on the plotted graphs.

Table 4a. Univariable and multivariable Cox regression analyses on the influence of nCT on all-cause mortality for diffuse and SRCC type gastric cancer

	Gastric - diffuse type						Gastric - SRCC subgroup					
	Univariable			Multivariable			Univariable			Multivariable		
	HR	[95% CI]	*p*	HR	[95% CI]	*p*	HR	[95% CI]	*p*	HR	[95% CI]	*p*
nCT	0.27	[0.18-0.40]	**<0.001**	0.29	[0.20-0.44]	**<0.001**	0.30	[0.17-0.54]	**<0.001**	0.33	[0.18-0.61]	**<0.001**
nCT*>90 days[1]	3.08	[2.03-4.66]	**<0.001**	2.84	[1.87-4.30]	**<0.001**	2.86	[1.54-5.28]	**<0.001**	2.61	[1.41-4.83]	**<0.001**
Additional year of age	1.02	[1.02-1.03]	**<0.001**	1.02	[1.01-1.02]	**<0.001**	1.02	[1.02-1.03]	**<0.001**	1.02	[1.02-1.03]	**<0.001**
Female sex	0.95	[0.84-1.06]	0.356	1.03	[0.92-1.15]	0.636	0.88	[0.75-1.04]	0.124	0.98	[0.83-1.15]	0.791
Previous malignancy	1.29	[1.08-1.53]	**0.005**	1.19	[0.99-1.42]	0.058	1.23	[0.94-1.61]	0.128	1.07	[0.81-1.42]	0.613
cT-stage												
T1	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
T2	3.58	[2.32-5.52]	**<0.001**	3.32	[2.14-5.16]	**<0.001**	3.44	[1.98-5.99]	**<0.001**	3.07	[1.75-5.41]	**<0.001**
T3	4.40	[2.82-6.86]	**<0.001**	3.79	[2.41-5.97]	**<0.001**	5.19	[2.94-9.17]	**<0.001**	4.32	[2.40-7.75]	**<0.001**
T4	7.49	[4.63-12.1]	**<0.001**	5.61	[3.43-9.2]	**<0.001**	9.59	[5.09-18.0]	**<0.001**	7.36	[3.87-14.0]	**<0.001**
Tx	3.18	[2.08-4.9]	**<0.001**	2.84	[1.85-4.4]	**<0.001**	3.00	[1.76-5.13]	**<0.001**	2.59	[1.50-4.46]	**<0.001**
cN-stage												
N0	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
N+	1.73	[1.51-2.0]	**<0.001**	1.57	[1.36-1.8]	**<0.001**	1.90	[1.56-2.31]	**<0.001**	1.74	[1.41-2.14]	**<0.001**
Nx	1.33	[1.14-1.5]	**<0.001**	1.27	[1.08-1.5]	**0.003**	1.39	[1.13-1.71]	**0.002**	1.30	[1.04-1.61]	**0.020**
cMx	1.52	[1.20-1.9]	**<0.001**	1.34	[1.05-1.7]	**0.021**	1.61	[1.17-2.22]	**0.004**	1.44	[1.03-2.03]	**0.034**
Year of surgery												
2004 – 2005	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
2006 – 2007	1.06	[0.84-1.3]	0.598	1.11	[0.87-1.4]	0.405	1.32	[0.97-1.80]	0.076	1.35	[0.98-1.85]	0.063
2008 – 2009	1.01	[0.80-1.3]	0.910	1.12	[0.88-1.4]	0.364	1.13	[0.83-1.56]	0.439	1.23	[0.88-1.72]	0.222
2010 – 2011	0.87	[0.69-1.1]	0.268	1.11	[0.85-1.4]	0.457	1.02	[0.74-1.40]	0.897	1.27	[0.89-1.82]	0.184
2012 – 2013	0.89	[0.70-1.1]	0.321	1.06	[0.81-1.4]	0.674	0.99	[0.71-1.38]	0.950	1.15	[0.79-1.67]	0.463
2014 – 2015	0.92	[0.72-1.2]	0.496	1.02	[0.76-1.4]	0.908	1.01	[0.71-1.43]	0.977	1.11	[0.73-1.70]	0.619
Hospital volume												
<20 gastrectomies	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
20-40 gastrectomies	0.91	[0.78-1.1]	0.271	1.00	[0.83-1.2]	0.989	1.02	[0.74-1.40]	0.897	1.27	[0.89-1.82]	0.184
>40 gastrectomies	0.87	[0.64-1.2]	0.397	1.06	[0.76-1.5]	0.728	0.99	[0.71-1.38]	0.950	1.15	[0.79-1.67]	0.463
Surgical treatment												
Total gastrectomy	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
Subtotal gastrectomy	0.71	[0.63-0.8]	**<0.001**	0.63	[0.56-0.7]	**<0.001**	1.01	[0.71-1.43]	**<0.001**	1.11	[0.73-1.70]	**<0.001**
Unknown type of procedure	1.08	[0.88-1.3]	0.478	0.94	[0.75-1.2]	0.565	0.90	[0.72-1.13]	0.368	1.00	[0.78-1.29]	0.969

Table 4a. Univariable and multivariable Cox regression analyses on the influence of nCT on all-cause mortality for SRCC and diffuse type gastric cancer. Bold values indicate significance ($p < 0.05$). HR = hazard ratio, CI = confidence interval and ref = reference. [1]For diffuse type gastric cancer, in multivariable analysis, patients receiving nCT had a significantly reduced all-cause mortality within 90 days (HR = 0.29) and after 90 days (HR = 0.29 * 2.84 = 0.84). For the gastric SRCC subgroup, in multivariable analysis, patients receiving nCT had a significantly reduced all-cause mortality within 90 days (HR = 0.33) and after 90 days (HR = 0.33 * 2.61 = 0.87).

Table 4b. Univariable and multivariable Cox regression analyses on the influence of nCT and nCRT on all-cause mortality for SRCC and diffuse type GEJ cancer.

	GEJ - diffuse type						GEJ - SRCC subgroup					
	Univariable			Multivariable			Univariable			Multivariable		
	HR	[95% CI]	*p*	HR	[95% CI]	*p*	HR	[95% CI]	*p*	HR	[95% CI]	*p*
Neoadjuvant therapy												
PS	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
nCT	0.64	[0.48-0.86]	**0.003**	0.63	[0.43-0.93]	**0.020**	0.61	[0.39-0.96]	**0.032**	0.53	[0.31-0.92]	**0.024**
Additional year of age	1.01	[0.99-1.02]	0.303	1.00	[0.99-1.02]	0.537	1.01	[0.99-1.03]	0.404			
Female sex	1.35	[0.97-1.88]	0.071	1.57	[1.11-2.24]	**0.011**	1.55	[0.94-2.55]	0.086	1.61	[0.96-2.71]	0.070
Previous malignancy	1.15	[0.73-1.81]	0.545	1.10	[0.68-1.78]	0.710	0.88	[0.44-1.77]	0.720			
cT-stage												
T1-2	Ref	-	-	Ref	-	-	Ref	-	-			
T3-4	1.00	[0.71-1.41]	0.994	1.00	[0.69-1.45]	0.993	1.00	[0.60-1.66]	0.998			
Tx	0.85	[0.58-1.24]	0.392	0.76	[0.51-1.14]	0.184	0.74	[0.39-1.41]	0.362			
cN-stage												
N0	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
N+	1.57	[1.15-2.15]	**0.005**	1.49	[1.06-2.11]	**0.023**	1.90	[1.16-3.11]	**0.011**	1.75	[1.05-2.93]	**0.032**
Nx	1.76	[1.10-2.81]	**0.017**	1.71	[1.05-2.79]	**0.030**	2.51	[1.24-5.10]	**0.011**	2.56	[1.20-5.45]	**0.015**
cMx	1.36	[0.79-2.36]	0.265	1.33	[0.73-2.42]	0.346	2.01	[0.96-4.24]	0.066	1.54	[0.71-3.33]	0.271
Year of surgery												
2004 – 2005	Ref	-	-	Ref	-	-	Ref	-	-			
2006 – 2007	0.96	[0.60-1.53]	0.853	1.04	[0.64-1.68]	0.889	1.70	[0.73-3.96]	0.219			
2008 – 2009	0.71	[0.44-1.15]	0.165	0.79	[0.46-1.36]	0.389	1.52	[0.66-3.52]	0.329			
2010 – 2011	0.81	[0.46-1.44]	0.475	1.16	[0.58-2.33]	0.678	1.27	[0.51-3.18]	0.611			
2012 – 2013	0.52	[0.29-0.94]	**0.030**	0.76	[0.38-1.52]	0.440	0.76	[0.26-2.27]	0.625			
2014 – 2015	0.55	[0.28-1.06]	0.074	0.82	[0.39-1.71]	0.592	1.07	[0.22-5.18]	0.930			
Year of surgery simplified (SRCC only)												
2004 – 2009							Ref	-	-	Ref	-	-
2010 – 2015							0.71	[0.43-1.17]	0.177	1.24	[0.67-2.31]	0.489
Hospital volume												
<20 resections	Ref	-	-	Ref	-	-	Ref	-	-			
20-40 resections	0.60	[0.41-0.88]	**0.008**	0.71	[0.46-1.10]	0.130	0.75	[0.41-1.39]	0.368			
>40 resections	0.74	[0.50-1.09]	0.128	0.59	[0.38-0.92]	**0.019**	0.87	[0.50-1.51]	0.610			
Surgical treatment												
Total gastrectomy	Ref	-	-	Ref	-	-	Ref	-	-			
Esophagectomy	1.00	[0.72-1.38]	1.000	1.09	[0.75-1.60]	0.640	0.97	[0.58-1.63]	0.919			
Procedure unknown	1.09	[0.52-2.31]	0.811	0.88	[0.40-1.94]	0.752	1.06	[0.36-3.12]	0.909			

Bold values indicate significance ($p < 0.05$). HR = hazard ratio, CI = confidence interval and ref = reference.

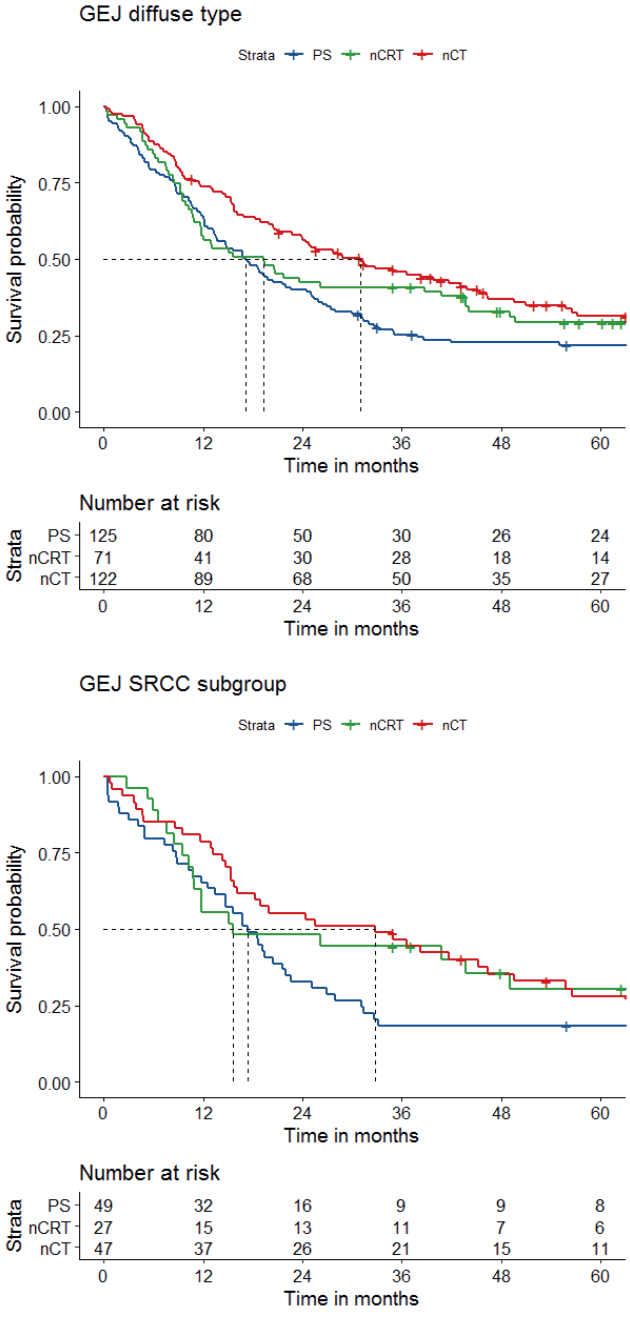


Figure 3 Overall 5-year survival for GEJ diffuse type carcinoma (top) and the GEJ SRCC subgroup (bottom). Kaplan-Meier plots and number of patients at risk are displayed. Median survival times are shown by interrupted lines. Censoring of patients is shown by a "+" on the plotted graphs.

DISCUSSION

In this large population-based study, nCT for patients with gastric and GEJ diffuse adenocarcinoma, including SRCC type, was associated with increased overall survival, compared to PS. This indicates that nCT should remain standard of care.

Messager et al. reported that PS should be considered as standard of care for gastric SRCC, because perioperative chemotherapy was not found to provide survival benefit in their cohort[13]. To evaluate this further, a French randomized controlled trial was initiated in 2012 (NCT01717924) aiming to evaluate survival of patients with SRCC after PS and adjuvant chemotherapy versus nCT, surgery and adjuvant chemotherapy[14,33], but inclusion has not yet been completed.

The current study found an association with longer survival in patients treated with nCT, both for diffuse type gastric and GEJ adenocarcinomas, including the SRCC subgroups, after multivariable analyses correcting for relevant baseline and treatment factors. For the gastric group, this reduction in all-cause mortality was strongest within 90 days postoperatively (HR=0.29), although a long-term reduction in mortality was also observed (HR=0.84). The associated increased short-term survival (lower 90-day postoperative mortality rates) may be caused by a better physical condition of patients in the nCT group due to selection bias. We believe a physiological effect of nCT causing a reduction in 90-day mortality is highly unlikely.

The associated increased long-term survival in the gastric and GEJ nCT group is likely a combination of a biological effect of nCT and selection bias. This biological effect of chemotherapy has been clearly demonstrated for gastric cancer overall in several prospective trials[5,10]. However, these populations mostly consisted of intestinal type tumors, with only a small proportion of diffuse types, which makes the evidence less convincing for the latter group. Regarding selection bias, the patients who are in good condition and without comorbidities and thus are expected to have a longer survival, are also expected to be the patients selected to undergo neoadjuvant chemotherapy. Unfortunately, comorbidities, WHO performance status and postoperative complications were not registered in the NCR during this period and could not be corrected for in the current study. Nevertheless, retrospective studies that do correct for

these factors will still contain residual selection bias and improvements in survival should always be interpreted with caution. Importantly, this limitation is present in all currently available studies since all studies are retrospective. Despite these limitations, the authors believe that based on the current results and all currently available literature there are insufficient arguments to omit nCT from standard of care.

A further argument in favour of nCT is that MAGIC(-like) regimens were administered during the period of the current study, whereas the more effective FLOT regimen was only implemented as standard of care since 2019. Indeed, although the FLOT4 trial was not powered for this subgroup analysis, the FLOT regimen showed a trend towards reduced mortality compared with the MAGIC regimen for diffuse type cancer (HR 0.85) and SRCC (HR 0.74)[10]. Hopefully, prospective trials, such as the ongoing French trial (NCT01717924) will provide a definitive answer on the added value of nCT in case of gastric SRCC[33].

For GEJ tumors, the PS and nCRT Kaplan Meier curves intersected in the current study. Hence, the proportional hazard assumption was not met. Since the nCRT group was small, splitting the HR was impossible and comparing PS with nCRT in a multivariable Cox regression was, unfortunately, impossible. Thus, results from the randomized Neo-AEGIS and ESOPEC trials comparing FLOT versus CROSS in esophageal and GEJ adenocarcinoma should be awaited[34,35].

For gastric diffuse type cancer, no significant difference in survival or R+ resection rate were found in low versus mid and high volume hospitals. However, for GEJ diffuse type cancer, undergoing surgery in hospitals with a high annual case volume was associated with markedly increased survival, compared to hospitals with a low annual case volume. Presumably, this difference is due to a difference in technical difficulty and the fact that initiation of centralization of gastric cancer started later. Indeed, centralization of gastroesophageal cancer care was initiated in 2006 in the Netherlands, based on earlier findings that centralization decreases postoperative morbidity and improves survival[36-38]. Hospitals performing esophagectomy were required to perform a minimum of 10 resections annually since 2006 and 20 resections annually since 2011. For gastrectomy, 10 resections were required annually since 2012 and 20 resections annually since 2013. Strikingly, for GEJ diffuse type adenocarcinomas resected in a low-volume hospital, overall survival was significantly worse when compared to higher volume hospitals. In

addition, multivariable analyses showed that R+ resection rates were twice as high in low-volume hospitals, which likely will have contributed to the difference in survival. Both selecting the optimal procedure and the technical performance of the procedure are challenging for GEJ tumors in general. For diffuse type tumors specifically, this is likely further complicated due to the more infiltrative character of the tumor[6,11,39]. For GEJ diffuse type adenocarcinomas especially, it is thus essential that the surgical team has a broad experience in operating these tumors, which supports centralization.

Because of the aforementioned centralization, collinearity was assessed between hospital volume, neoadjuvant therapy and year of surgery and was shown to be of limited influence on the current study results. Furthermore, aside from the previously discussed selection bias, we believe we were effectively able to deal with most, if not all, forms of bias in our analyses. To prevent immortal time bias in the comparison between PS and nCT, survival duration was calculated from the date of surgery. As a further measure to prevent immortal time bias and reduce selection bias, the groups were selected based upon neoadjuvant therapy only, despite the fact that in the Netherlands, neoadjuvant chemotherapy is always given with the intention to also give adjuvant therapy (perioperative therapy). Historical bias was prevented by correction for the year of resection. Lastly, hospital bias was minimized since it was a population-based study which included all hospitals in the Netherlands and a correction was made for hospital annual case volume.

A limitation of the SRCC subgroup analyses is that the definition of SRCC differed over the years and was dependent on the interpretation of the evaluating pathologist. As this is a worldwide issue, a recent consensus on the pathological definition was published, with only SRCC cancers with at least 90% poorly cohesive cells having signet ring cell morphology classified as SRCC[18]. Unfortunately, such agreements were not available during the study period and therefore the SRCC definition and coding is variable in our cohort. However, all currently available retrospective studies, including the study by Messager et al., have also been struggling with the uniformity of the SRCC definition and selection bias[13]. Despite these limitations, the current study is the largest nationwide population-based study in the field and may aid policy making and clinical decision making.

Our results may have the following implications: i. although these results and the results from the only other large population study by Messager et al. are retrospective and thus subject to bias, the conjunction of all currently available literature provides insufficient arguments to omit nCT in the standard curative treatment of gastric and GEJ diffuse type carcinoma, including SRCC[13,14,40]. Our results show that administering nCT in patients with diffuse type gastric and GEJ cancer is actually associated with a better survival compared to surgery alone and should therefore remain standard of care. ii. For GEJ diffuse type carcinoma, treatment should be centralized and resections should not be performed in hospitals with low annual volumes since this was associated with more R+ resections and reduced survival in the current population study.

CONCLUSION

This population-based study shows that, in patients with gastric or GEJ diffuse type adenocarcinoma, including SRCC, nCT was associated with better survival when compared to PS. Hence, nCT should remain standard of care in these patients. Moreover, in patients with GEJ adenocarcinoma, surgery in hospitals with low annual case volumes was associated with more R+ resections and a lower survival. Thus, centralization of care is advised for these patients.

REFERENCES

1. Lauren P. The Two Histological Main Types of Gastric Carcinoma: Diffuse and so-called Intestinal-type Carcinoma. An Attempt at a Histoclinical Classification. Acta Pathol Microbiol Scand 1965;64:31–49.
2. Jass JR, Sobin LH, Watanabe H. The World Health Organization's histologic classification of gastrointestinal tumors. A commentary on the second edition. Cancer 1990;66:2162–7.
3. Dassen AE, Dikken JL, Bosscha K, Wouters MWJM, Cats A, Van De Velde CJH, et al. Gastric cancer: Decreasing incidence but stable survival in the Netherlands. Acta Oncol (Madr) 2014;53:138–42.
4. Dikken JL, Lemmens VE, Wouters MWJM, Wijnhoven BP, Siersema PD, Nieuwenhuijzen GA, et al. Increased incidence and survival for oesophageal cancer but not for gastric cardia cancer in the Netherlands. Eur J Cancer 2012;48:1624–32.
5. Cunningham D, Allum WWH, Stenning SSP, Thompson JNJ, Van de Velde, CJH Nicolson M, Scarffe J, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11–20.
6. Piessen G, Messager M, Leteurtre E, Jean-Pierre T, Mariette C. Signet ring cell histology is an independent predictor of poor prognosis in gastric adenocarcinoma regardless of tumoral clinical presentation. Ann Surg 2009;250:878–87.
7. Kim JP, Kim SC, Yang HK. Prognostic significance of signet ring cell carcinoma of the stomach. Surg Oncol 1994;3:221–7.
8. Li C, Kim S, Lai JF, Hyung WJ, Choi WH, Choi SH, et al. Advanced gastric carcinoma with signet ring cell histology. Oncology 2007;72:64–8.
9. Yokota T, Kunii Y, Teshima S, Yamada Y, Saito T, Kikuchi S, et al. Signet ring cell carcinoma of the stomach: A clinicopathological comparison with the other histological types. Tohoku J Exp Med 1998;186:121–30.
10. Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ra. Lancet 2019;393:1948–57.
11. Nafteux PR, Lerut TE, Villeneuve PJ, Dhaenens JM, De Hertogh G, Moons J, et al. Signet ring cells in esophageal and gastroesophageal junction carcinomas have a more aggressive biological behavior. Ann Surg 2014;260:1023–9.
12. van der Kaaij RT, Koemans WJ, van Putten M, Snaebjornsson P, Luijten JCHBM, van Dieren JM, et al. A population-based study on intestinal and diffuse type adenocarcinoma of the oesophagus and stomach in the Netherlands between 1989 and 2015. Eur J Cancer 2020;130:23–31.
13. Messager M, Lefevre JH, Pichot-Delahaye V, Souadka A, Piessen G, Mariette C. The impact of perioperative chemotherapy on survival in patients with gastric signet ring cell adenocarcinoma: A multicenter comparative study. Ann Surg 2011;254:684–93.
14. D'Ugo D, Agnes A, Grieco M, Biondi A, Persiani R. Global updates in the treatment of gastric cancer: a systematic review. Part 2: perioperative management, multimodal therapies, new technologies, standardization of the surgical treatment and educational aspects. Updates Surg 2020:12–8.
15. Moehler M, Baltin CTH, Ebert M, Fischbach W, Gockel I, Grenacher L, et al. International comparison of the German evidence-based S3-guidelines on the diagnosis and multimodal treatment of early and locally advanced gastric cancer, including adenocarcinoma of the lower esophagus. Gastric Cancer 2015;18:550–63. -x.
16. Hamilton SR., Aaltonen LA. World Health Organization classification of tumours Pathology and Genetics of Tumours of the Digestive System. IARC Press Int Agency Res Cancer 2000.
17. Stichting PALGA. Landelijke PALGA Protocol: Oesofagus-Maagcarcinoom 2019:versie 45.
18. Mariette C, Carneiro F, Grabsch HI, van der Post RS, Allum W, de Manzoni G, et al. Consensus on the pathological definition and classification of poorly cohesive gastric carcinoma. Gastric Cancer 2019;22:0.
19. Verhage RJJ, Zandvoort HJA, Ten Kate FJW, Van Hillegersberg R. How to define a positive circumferential resection margin in T3 adenocarcinoma of the esophagus. Am J Surg Pathol

2011;35:919–26.
20. Washington K. 7th edition of the AJCC cancer staging manual: Stomach. Ann Surg Oncol 2010;17:3077–9.
21. Integraal Kankercentrum Nederland. Richtlijn Diagnostiek, behandeling en follow-up van het maagcarcinoom 2009 2009.
22. Integraal Kankercentrum Nederland. Diagnostiek, behandeling en follow-up van het maagcarcinoom 2016 2016:1–7. http://www.oncoline.nl/uploaded/docs/Maagcarcinoom/Richtlijn maagcarcinoom.pdf.
23. van Hagen P, Hulshof MCCM, van Lanschot JJB, Steyerberg EWW, van Berge Henegouwen MI, Wijnhoven BPLP, et al. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. N Engl J Med 2012;366:2074–84.
24. Van Der Kruijssen DEW, Brouwer NPM, Van Der Kuil AJS, Verhoeven RHA, Elias SG, Vink GR, et al. Interaction between Primary Tumor Resection, Primary Tumor Location, and Survival in Synchronous Metastatic Colorectal Cancer: A Population-Based Study. Am J Clin Oncol Cancer Clin Trials 2021;44:315–24.
25. Modest DP, Ricard I, Stintzing S, Fischer von Weikersthal L, Decker T, Kiani A, et al. Evaluation of survival across several treatment lines in metastatic colorectal cancer: Analysis of the FIRE-3 trial (AIO KRK0306). Eur J Cancer 2017;84:262–9.
26. Walters DM, McMurry TL, Isbell JM, Stukenborg GJ, Kozower BD. Understanding mortality as a quality indicator after esophagectomy. Ann Thorac Surg 2014;98:506–12.
27. Low DE, Alderson D, Cecconello I, Chang AC, Darling GE, D'Journo XB, et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Ann Surg 2015;262:286–94.
28. Baiocchi GL, Giacopuzzi S, Marrelli D, Reim D, Piessen G, Matos da Costa P, et al. International consensus on a complications list after gastrectomy for cancer. Gastric Cancer 2019;22:172–89. 5.
29. Concato J, Peduzzi P, Holford TR, Feinstein AR. Importance of events per independent variable in proportional hazards analysis I. Background, goals, and general strategy. J Clin Epidemiol 1995;48:1495–501.
30. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis II. J Clin Epidemiol 1995;48:1503–10.
31. Zou G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. Am J Epidemiol 2004;159:702–6.
32. Knol MJ, Le Cessie S, Algra A, Vandenbroucke JP, Groenwold RHH. Overestimation of risk ratios by odds ratios in trials and cohort studies: Alternatives to logistic regression. Cmaj 2012;184:895–9..
33. Piessen G, Messager M, Le Malicot K, Robb WB, Di Fiore F, Guilbert M, et al. Phase II/III multicentre randomised controlled trial evaluating a strategy of primary surgery and adjuvant chemotherapy versus peri-operative chemotherapy for resectable gastric signet ring cell adenocarcinomas - PRODIGE 19 - FFCD1103 - ADCI002. BMC Cancer 2013;13.
34. Reynolds J V., Preston SR, O'Neill B, Baeksgaard L, Griffin SM, Mariette C, et al. ICORG 10-14: NEOadjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric junction International Study (Neo-AEGIS). BMC Cancer 2017;17:1–10.
35. Hoeppner J, Lordick F, Brunner T, Glatz T, Bronsert P, Röthling N, et al. ESOPEC: Prospective randomized controlled multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (NCT02509286). BMC Cancer 2016;16:1–10.
36. van Putten M, Nelen SD, Lemmens VEPP, Stoot JHMB, Hartgrink HH, Gisbertz SS, et al. Overall survival before and after centralization of gastric cancer surgery in the Netherlands. Br J Surg 2018;105:1807–15.
37. Jensen LS, Nielsen H, Mortensen PB, Pilegaard HK, Johnsen SP. Enforcing centralization for gastric cancer in Denmark. Eur J Surg Oncol 2010;36:S50–4.
38. Nelen SD, Heuthorst L, Verhoeven RHA, Polat F, Kruyt PM, Reijnders K, et al. Impact of Centralizing Gastric Cancer Surgery on Treatment, Morbidity, and Mortality. J Gastrointest Surg 2017;21:2000–8.

39. Lee JH, Chang KK, Yoon C, Tang LH, Strong VE, Yoon SS. Lauren Histologic Type Is the Most Important Factor Associated with Pattern of Recurrence Following Resection of Gastric Adenocarcinoma. Ann Surg 2018;267:105–13.
40. Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v38–49.

SUPPLEMENTARY FILES

Supplementary File 1 - Proportional hazard assumption, statistical details

A key assumption of the Cox regression is proportional hazards, which means that the HR assigned to a variable is constant over time (Therneau et al: "Modeling Survival Data: Extending the Cox Model", 2000). For example, 100 patients receiving "treatment A" are compared with 100 patients receiving "treatment B" and the results yield a hazard ratio of 0.5. The difference between treatment A and B could for example be mortality at 1 year of 10 versus 20 patients, at 3 years of 20 versus 40 patients and at 5 years of 30 versus 60 patients. Hence, the relative difference (not the absolute difference) between treatment groups remains roughly constant over time.

In the current study, the proportional hazard assumptions were assessed in two ways. Kaplan Meier curves were plotted and visually checked for converging or even intersecting lines and for insufficiently diverging lines (i.e. lines showing the same absolute difference over time, but not the same relative difference), all of which indicate that the proportional hazard assumption is not met. In addition, the proportional hazard assumption was directly tested on the outcome variables in the definitive multivariable cox regression models via Schoenfeld's global test, which rejects the proportional hazard assumption (H_0) if $p<0.05$ (Abeysekera et al: J Natl Sci Found Sri Lanka 37:41-51, 2009).

Results of the proportional hazard assumption assessments per subgroup are described in the table in Supplementary file 2. In the gastric groups, an interaction variable "nCT[yes/no]*>90 days[yes/no]" was added to the Cox regression with the "survSplit" function from the "survival" package in R (https://www.rdocumentation.org/packages/survival/versions/3.2-3/topics/survSplit). Hence, a HR for mortality within 90 days and after 90 days was provided (Borucka: "Extensions of Cox Model for Non-Proportional Hazards Purpose", Paper SP07, PhUSE annu. Conf. 2013). After addition of this interaction variable, the proportional hazard assumption was no longer rejected. The 90 day mortality was used for the split, since this allows for easy interpretation of the HRs by clinicians reading the current paper and since 90 day mortality is commonly regarded a parameter for surgery-related mortality (Walters et al: Ann Thorac Surg 98:506–12, 2014; Low et al: Ann Surg 262:286-94, 2015).

In the GEJ groups, the Kaplan Meier nCRT curve clearly intersects with the PS curve (Figure 3), hence the proportional hazard assumption (H_0) was rejected, even though Schoenfeld's tests p values were 0.100 and 0.120. Due to the small numbers of the nCRT group, it wouldn't be possible to split the HR. Hence the nCRT group was removed from the Cox regression (Table 4b). Furthermore, the Kaplan Meier <20 annual resection curve sufficiently diverges from the 20-40 annual resection curve (Supplementary File 7), hence the proportional hazard assumption (H_0) was accepted, even though Schoenfeld's tests p value was 0.028.

Supplementary File 2 Proportional hazard assumptions, assessment and corrections

Primary analysis						
	Gastric - diffuse type	Gastric - SRCC subgroup	GEJ - diffuse type		GEJ - SRCC subgroup	
	nCT versus PS	nCT versus PS	nCRT versus PS	nCT versus PS	nCRT versus PS	nCT versus PS
Without correction:						
Kaplan Meier curves	Insufficiently diverging	Insufficiently diverging	Intersecting	Sufficiently diverging	Intersecting	Sufficiently diverging
Schoenfeld's test	X^2 statistic=7.31, p=0.0069	X^2 statistic=4.70, p=0.030	X^2 statistic=2.712, p=0.100	X^2 statistic=0.0333, p=0.855	X^2 statistic=2.47, p=0.120	X^2 statistic=0.0312, p=0.860
Proportional hazard assumption (H_0)	Rejected	Rejected	Rejected	Accepted	Rejected	Accepted
Presumed cause of rejection	Difference in 90 day mortality (= surgery related mortality)	Difference in 90 day mortality (= surgery related mortality)**	Small sample size of nCRT group		Small sample size of nCRT group	
Correction	Interaction variable "nCT[yes/no]*>90 days[yes/no]" added	Interaction variable "nCT[yes/no]*>90 days[yes/no]" added	Exclusion of nCRT group from Cox regression		Exclusion of nCRT group from Cox regression	
After correction:						
Schoenfeld's test	nCT[yes/no]: X^2 statistic=0.024, p=0.877; nCT[yes/no]*>90 days[yes/no]: X^2 statistic=0.050, p=0.824	nCT[yes/no]: X^2 statistic=0.325, p=0.569; nCT[yes/no]*>90 days[yes/no]: X^2 statistic=0.287, p=0.592	Not applicable		Not applicable	
Proportional hazard assumption (H_0)	Accepted	Accepted	Not applicable		Not applicable	

Post hoc analyses				
	Gastric - diffuse type		GEJ - diffuse type	
	Annual resections <20 versus 20-40	Annual resections <20 versus >40	Annual resections <20 versus 20-40	Annual resections <20 versus >40
Without correction:				
Kaplan Meier curves	Overlapping	Overlapping	Sufficiently diverging	Sufficiently diverging
Schoenfeld's test	X^2 statistic=0.0187, p=0.89	X^2 statistic=1.566, p=0.21	X^2 statistic=4.810, p=0.028	X^2 statistic=0.0294, p=0.864
Proportional hazard assumption (H_0)	Accepted	Accepted	Accepted	Accepted

Supplementary file 3 Treatment characteristics of 984 patients who were diagnosed with a signet ring cell carcinoma, divided per location

	Gastric (n=861)		GEJ (n=123)	
	No. (%)	Missing values (%)	No. (%)	Missing values (%)
Neoadjuvant treatment		0 (0)		0 (0)
Chemotherapy*	398 (46)		47 (38)	
Chemoradiotherapy	0 (0)		27 (22)	
Radiotherapy only	0 (0)		0 (0)	
None	463 (54)		49 (40)	
Surgical treatment		0 (0)		0 (0)
Subtotal gastrectomy	503 (58)		n.a.	
Total gastrectomy	287 (33)		23 (19)	
Transthoracic esophagectomy	n.a.		16 (13)	
Transhiatal esophagectomy	n.a.		21 (17)	
Unknown type of resection	71 (8)		63 (51)	
Adjuvant treatment		0 (0)		0 (0)
Chemotherapy*	219 (25)		20 (17)	
Chemoradiotherapy$	36 (4)		2 (2)	
Radiotherapy only	0 (0)		0 (0)	
None	606 (70)		101 (82)	

Percentages may not add up to 100% due to rounding. *214 patients in de gastric and 20 patients in the GEJ group underwent aCT in the context of perioperative chemotherapy. Of these patients, 38 in the gastric group and 3 in the GEJ underwent additional radiotherapy. 5 patients in the gastric group did not undergo nCT. $24 patients in the gastric and 1 patient in the GEJ group underwent nCT.

Supplementary File 4 Multivariable Poisson regression on treatment factors associated with the occurrence of an R+ resection for diffuse type gastric cancer, corrected by patient and tumor characteristics.

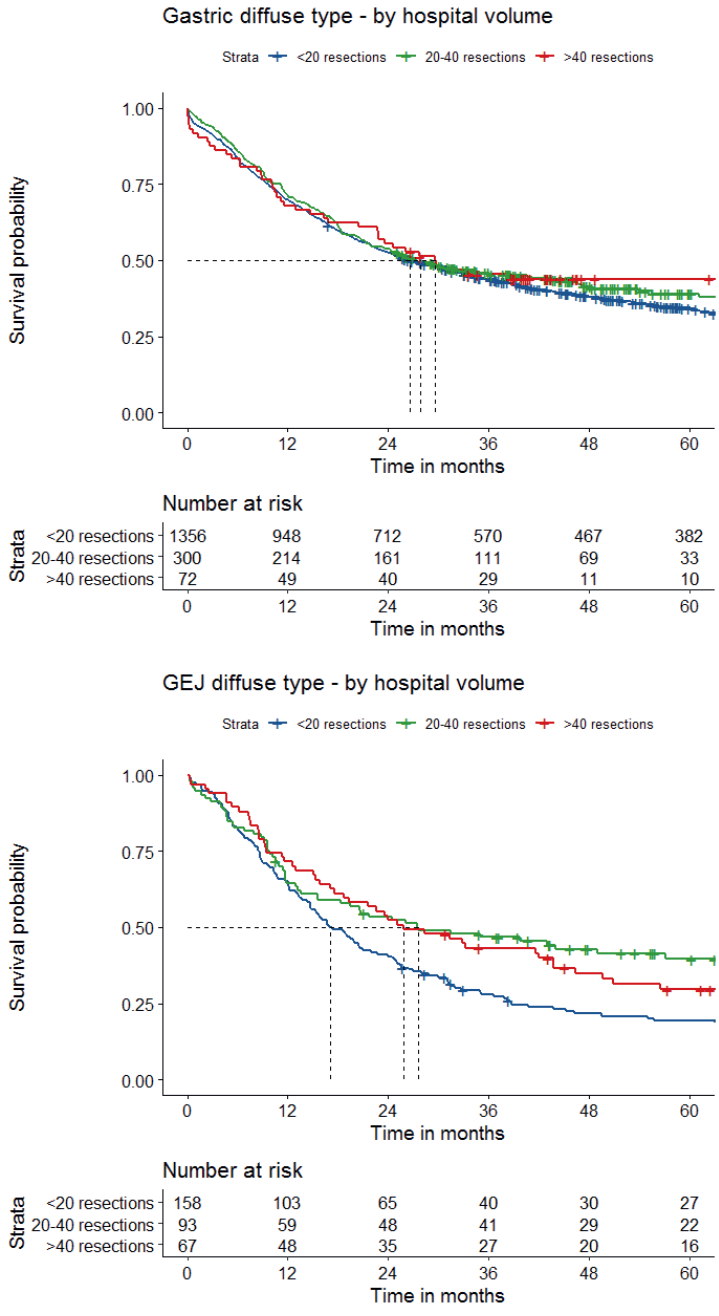
	Gastric - diffuse type					
	Univariable			Multivariable		
	RR	[95% CI]	*p*	RR	[95% CI]	*p*
Hospital volume*						
<20 resections	Ref	-	-	Ref	-	-
20-40 resections	0.73	[0.56-0.97]	**0.028**	0.81	[0.60-1.09]	0.159
>40 resections	0.69	[0.40-1.20]	0.189	0.92	[0.52-1.62]	0.767
nCT	0.85	[0.71-1.02]	0.085	0.81	[0.65-1.02]	0.079
Additional year of age	1.01	[1.00-1.01]	0.065	1.01	[1.00-1.01]	0.176
Female sex	1.01	[0.84-1.22]	0.885	1.09	[0.91-1.31]	0.339
Previous malignancy	1.01	[0.75-1.35]	0.954	1.02	[0.76-1.37]	0.886
cT-stage						
T1	Ref	-	-	Ref	-	-
T2	5.35	[1.74-16.44]	**0.003**	5.34	[1.73-16.42]	**0.004**
T3	6.81	[2.20-21.04]	**0.001**	5.88	[1.88-18.34]	**0.002**
T4	12.17	[3.92-37.76]	**<0.001**	9.16	[2.93-28.60]	**<0.001**
Tx	4.67	[1.53-14.27]	**0.007**	4.20	[1.38-12.78]	**0.012**
cN-stage						
N0	Ref	-	-	Ref	-	-
N+	1.74	[1.42-2.13]	**<0.001**	1.49	[1.20-1.84]	**<0.001**
Nx	1.38	[1.08-1.78]	**0.012**	1.25	[0.97-1.61]	0.080
cMx	1.83	[1.35-2.47]	**<0.001**	1.38	[0.99-1.92]	0.056
Year of surgery						
2004 – 2005	Ref	-	-	Ref	-	-
2006 – 2007	0.96	[0.65-1.42]	0.849	1.00	[0.70-1.43]	0.987
2008 – 2009	1.20	[0.83-1.74]	0.330	1.33	[0.93-1.91]	0.121
2010 – 2011	0.88	[0.60-1.30]	0.515	1.15	[0.76-1.73]	0.512
2012 – 2013	0.74	[0.50-1.10]	0.142	0.92	[0.61-1.39]	0.693
2014 – 2015	0.74	[0.50-1.11]	0.149	0.89	[0.57-1.39]	0.610
Surgical treatment						
Total gastrectomy	Ref	-	-	Ref	-	-
Subtotal gastrectomy	0.67	[0.55-0.81]	**<0.001**	0.63	[0.52-0.77]	**<0.001**
Unknown type of procedure	1.26	[0.95-1.67]	0.108	1.00	[0.73-1.35]	0.981

Bold values indicate significance ($p < 0.05$). RR= relative risk, CI = confidence interval and ref = reference.

Supplementary File 5 Multivariable Poisson regression on treatment factors associated with the occurrence of an R+ resection for diffuse GEJ cancer, corrected by patient and tumor characteristics.

	GEJ - diffuse type								
	Univariable			Multivariable			Multivariable without annual hospital volume		
	RR	[95% CI]	*p*	RR	[95% CI]	*p*	RR	[95% CI]	*p*
Neoadjuvant treatment									
PS	Ref	-	-	Ref	-	-			
nCT	0.83	[0.53-1.28]	0.391	0,70	[0.41-1.19]	0.188	0.67	[0.39-1.98]	0.142
nCRT	0.40	[0.20-0.82]	**0.012**	0,38	[0.17-0.84]	**0.017**	0.33	[0.15-2.21]	**0.006**
Additional year of age	0.99	[0.98-1.01]	0.404	0.99	[0.97-1.01]	0.245	0.99	[0.97-1.31]	0.250
Female sex	1.56	[1.00-2.43]	**0.048**	1.67	[1.03-2.71]	**0.037**	1.58	[0.99-1.69]	0.056
Previous malignancy	1.30	[0.71-2.36]	0.395	1.16	[0.65-2.05]	0.619	1.18	[0.68-3.03]	0.556
cT-stage									
T1-2	Ref	-	-	Ref	-	-	Ref	-	-
T3-4	0.95	[0.58-1.53]	0.825	1,04	[0.66-1.65]	0.864	1.01	[0.63-4.28]	0.980
Tx	0.81	[0.44-1.48]	0.488	0,69	[0.38-1.26]	0.224	0.69	[0.38-2.31]	0.236
cN-stage									
N0	Ref	-	-	Ref	-	-	Ref	-	-
N+	1.61	[0.98-2.63]	0.058	1,49	[0.91-2.45]	0.116	1.50	[0.91-1.85]	0.114
Nx	2.11	[1.07-4.13]	**0.030**	1,71	[0.83-3.53]	0.146	1.83	[0.90-2.24]	0.096
cMx-stage	1.93	[0.95-3.91]	0.067	1.75	[0.85-3.60]	0.129	1.70	[0.81-2.47]	0.162
Year of surgery									
2004 – 2005	Ref	-	-	Ref	-	-	Ref	-	-
2006 – 2007	0.76	[0.38-1.53]	0.445	0,84	[0.44-1.60]	0.592	0.88	[0.45-3.96]	0.710
2008 – 2009	0.58	[0.28-1.22]	0.155	0,71	[0.34-1.50]	0.369	0.71	[0.34-3.11]	0.380
2010 – 2011	0.72	[0.35-1.49]	0.376	1,33	[0.55-3.22]	0.522	1.33	[0.55-4.12]	0.533
2012 – 2013	0.65	[0.31-1.38]	0.261	1,42	[0.61-3.30]	0.414	1.26	[0.55-4.13]	0.589
2014 – 2015	0.30	[0.11-0.81]	**0.018**	0,69	[0.25-1.87]	0.461	0.63	[0.23-3.94]	0.363
Hospital volume									
<20 resections	Ref	-	-	Ref	-	-			
20-40 resections	0.57	[0.34-0.96]	**0.036**	0,67	[0.39-1.18]	0.167			
>40 resections	0.51	[0.27-0.95]	**0.035**	0,47	[0.25-0.91]	**0.025**			
Surgical treatment									
Total gastrectomy	Ref	-	-	Ref	-	-	Ref	-	-
Esophagectomy	0.94	[0.56-1.56]	0.804	1,38	[0.80-2.36]	0.247	1.06	[0.64-3.77]	0.813
Type of procedure unknown	1.63	[0.60-4.41]	0.341	1,62	[0.61-4.33]	0.333	1.63	[0.61-3.75]	0.331

Bold values indicate significance ($p < 0.05$). RR= relative risk, CI = confidence interval and ref = reference.



Supplementary File 6 Overall 5-year survival for diffuse type gastric carcinoma (top) and GEJ diffuse type carcinoma (bottom), stratified by hospital volume. Kaplan-Meier plots and number of patients at risk are displayed. Median survival times are shown by interrupted lines. Censoring of patients is shown by a "+" on the plotted graphs.

Supplementary File 7 Univariable and multivariable Cox regression analyses on all-cause mortality for diffuse type GEJ cancer, without exclusion of the nCRT group.

	GEJ - diffuse type								
	Univariable			Multivariable			Multivariable without annual hospital volume		
	RR	[95% CI]	*p*	RR	[95% CI]	*p*	RR	[95% CI]	*p*
Neoadjuvant treatment									
PS	Ref	-	-	Ref	-	-			
nCT	0.65	[0.48-0.86]	**0.003**	0.64	[0.44-0.92]	**0.017**	0.62	[0.43-0.90]	**0.013**
nCRT*	0.77	[0.55-1.08]	0.131	0.89	[0.56-1.42]	0.632	0.82	[0.51-1.30]	0.387
Additional year of age	1.00	[0.99-1.02]	0.458	1.00	[0.99-1.02]	0.488	1.00	[0.99-1.02]	0.467
Female sex	1.24	[0.91-1.68]	0.168	1.45	[1.05-2.00]	**0.025**	1.41	[1.03-1.95]	**0.034**
Previous malignancy	1.03	[0.68-1.58]	0.878	1.02	[0.65-1.60]	0.927	1.00	[0.64-1.56]	0.996
cT-stage									
T1-2	Ref	-	-	Ref	-	-	Ref	-	-
T3-4	1.08	[0.80-1.47]	0.604	1.03	[0.74-1.42]	0.880	1.06	[0.77-1.47]	0.714
Tx	0.95	[0.66-1.36]	0.781	0.85	[0.58-1.24]	0.408	0.90	[0.62-1.31]	0.570
cN-stage									
N0	Ref	-	-	Ref	-	-	Ref	-	-
N+	1.66	[1.25-2.19]	**<0.001**	1.66	[1.22-2.25]	**<0.001**	1.62	[1.20-2.18]	**0.002**
Nx	1.89	[1.20-2.96]	**0.006**	1.83	[1.14-2.93]	**0.012**	1.84	[1.15-2.94]	**0.011**
cMx-stage	1.36	[0.79-2.33]	0.270	1.28	[0.71-2.31]	0.416	1.21	[0.67-2.16]	0.530
Year of surgery									
2004 – 2005	Ref	-	-	Ref	-	-	Ref	-	-
2006 – 2007	1.05	[0.65-1.68]	0.852	1.13	[0.70-1.82]	0.630	1.16	[0.71-1.87]	0.556
2008 – 2009	0.80	[0.50-1.29]	0.369	0.91	[0.54-1.55]	0.740	0.90	[0.53-1.52]	0.696
2010 – 2011	0.88	[0.53-1.46]	0.614	1.16	[0.62-2.16]	0.636	1.11	[0.59-2.08]	0.744
2012 – 2013	0.55	[0.32-0.93]	**0.024**	0.77	[0.41-1.44]	0.410	0.68	[0.36-1.28]	0.231
2014 – 2015	0.79	[0.46-1.34]	0.373	1.16	[0.62-2.18]	0.647	1.04	[0.56-1.94]	0.897
Hospital volume									
<20 resections	Ref	-	-	Ref	-	-			
20-40 resections	0.64	[0.47-0.87]	**0.005**	0.69	[0.47-1.02]	0.060			
>40 resections	0.74	[0.53-1.03]	0.073	0.60	[0.41-0.89]	**0.010**			
Surgical treatment									
Total gastrectomy	Ref	-	-	Ref	-	-	Ref	-	-
Esophagectomy	0.97	[0.72-1.32]	0.867	1.11	[0.77-1.59]	0.593	0.89	[0.64-1.25]	0.508
Type of procedure unknown	1.09	[0.52-2.28]	0.829	0.90	[0.42-1.97]	0.801	0.93	[0.43-2.03]	0.863

Bold values indicate significance ($p < 0.05$). HR = hazard ratio, CI = confidence interval and ref = reference. *nCRT does not comply with the proportional hazard assumption, hence nCRT can be used as a correction for the remaining variables (i.e. hospital volume), but no conclusions should be drawn from the specific nCRT HR, 95% CI and p value.

Supplementary File 8 Associations between Neoadjuvant treatment, year of surgery and hospital volume

A	Gastric - diffuse type						**B**	GEJ - diffuse type						
	Neoadjuvant treatment							Neoadjuvant treatment						
	PS		nCT					PS		nCT		nCRT		
n (%)	889		839			*p*		125		122		71		*p*
Year of surgery						**<0.001**								**<0.001**
2004 – 2005	128	(14)	0	(0)				26	(21)	2	(2)	1	(1)	
2006 – 2007	241	(27)	62	(7)				51	(41)	13	(11)	1	(1)	
2008 – 2009	152	(17)	156	(19)				27	(22)	36	(30)	3	(4)	
2010 – 2011	124	(14)	194	(23)				7	(6)	24	(20)	22	(31)	
2012 – 2013	142	(16)	206	(25)				9	(7)	24	(20)	21	(30)	
2014 – 2015	102	(11)	221	(26)				5	(4)	23	(19)	23	(32)	
Hospital volume						**<0.001**								**<0.001**
<20 resections	755	(85)	601	(72)				84	(67)	64	(52)	10	(14)	
20-40 resections	107	(12)	193	(23)				22	(18)	37	(30)	34	(48)	
>40 resections	27	(3)	45	(5)				19	(15)	21	(17)	27	(38)	

C	Hospital volume, annual resections							**D**	Hospital volume, annual resections						
	<20		20-40		>40				<20		20-40		>40		
n (%)	1356		300		72		*p*		158		93		67		*p*
Year of surgery							**<0.001**								**<0.001**
2004 – 2005	127	(9)	0	(0)	1	(1)			24	(15)	1	(1)	4	(6)	
2006 – 2007	290	(21)	10	(3)	3	(4)			46	(29)	8	(9)	11	(16)	
2008 – 2009	285	(21)	21	(7)	2	(3)			39	(25)	18	(19)	9	(13)	
2010 – 2011	276	(20)	42	(14)	0	(0)			25	(16)	13	(14)	15	(22)	
2012 – 2013	253	(19)	75	(25)	20	(28)			13	(8)	25	(27)	16	(24)	
2014 – 2015	125	(9)	152	(51)	46	(64)			11	(7)	28	(30)	12	(18)	

Percentages may not add up to 100% due to rounding. Table A displays the influence of year of surgery and hospital volume on the comparison of PS with nCT in the gastric diffuse type group. Table B displays this influence in the GEJ diffuse type group. Table C displays the influence of year of surgery on the comparison of low, mid and high volume centers in the gastric diffuse type group. Table D displays this influence in the GEJ diffuse type group.

Chapter 8

Unplanned omission from surgical resection after preoperative chemotherapy for gastric cancer: a population-based cohort study

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Submitted

ABSTRACT

Background: Despite prognostic benefits, preoperative chemotherapy for gastric cancer is associated with the risk of treatment-related toxicities or disease progression during chemotherapy. This study aimed at providing insight in patients who start preoperative chemotherapy, but do not proceed to surgical resection.

Methods: All patients who started preoperative chemotherapy for gastroesophageal junction and gastric adenocarcinoma diagnosed in 2015-2016 were selected from the population-based Netherlands Cancer Registry. Outcomes included omission from surgical resection, reasons for not proceeding to surgical resection (only available for 2015) and 1-year overall survival.

Results: Some 561 patients started preoperative chemotherapy of which 59 patients (10.5%) did not proceed to surgical resection. Fifteen patients (2.7%) deceased during or ≤30 days after ending preoperative chemotherapy. Of the patients who did not proceed to surgery in 2015, the main reason was disease progression (54.2%). One-year overall survival of the patients who underwent preoperative chemotherapy followed by surgical resection was 85.5%, and 20.3% in the patients who did not undergo surgical resection following preoperative chemotherapy.

Conclusion: From all patients who start preoperative chemotherapy for gastroesophageal cancer with curative intent, 1 in 10 does not proceed to surgical resection. Accurate patient selection for preoperative chemotherapy should be the focus of future research to ultimately improve survival of patients with gastroesophageal junction and gastric adenocarcinoma.

BACKGROUND

Perioperative chemotherapy has been established as an integrated element of the curative treatment of gastric cancer, improving overall survival compared to surgery alone[1,2]. Despite the prognostic benefits, perioperative chemotherapy is not without the risk of complications[3]. As surgical resection remains the mainstay treatment for resectable gastric cancer and postoperative morbidity and mortality rates are decreasing due to improved quality measures[4], such as centralization[5-8], and enhanced perioperative care[9,10], there is an increasing need to balance the potential prognostic benefit of chemotherapy and the risk of treatment-associated toxicities that might prevent patients from undergoing surgery[3].

Several studies have focused on complications during preoperative therapy and their effects on surgical morbidity and short- and long-term survival, concluding that complications during preoperative therapy may negatively affect short- and long-term survival[3,11,12]. Randomized controlled intervention trials report omission from surgical resection after starting preoperative therapy in up to 12% of patients (11.8% [28/237][1], 11.6% [41/354][13], 5.3% [21/392][14], 4.5% [16/352][13], 3.5% [4/113][2]) and mortality rates of ≤1% during preoperative therapy for gastric cancer (0.8% [2/237][1], 0.9% [1/113][2] and 1.0% [4/392][14]). However, trial populations are often carefully selected based on strict inclusion criteria – e.g. within a certain age range, limited comorbidities or good performance status. The estimates of treatment-related toxicities from these trials are therefore less generalizable to the general patient population[15].

Therefore, the aim of this population-based cohort study was to describe the patients with gastroesophageal junction or gastric adenocarcinoma who started preoperative chemotherapy and did not proceed to surgical resection, as well as to provide insight in reasons why these patients did not proceed to surgical resection.

METHODS

Study design

This population-based observational cohort study included data from the Netherlands Cancer Registry (NCR). The NCR registers all newly diagnosed cancer cases based on notification of all newly diagnosed malignancies in the Netherlands by the national automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge diagnoses, radiotherapy institutions and diagnosis therapy combinations. The NCR stores data on patient, tumor and treatment characteristics. Data is routinely extracted from hospital records by trained data managers. Information on a patient's vital status is updated through an annual linkage with the municipal personal records database, in which all deceased and emigrated persons in the Netherlands are registered.

This study was approved by the Privacy Review Board of the NCR and did not require approval from an ethics committee in the Netherlands according to the Central Committee on Research involving Human Subjects.

Study population

For the purpose of this study, all patients with gastroesophageal junction or gastric adenocarcinoma in the Netherlands who started preoperative chemotherapy in 2015 and 2016 were selected. Patients with distant metastases (clinical M1) and a histologic tumor type other than adenocarcinoma were excluded. Data on patient and treatment-related characteristics, histopathological characteristics, and follow-up were extracted from the NCR.

Patients were diagnosed according to the Dutch national guidelines for patients with gastric cancer[16]. The diagnostic work-up consisted of at least endoscopy with tumor biopsy and computed tomography (CT). Staging laparoscopy and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT were also frequently performed, although indications for these modalities (≥ T3 and/or ≥ N1 tumors) were only included in the revised guidelines as of July 2016. Patients were staged according to the 7th edition of the Union for International Cancer Control (UICC) TNM staging system[17].

Treatment

From 2015 onwards, the NCR stored data on a patient level regarding the chemotherapy regimens, treatment intention and starting dates of treatment. Preoperative chemotherapy, which is indicated in all patients with resectable gastric adenocarcinoma (clinical stage >I), generally consisted of a regimen with 3 cycles of triplet chemotherapy consisting of epirubicin, cisplatin or oxaliplatin, and capecitabine or fluorouracil in the Netherlands in 2015 and 2016[1,18]. Occasionally, a doublet chemotherapy regimen such as capecitabine and oxaliplatin was preferred. The final choice of chemotherapy regimen was at the discretion of the treating medical oncologist. Surgery was defined as an actual surgical resection and generally consisted of a (sub)total gastrectomy along with a D1+ or D2 lymphadenectomy without pancreaticosplenectomy.

Outcome measures

Whether or not surgical resection was performed was routinely registered by the NCR. Reasons for not proceeding to surgical resection in patients who started preoperative chemotherapy were registered by the NCR based on standardized categories (i.e. disease progression, impaired physical functioning and patient preference) for patients diagnosed in 2015 only.

Mortality during preoperative chemotherapy was calculated as all-cause mortality ≤30 days after ending the most recent cycle and always before the intended surgical resection[19]. The last day of preoperative chemotherapy was defined as the last day of the last cycle. Mortality during preoperative chemotherapy according to the aforementioned definition was added as a reason for not proceeding to surgery after starting preoperative chemotherapy.

Follow-up time included at least 12 months from starting preoperative therapy of all patients and was completed until January 1st, 2018. Survival time was defined as time from diagnosis to death or until January 1st, 2018 for patients who were still alive.

Statistical analysis

Patient and treatment-related characteristics were described as counts with percentages, mean (± standard deviation [SD]) or median (interquartile range [IQR]). Patients who did not undergo

surgical resection after starting preoperative chemotherapy, as well as patients who deceased during preoperative chemotherapy or the subsequent waiting period were described.

To be able to identify potential predictive factors for omission from surgical resection after starting preoperative chemotherapy, missing values were imputed using multivariate imputation by chained equations and subsequently predictor selection was performed using lasso (Least Absolute Shrinkage and Selection Operator) penalized regression because of an expected low event per predictor variable ratio[20] (see Supplementary material for details). Survival curves were obtained using the Kaplan–Meier method.

Statistical analysis was performed using R open-source software ('mice'[21] and 'glmnet'[22] packages, version 3.5.1) and GraphPad Prism version 7.04 (La Jolla, California, USA).

RESULTS

Study population

In 2015 and 2016, 561 patients started preoperative chemotherapy for gastroesophageal junction or gastric adenocarcinoma in the Netherlands. The majority of patients was male (64.9%), with a mean age of 63.3 years. Fourteen patients (2.5%) had a WHO performance status at diagnosis of 2 or 3. Comorbidities were present in 57.8% of patients. Most tumors were clinical T2 or T3 stage (36.4% and 36.9%, respectively) without lymph node metastases (cN0: 52.6%). Tumor locations included the gastroesophageal junction in 22.8% (Siewert type II and III), the proximal part of the stomach in 21.6% and distal part of the stomach in 33.3% of patients. Most tumors were poorly differentiated (52.6%). As preoperative chemotherapy regimens, EOX (44.4%) and ECX (42.8%) were mostly administered. Four patients (0.7%), all with a WHO performance status of 0-1, received doublet chemotherapy. A complete overview of patient and treatment-related characteristics is presented in Table 1.

Surgical resection of the primary tumor was performed at a median of 50 days (IQR: 42 - 64 days) after the last day of preoperative chemotherapy.

Omission from surgery

No surgical resection was performed in 59 patients (10.5%). These patients had a mean age of 66.1 years and mostly a poorly differentiated adenocarcinoma (49.2%). The gastroesophageal junction was the most frequent anatomical location of the tumor (30.5%).

The most frequently reported reasons for not performing surgical resection in 2015 were disease progression in 54.2% (13/24) (Table 2) and mortality during or ≤30 days of ending preoperative chemotherapy in 29.2% (7/24).

Of the 15 patients (2.7%) who deceased during preoperative chemotherapy in the entire cohort (2015 and 2016), the majority was male (60.0%), with a mean age of 68.5 years. Most patients had comorbidities in ≥2 categories (46.7%), of which hypertension and cardiovascular comorbidities were the most frequently present (53.3% and 26.7%, respectively).

Furthermore, most patients had a tumor with a clinical T2 stage (60.0%) without lymph node metastases (cN0: 73.3%). A detailed description of these patient demographics is included in Table 1.

No stable predictors for unplanned omission from surgical resection could be identified using lasso penalized regression. The coefficients of all pre-defined predictors (age, sex, BMI at diagnosis, performance status, number of comorbidity categories, tumor location, clinical T status, clinical N status, tumor histology and Lauren classification) were shrunken to 0. As such, no stable predictors were retained and the subsequent multivariable logistic regression analysis could not be performed.

Survival

Kaplan-Meier survival curves for 1-year overall survival of all patients that started preoperative chemotherapy per treatment group (i.e. preoperative chemotherapy followed by surgical resection and preoperative chemotherapy without surgical resection) are depicted in Figure 1. One-year overall survival of the patients who underwent preoperative chemotherapy followed by surgical resection was 85.5%. One-year overall survival of the patients who did not undergo surgical resection was 20.3%.

Table 1. Characteristics of patients who started preoperative chemotherapy for gastroesophageal or gastric cancer in the Netherlands in 2015 and 2016.

Characteristics	All n = 561 (%)	Omission from surgical resection n = 59 (%)	Deceased during preoperative chemotherapy[a] n = 15 (%)
Age, years (mean ± SD)	63.3 ± 10.5	66.1 ± 8.0	68.5 ± 4.1
Sex			
Male	364 (65)	39 (66)	9 (60)
Female	197 (35)	20 (34)	6 (40)
BMI, kg/m^2 (mean ± SD)	25.4 ± 4.0	25.3 ± 4.4	27.9 ± 4.6
Unknown	181 (32)	26 (44)	6 (40)
WHO performance status			
0	267 (48)	25 (42)	8 (53)
1	150 (27)	21 (36)	3 (20)
2	12 (2)	2 (3)	0 (0)
3	2 (<1)	0 (0)	0 (0)
Unknown	130 (23)	11 (19)	4 (27)
Comorbidity categories[b]			
None	189 (34)	15 (25)	4 (27)
One category	160 (29)	24 (41)	4 (27)
Two or more categories	164 (29)	19 (32)	7 (47)
Unknown	48 (9)	1 (2)	0 (0)
Specific comorbidities			
Hypertension	151 (27)	21 (36)	8 (53)
Cardiovascular comorbidities (other than hypertension)	122 (22)	13 (22)	4 (27)
Diabetes mellitus	74 (13)	9 (15)	3 (20)
Pulmonary comorbidities	64 (11)	11 (19)	3 (20)
History of cancer	48 (9)	6 (10)	0 (0)
Gastrointestinal comorbidities	50 (9)	2 (3)	1 (7)
Tumor location			
Gastroesophageal junction (distal esophagus/cardia)	128 (23)	18 (31)	4 (27)
Proximal (fundus/corpus)	121 (22)	11 (19)	2 (13)
Distal (antrum/pylorus)	187 (33)	17 (29)	7 (47)
Overlapping/ not specified	125 (22)	13 (22)	2 (13)
Clinical T stage[c]			
T1	15 (3)	1 (2)	0 (0)
T2	204 (36)	19 (32)	9 (60)
T3	207 (37)	27 (46)	4 (27)
T4a	29 (5)	5 (9)	0 (0)
T4b	16 (3)	1 (2)	0 (0)
Unknown	90 (16)	6 (10)	2 (13)
Clinical N stage[c]			
N0	295 (53)	32 (54)	11 (73)
N1	151 (27)	14 (24)	2 (13)
N2	90 (16)	11 (19)	2 (13)
N3	7 (1)	1 (2)	0 (0)
Unknown	18 (3)	1 (2)	0 (0)
Clinical tumor stage[c]			
IA	11 (2)	0 (0)	0 (0)
IB	142 (25)	16 (27)	7 (47)
IIA	117 (21)	11 (19)	3 (20)
IIB	74 (13)	7 (12)	0 (0)
IIIA	74 (13)	11 (19)	2 (13)
IIIB	47 (8)	7 (12)	1 (7)
IIIC	8 (1)	1 (2)	0 (0)
Unknown	88 (16)	6 (10)	2 (13)

Lauren classification	224 (40)	12 (20)	2 (13)
Intestinal type	209 (37)	24 (41)	4 (27)
Diffuse type	10 (2)	0 (0)	0 (0)
Indeterminate	118 (21)	23 (39)	9 (60)
Not otherwise specified			
Tumor differentiation	135 (24)	10 (17)	4 (27)
Good to moderate	295 (53)	29 (49)	6 (40)
Poor to undifferentiated	131 (23)	20 (34)	5 (33)
Unknown			
Chemotherapy regimen	249 (44)	26 (44)	5 (33)
EOX	240 (43)	29 (49)	9 (60)
ECX	29 (5)	4 (7)	1 (7)
ECF	11 (2)	0 (0)	0 (0)
DOC	1 (<1)	0 (0)	0 (0)
DCF	6 (1)	0 (0)	0 (0)
EOF	1 (<1)	0 (0)	0 (0)
FOLFOX	3 (1)	0 (0)	0 (0)
CAPOX	21 (4)	0 (0)	0 (0)
Unknown			
Year of diagnosis			
2015	294 (52)	24 (41)	7 (47)
2016	267 (48)	35 (59)	8 (53)

Percentages may not add up to 100% due to rounding. BMI: body mass index at diagnosis; CAPOX: capecitabine, oxaliplatin; DCF: docetaxel, cisplatin, 5-fluorouracil; DOC: docetaxel, oxaliplatin, capecitabine; ECX: epirubicin, cisplatin, capecitabine (Xeloda); ECF: epirubicin, cisplatin, 5-fluorouracil; EOF: epirubicine, oxaliplatin, 5-fluorouracil; EOX: epirubicin, oxaliplatin, capecitabine (Xeloda); FOLFOX: oxaliplatin, 5-fluorouracil; SD: standard deviation; WHO: World Health Organization. a. The patients who deceased during preoperative chemotherapy are also included in the patients who did not undergo surgical resection. b. Closely related comorbidities were considered as one category. c. Based on UICC TNM 7th edition.

Table 2. Reasons for not proceeding to surgery in patients that started preoperative chemotherapy for gastroesophageal junction or gastric cancer in 2015.

Reason	All n = 24 (%)
Disease progression	13 (54)
Impaired physical functioning	1 (4)
Patient preference	1 (4)
Mortality during preoperative chemotherapy	7 (29)
Other/unknown	2 (8)

DISCUSSION

This population-based observational cohort study aimed to gain insight in the patients with gastroesophageal junction or gastric cancer who do not proceed to surgical resection after starting preoperative chemotherapy, as well as to describe reasons why these patients who do not proceed to surgical resection. Our study demonstrated that 1 in 10 patients (10.5%) who started preoperative chemotherapy for gastric cancer did not undergo the planned gastrectomy, for which no predictive factors could be identified.

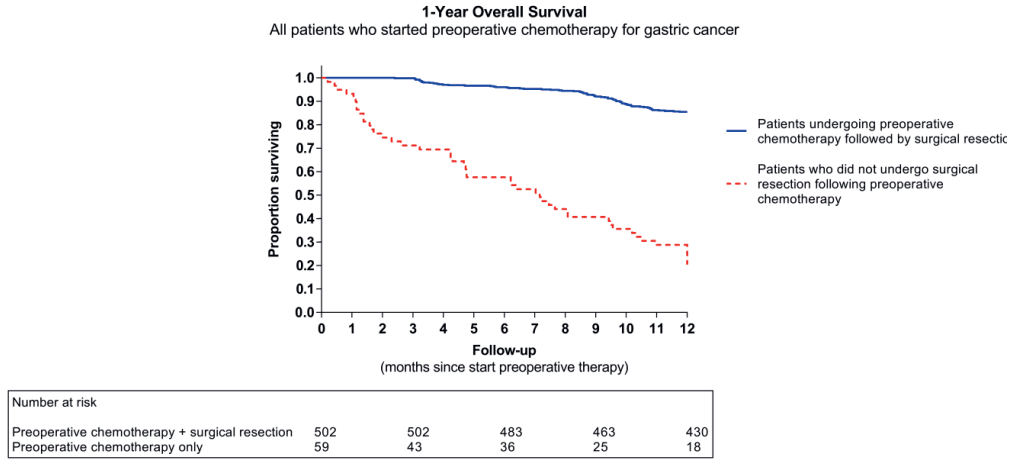

Figure 1. Kaplan-Meier estimates of overall survival for patients who started preoperative chemotherapy for gastroesophageal junction or gastric cancer in 2015 and 2016. The categorization of patients by treatment, results in immortal time bias from the start of preoperative chemotherapy until the date of surgery for patients who underwent preoperative chemotherapy followed by surgery (blue curve).

Preoperative chemotherapy with the triplet ECX, as part of a perioperative chemotherapy approach, has been shown to provide a 13% improvement in 5-year overall survival rates compared to surgery alone[1]. Other multimodality treatment approaches include the more recently introduced docetaxel-based triplet FLOT[13], preoperative chemoradiotherapy according to the CROSS regimen for esophageal and gastroesophageal junction cancer[23] or upfront surgery with consideration for postoperative chemo(radio)therapy for gastroesophageal junction and gastric cancer[24-27]. When choosing the most appropriate treatment regimen for the individual patient, physicians must balance the risk of treatment-associated toxicities during preoperative treatment that might prevent the patient from proceeding to surgery against the risk of patients poorly tolerating postoperative treatment after upfront surgery.

The use of preoperative chemotherapy and other forms of multimodality therapy for gastric adenocarcinoma has increased remarkably over the years, from 34% of patients who underwent gastrectomy in 2006 to 65% in 2014 in the United States of America[28]. In the Netherlands, 50-55% of the patients who underwent a gastrectomy received preoperative chemotherapy between 2011-2014, which increased to 61% in 2017[4,29]. Several factors have been demonstrated

to contribute to whether or not multimodality treatment is applied. Younger age, male sex, comorbidities, higher clinical T and N classification, cardiac tumors and consultation of ≥ 3 upper gastrointestinal specialists were significantly associated with more frequent multimodality treatment receipt in population-based studies[28,30-32]. Furthermore, racial and ethnic disparities existed in the probability of receiving perioperative treatment, as well as significant hospital variation[28,33].

Unfortunately, all the aforementioned studies regarding multimodality treatment recipience excluded patients who started preoperative treatment, but did not proceed to potentially curative surgery for any reason. The inclusion of this patient population however would be more representative of daily clinical practice and is critical for incorporation of results of randomized clinical trials into clinical practice[30,34]. Only one – non-randomized – study included all patients with gastric adenocarcinoma that were evaluated for gastrectomy and specifically focused on the frequency of gastrectomy after preoperative chemotherapy. They included 533 patients from The University of Texas MD Anderson Cancer Center from 1995-2014, and demonstrated that only 71.1% (64/90) of patients who started preoperative chemotherapy underwent a potentially curative resection[34]. For the current study and the MAGIC trial[1], these numbers were higher (89.5% and 88.1% of patients underwent surgical resection after starting preoperative chemotherapy, respectively). In the more recent CRITICS-I and FLOT-AIO4 trials even 94-95% of the patients who started preoperative chemotherapy proceeded to surgery[14,35]. This variation might be explained by differences between study populations (randomized clinical trials versus the general patient population) and chemotherapy tolerance, as well as historical differences, as it has been demonstrated that after the current centralization of gastric cancer surgery resection rates increased[36]. The increased possibilities of minimally invasive surgery may also contribute to the fact that more patients are deemed fit enough for surgery in the recent years. Better staging of patients with a pretreatment staging laparoscopy and 18F-FDG PET/CT might furthermore improve accurate patient selection for multimodality treatment.

The aforementioned differences in study populations may also account for the observed variation in mortality rates during preoperative chemotherapy. In the current study, 2.7% of patients deceased during or within ≤30 days after ending preoperative chemotherapy. As a proxy for toxicity, this is more in line with the findings from the MD Anderson Cancer study in

which toxicity or worsening physical status accounted for not proceeding to surgery in 2.2%[34], than with the percentages from the MAGIC (0.8%) and CRITICS-I trials (1.0%)[1,14].

Our finding that progression of disease is the most prevalent reason for not undergoing a potentially curative resection is in line with the MD Anderson Cancer Center study, which noted progressive disease on imaging during preoperative chemotherapy in 18.9% of patients (17/90)[34]. However, it is questionable whether this phenomenon is indeed disease progression, or in fact reflects occult systemic disease at the time of starting preoperative chemotherapy. In the latter situation, preoperative chemotherapy might provide time for distant metastases to become apparent on restaging imaging, and thus prevent surgical resection with corresponding risk of postoperative morbidity in patients with distant metastases who might not benefit from a resection in terms of survival. This might also be true for the patients in the current study who did not undergo 18F-FDG-PET/CT and staging laparoscopy and might not have been properly staged before treatment, as these diagnostic modalities were only added to the national staging guidelines in July 2016. Hence, the reported disease progression in these patients might instead correspond to understaged micrometastatic disease.

It must be noted that the results of the current study are only applicable to those patients who started preoperative chemotherapy for gastroesophageal junction and gastric cancer. In general, these patients have a better physical condition than patients who are not deemed fit enough for perioperative chemotherapy and undergo upfront surgery. Second, this analysis was conducted in the era before FLOT. As FLOT is a more effective triplet with comparable toxicity, disease progression during this new triplet may be less than as described in our study.
Furthermore, it is important to realize that our descriptive study merely describes current clinical practice. Baseline differences between patient groups are likely to influence for example the observed differences in the 1-year overall survival curves for the two treatment groups (as depicted in Figure 1. Therefore, these results warrant careful interpretation and no statistical test was performed for this comparison.

Certain limitations apply to the current study. Even though the data in the NCR is extracted from hospital records by trained data managers, the results generated out of population-based database studies are dependent upon the reliability of the methodology and accuracy of data

collection, which is a limitation shared by all national databases. Missing data and coding inconsistencies may introduce bias and inaccuracy. In addition, the study was limited by the variables in the data set, which did not include details about the exact cause of death or information on hospital volumes. As hospital variation is known to influence the probability of receiving surgical treatment for resectable gastric cancer as well as adjuvant chemotherapy completion rates[33,37], this might also be a factor influencing the probability of receiving surgical treatment after starting preoperative chemotherapy.

Significant strengths of the study are the population-based design with virtually complete inclusion of all patients in the Netherlands who started preoperative chemotherapy for gastroesophageal junction and gastric adenocarcinoma. As such, the results of the study are very representative of daily clinical practice and generalizable for Western patients.

No stable patient or tumor-related predictors for omission from surgery could be identified in our study. This could be due to a lack of power or study size, or the fact that the analyzed predictors (i.e., age, sex, BMI, performance status, number of comorbidity categories, tumor location, clinical T status, clinical N status, tumor histology and Lauren classification) were not suited for prediction of not proceeding to surgery. To more accurately identify those patients who benefit from upfront surgery, better predictors are needed. These predictors may be used to develop a composite impression of patients who start preoperative therapy, but might not proceed to surgery, and in whom additional counseling or interventions during preoperative therapy might be beneficial. Contrarily, preoperative therapy may also be considered as an effective means for selecting patients who are fit enough to undergo surgical resection. Whether or not preoperative chemotherapy should function as selection mechanism for patients who are eligible for surgery, or patients should be selected for preoperative chemotherapy remains unresolved.

Lastly, the same perioperative treatment regimens are used for all patients with gastric cancer and do not differentiate among molecular subtypes. Classification of gastric carcinomas based on molecular subtypes might however be used to determine prognosis and to customize treatment[38]. For example, it has been suggested in preclinical trials that patients with microsatellite unstable tumors might not benefit from chemotherapy[38]. Future prospective

studies should aim to evaluate these customized treatment strategies in order to establish their use in clinical practice.

CONCLUSION

In summary, our study contributes to the body of research on the application of preoperative chemotherapy for patients with gastroesophageal junction and gastric cancer in clinical practice by assessing the frequency of not proceeding to surgical resection after starting preoperative chemotherapy. From all patients who start preoperative chemotherapy for gastroesophageal cancer with curative intent, 1 in 10 does not proceed to surgical resection. This is an important consideration in selecting patients for preoperative treatment. Future research should aim to investigate whether this can be further optimized and whether this patient group that does not proceed to surgery can be selected prior to treatment. If so, interventions and counseling might result in a larger proportion of patients who will undergo surgery.

REFERENCES

1. Cunningham D, Allum WWH, Stenning SSP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11–20.
2. Ychou M, Boige V, Pignon J, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715.
3. Markar SR, Johar A, Maisey N, et al. Complications during neoadjuvant therapy and prognosis following surgery for esophageal cancer. Dis Esophagus 2018;31.
4. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, et al. Early outcomes from the Dutch Upper Gastrointestinal Cancer Audit. Br J Surg 2016;103:1855–63.
5. Brusselaers N, Mattsson F, Lagergren J. Hospital and surgeon volume in relation to long-term survival after oesophagectomy: systematic review and meta-analysis. Gut 2014;63:1393–400.
6. Coupland VH, Lagergren J, Lüchtenborg M, et al. Hospital volume, proportion resected and mortality from oesophageal and gastric cancer: a population-based study in England, 2004–2008. Gut 2013;62:961–6.
7. Derogar M, Sadr-Azodi O, Johar A, et al. Hospital and Surgeon Volume in Relation to Survival After Esophageal Cancer Surgery in a Population-Based Study. J Clin Oncol 2013;31:551–7.
8. Anderson O, Ni Z, Møller H, et al. Hospital volume and survival in oesophagectomy and gastrectomy for cancer. Eur J Cancer 2011;47:2408–14.
9. Findlay JM, Gillies RS, Millo J, et al. Enhanced recovery for esophagectomy: a systematic review and evidence-based guidelines. Ann Surg 2014;259:413–31.
10. Markar SR, Schmidt H, Kunz S, et al. Evolution of standardized clinical pathways: refining multidisciplinary care and process to improve outcomes of the surgical treatment of esophageal cancer. J Gastrointest Surg 2014;18:1238–46.
11. Robb WB, Messager M, Gronnier C, et al. High-Grade Toxicity to Neoadjuvant Treatment for Upper Gastrointestinal Carcinomas: What is the Impact on Perioperative and Oncologic Outcomes? Ann Surg Oncol 2015;22:3632–9.
12. Mariette C, Brouquet A, Tzanis D, et al. What is the impact of neoadjuvant chemoradiation on outcomes in gastro-intestinal cancer? J Visc Surg 2017;154:185–95.
13. Al-Batran S, Homann N, Schmalenberg H, et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO). J Clin Oncol 2017;35:4004–4004.
14. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol 2018;19:616–28.
15. Kennedy-Martin T, Curtis S, Faries D, et al. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. Trials 2015;16.
16. Vennix S, Pelzers L, Bouvy N, et al. Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev 2014;(4):CD0052:CD005200.
17. Sobin L, Gospodarowicz M WC (Eds). TNM : classification of malignant tumours. 2009.
18. Cunningham D, Starling N, Rao S, et al. Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer. N Engl J Med 2008;358:36–46.
19. Wallington M, Saxon EB, Bomb M, et al. 30-day mortality after systemic anticancer treatment for breast and lung cancer in England: a population-based, observational study. Lancet Oncol 2016;17:1203–16.
20. Pavlou M, Ambler G, Seaman SR, et al. How to develop a more accurate risk prediction model when there are few events. BMJ 2015;351:h3868.
21. Van Buuren S, Groothuis-Oudshoorn K. Multivariate Imputation by Chained Equations. J Stat Softw 2011;45:1–67.

22. Friedman J, Hastie T, Tibshirani R. Regularization Paths for Generalized Linear Models via Coordinate Descent. J Stat Softw 2010;33:1–22.
23. van Hagen P, Hulshof MCCM, van Lanschot JJB, et al. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. N Engl J Med 2012;366:2074–84.
24. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after Surgery Compared with Surgery Alone for Adenocarcinoma of the Stomach or Gastroesophageal Junction. N Engl J Med 2001;345:725–30.
25. Bang Y-J, Kim Y-W, Yang H-K, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012;379:315–21.
26. Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant Chemotherapy for Gastric Cancer with S-1, an Oral Fluoropyrimidine. N Engl J Med 2007;357:1810–20.
27. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, et al. Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer. JAMA 2010;303:1729.
28. Ikoma N, Cormier JN, Feig B, et al. Racial disparities in preoperative chemotherapy use in gastric cancer patients in the United States: Analysis of the National Cancer Data Base, 2006-2014. Cancer 2018;124:998–1007.
29. Dutch Institute for Clinical Auditing - Dutch Upper GI Cancer Audit. Jaarraportage 2017 2017.
30. Trip AK, Stiekema J, Visser O, Dikken JL, et al. Recent trends and predictors of multimodality treatment for oesophageal, oesophagogastric junction, and gastric cancer: A Dutch cohort-study. Acta Oncol (Madr) 2015;54:1754–62.
31. Sherman KL, Merkow RP, Bilimoria KY, et al. Treatment Trends and Predictors of Adjuvant and Neoadjuvant Therapy for Gastric Adenocarcinoma in the United States. Ann Surg Oncol 2013;20:362–70.
32. Beck N, Busweiler LAD, Schouwenburg MG, et al. Factors contributing to variation in the use of multimodality treatment in patients with gastric cancer: A Dutch population based study. Eur J Surg Oncol 2018;44:260–7.
33. Schouwenburg MG, Busweiler LAD, Beck N, et al. Hospital variation and the impact of postoperative complications on the use of perioperative chemo(radio)therapy in resectable gastric cancer. Results from the Dutch Upper GI Cancer Audit. Eur J Surg Oncol 2018;44:532–8.
34. Badgwell B, Blum M, Elimova E, et al. Frequency of Resection After Preoperative Chemotherapy or Chemoradiotherapy for Gastric Adenocarcinoma. Ann Surg Oncol 2016;23:1948–55.
35. Al-Batran S-E, Hofheinz RD, Pauligk C, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol 2016;17:1697–708.
36. van Putten M, Nelen SD, Lemmens VEPP, et al. Overall survival before and after centralization of gastric cancer surgery in the Netherlands. Br J Surg 2018;105:1807–15.
37. Van Putten M, Verhoeven RHA, Van Sandick JW, et al. Hospital of diagnosis and probability of having surgical treatment for resectable gastric cancer. Br J Surg 2016;103:233–41.
38. Van Cutsem E, Sagaert X, Topal B, et al. Gastric cancer. Lancet 2016;388:2654–64.

SUPPLEMENTARY FILES

Supplement to: Borggreve AS, Gertsen EC, Ruurda JP, et al. Unplanned omission from surgical resection after preoperative chemotherapy for gastric cancer: a population-based cohort study.

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Methods

Statistical analysis for predictive factor identification

To be able to identify potential predictive factors for omission from surgical resection after starting preoperative chemotherapy, missing values in the variables to be entered in the lasso penalized regression model were imputed using multiple imputation (Multivariate Imputation by Chained Equations, 30 imputed datasets with a maximum number of 20 iterations for each imputation).1,2 Next, predictor selection was performed using lasso (Least Absolute Shrinkage and Selection Operator) penalized regression because of an expected low event per predictor variable ratio.3 In each imputed dataset, lasso regression was applied and the lambda plus one standard error criterion (gained through 10-fold cross-validation) was used to select variables. This resulted in 30 sets of variables being selected in the 30 imputed sets. Variable selection for the multivariable logistic regression model took place using the majority rule, i.e. if the predictor was retained within the model in at least 15 of the imputation sets, it was included in the final model. The multivariable logistic regression model was fitted with these selected predictors in each imputation set, and model coefficients were pooled using Rubin's rules. Variables to be entered in the lasso penalized regression model with omission from surgery as outcome were based on clinical reasoning, and consisted of age, sex, body mass index at diagnosis (BMI), performance status, number of comorbidity categories, tumor location, clinical T status, clinical N status, tumor histology and Lauren classification.

Results

Predictive factors

Lasso penalized regression with omission from surgical resection as outcome in the 30 imputed datasets resulted in shrinkage of the coefficients of all pre-defined predictors (age, sex, BMI at diagnosis, performance status, number of comorbidity categories, tumor location, clinical T status, clinical N status, tumor histology and Lauren classification) to 0. As such, no stable predictors were retained and the subsequent multivariable logistic regression analysis could not be performed.

References

1. 1. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393. doi:doi: 10.1136/bmj.b2393.
2. 2. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30(4):377-399. doi:10.1002/sim.4067.
3. 3. Pavlou M, Ambler G, Seaman SR, et al. How to develop a more accurate risk prediction model when there are few events. BMJ. 2015;351:h3868. doi:10.1136/BMJ.H3868.

Chapter 9

Refraining from resection in patients with potentially curable gastric carcinoma

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ABSTRACT

Background: Surgical resection is the cornerstone of curative treatment for gastric cancer. The aim of this study was to evaluate reasons for and patient- and tumor characteristics that are associated with refraining from surgical resection in patients with potentially curable gastric cancer.

Methods: Between 2015-2017, all patients with potentially curable gastric adenocarcinoma (cT1- 4a-x, cN0-3-x, cM0) were included from the Netherlands Cancer Registry (NCR). Patients were divided into a resection (RG) and a no-resection group (nRG). Reasons for not undergoing resection as registered by the NCR were evaluated. Using multivariable logistic regression analyses, patient and tumor characteristics associated with refraining from resection were assessed.

Results: Of the 1679 analyzed patients with potentially curable disease, 1127 patients (67%) underwent resection, and 552 patients (33%) did not. Most common registered reasons for refraining from surgery were patient refusal (25%), low performance status (23%), comorbidity and extent of disease (both 10%). Factors associated with not undergoing resection were: age ≥80 years (OR 4.77, [95%CI 2.27-10.06], p< 0.001), low Social-Economic-Status (SES) (OR 2.68 [95%CI 1.31-5.46], p=0.007), WHO performance status 3-4 (OR 10.48 [95%CI 2.41-45.73], p=0.002) with several accompanying comorbidities, unclassified Lauren classification (OR 3.93 [95%CI 1.61- 9.56], p=0.003) and overlapping/diffuse tumors (OR 3.51, [95%CI 1.54-8.05], p=0.003).

Conclusion: A third of patients with potentially curable gastric cancer did not undergo resection. Most frequent registered reasons for refraining from surgery were patient refusal, performance status, comorbidity and extent of disease. Additionally, multivariable analyses identified higher age, lower SES, and poor tumor characteristics as associated factors.

BACKGROUND

In Europe, 133 thousand new gastric cancer cases were diagnosed in 2018[1]. The cornerstone of curative treatment is gastrectomy with lymphadenectomy[2], and physically fit patients will also be offered perioperative chemotherapy to improve survival[3,4]. Evolving pre-operative staging possibilities, for example by means of fluorodeoxyglucose positron emission tomography (FDG-PET) with computed tomography (CT) and staging laparoscopy[5], result in a better distinction between curable and non-curable disease. Due to metastasized or irresectable disease amongst others, only a small proportion of the newly diagnosed gastric cancer patients can be treated with curative intent[6-8]. Nevertheless, some patients with potentially curable disease (cT1-4a-x, N0-3-x, M0-x) do not undergo a resection[6,8,9]. The reasons for refraining from surgery for potentially curable gastric cancer have not been evaluated before and might provide insight into how the number of patients receiving curative treatment can be increased. Therefore, the aim of the current study is to evaluate reasons for refraining from surgery and to determine which patient and tumor characteristics are associated with refraining from surgical resection.

METHODS

Study design

This population-based cohort study was conducted with data from the Netherlands Cancer Registry (NCR), which registers patient, tumor and treatment-related data on all patients with newly diagnosed cancer. New cancer cases are reported by the National Automated Pathology Archive (PALGA) and annually a link is made to the National Registry of Hospital Discharge Diagnoses to supplement the database with newly diagnosed patients. Based on a linkage of the municipal personal records database, the vital status of patients registered in the NCR is annually updated. All data registration is done by trained data managers who routinely collect data from hospital records, thereby using the NCR's manual for registration and coding. The Privacy Review Board of the NCR and the scientific committee of the Dutch Upper-GI Cancer Group (DUCG) approved this study.

Study population

In this study, all patients with potentially curable non-cardia gastric cancer (cT1-4a-x, N0- 3-x, M0-x) in the period January 2015 – December 2017 were included from the NCR. Patients in whom metastatic disease was only found during explorative surgery were included, in order not to miss patients who were initially diagnosed with a potentially curable carcinoma. Exclusion criteria consisted of prophylactic resections, metastatic disease (cM1) and tumors invading adjacent organs (cT4b).

Patients should have had diagnostic work-up according to the nationwide guidelines, consisting of at least gastroscopy with biopsies and CT scan of thorax and abdomen. After 2016, FDG-PET/CT and staging laparoscopy were routinely performed for advanced tumors (≥cT3 and/or N+). Curative treatment consisted of perioperative chemotherapy if deemed fit enough, followed by (sub)total gastrectomy with lymphadenectomy[2]. Tumors were staged according to the 7th or 8th (in case of 2017) edition of the International Union Against Cancer (UICC) TNM staging system[10,11].

Statistical analysis and outcome measures

Patients were divided into a resection group (RG) and a no-resection group (nRG). The resection group consisted of all patients who underwent any curative surgical treatment by means of (sub)total gastrectomy, endoscopic submucosal dissection or endoscopic mucosal resection. Patients in whom resection was intended but was waived due to detected metastases or irresectable disease at the start of the procedure were assigned to the nRG. Patient, tumor and treatment-related characteristics were appraised and described as mean (± standard deviation) or median (range) in case of continuous variables and as frequencies (percentages) in case of categorical variables. Depending on the variable type, the Chi-square test (or Fisher's Exact test) and student's t-test (or MannWhitney U test) were used to compare groups. Multivariable logistic regression analyses were performed to identify associations between patient and tumor characteristics and refraining from surgery. Results were expressed in odds ratios (OR) with 95% confidence intervals (95%CI). Differences in survival between both groups were assessed using a Kaplan Meier curve. The frequency of missing values is reported per table. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY) and a p-value <0.05 was considered statistically significant.

In addition to the aforementioned registered patient, tumor and treatment-related data, the NCR also registers reasons to refrain from treatment (both chemotherapeutic and surgical treatment) since 2015. These reasons are subdivided into several categories, including comorbidities, performance status, social context, age, short life expectancy, refusal or patient's/family's wish, extent of disease or tumor progression, hospital's policy, other treatment with curative intent, low tumor load, complications or toxicity due to previous therapy, other and unknown.

RESULTS

Study population

In total, 1694 patients with potentially curable gastric cancer were selected from the NCR. Patients who underwent prophylactic resection (n=10) were excluded, as well as patients in whom essential data was missing (n=5). The remaining 1679 patients were divided into the RG (n=1127, 67%) and nRG (n=552, 33%), based on the treatment strategies presented in Figure 1. The nRG consisted of older patients (79.6 vs. 68.9 years, $p<0.001$) and patients with a lower Social-Economic-Status (43% vs. 34%, $p<0.001$ (Table 1). In the nRG, more unstaged (cTx 48% vs. 23%, $p<0.001$; cNx: 29% vs. 5%, $p<0.001$) and more overlapping/diffuse tumors (21% vs. 15%, $p<0.001$) were found (Table 2). In Table 3, treatment characteristics of both groups are reported.

Reasons to refrain from surgery

Overall, the percentage non-resected patients increased from 29% in 2015 to 35% in 2016 and remained 35% in 2017. Refusal / patient's wish was the most frequent reason for refraining from surgical resection, accounting for 25% overall (Table 4). Secondly, performance status accounted for 23%, followed by comorbidities (10%). Extent of disease / tumor progression was a frequent reason to refrain from surgery in 2015 accounting for 15% and decreased to 4% in 2017 ($p=0.004$). Other reasons were short life expectancy, social context and other (not specified) or unknown reasons.

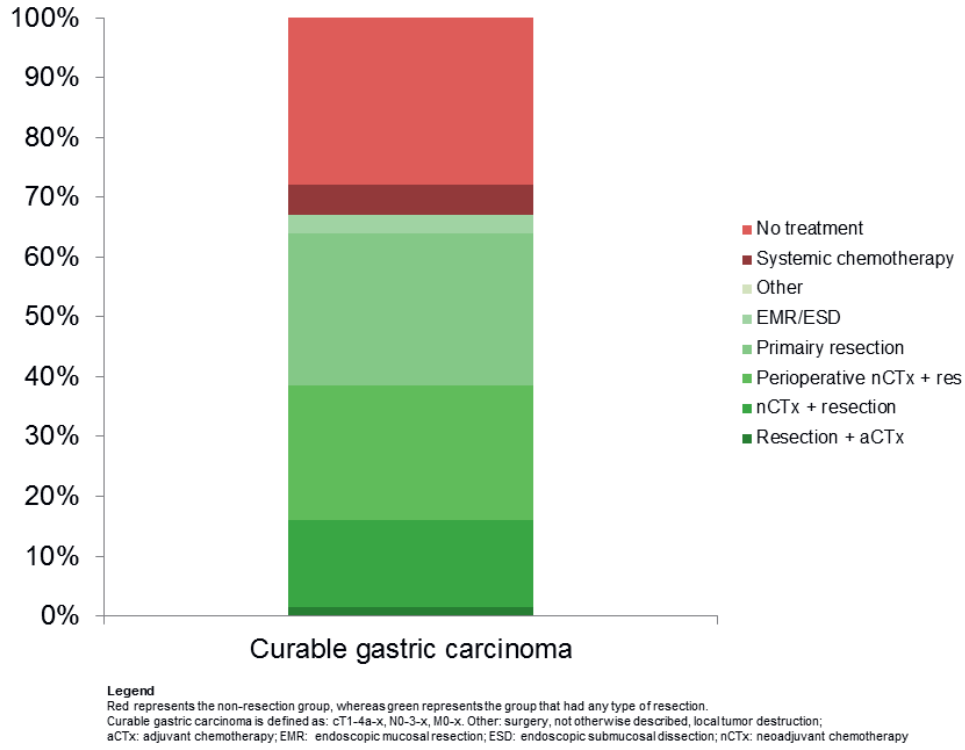

Figure 1. Treatment strategies for 1679 patients diagnosed with potentially curable gastric cancer

When focusing on patient and tumor characteristics per reason to refrain from resection (Supplementary file S1), it was found that 25% of patients in the group that had performance status as the reason to refrain from surgery, had a WHO 0-2 performance status or no comorbidities (10%), and in the group that had comorbidity as reason, 4% had no comorbidities. In the group that had extent of disease / tumor progression as reason, 40% had a cT2 tumor and almost half of the patients (44%) had cN0. These results point out discrepancies between the given reasons for refraining from resection and the actual physical condition or tumor stage of the patient.

Table 1. Baseline characteristics of 1679 patients who were diagnosed with potentially curable gastric cancer

	Resection n = 1127	No resection n = 552	*p*-value	Missing values (%)
Patient characteristics				
Age, years (mean ± SD)	68.9 ± 11.6	79.6 ± 9.9	<0.001	0 (0)
BMI, kg/m^2 (mean ± SD)	25.3 ± 4.2	24.7 ± 5.1	0.085	817 (49)
Gender (% male)	684 (61)	325 (59)	0.476	0 (0)
Social-Economic-Status			<0.001	0 (0)
Low	388 (34)	238 (43)		
Medium	446 (40)	210 (38)		
High	293 (26)	104 (19)		
ASA-classification			<0.001	702 (42)
I	66 (7)	3 (8)		
II	541 (58)	18 (49)		
III	315 (34)	14 (38)		
IV	18 (2)	1 (3)		
V	0 (0)	1 (3)		
Performance status			<0.001	688 (41)
WHO 0	402 (54)	56 (23)		
WHO 1	283 (38)	97 (40)		
WHO 2	51 (7)	54 (22)		
WHO 3	10 (1)	32 (13)		
WHO 4	2 (<1)	4 (2)		
Comorbidities				137 (8)
Pulmonary	142 (14)	106 (20)	0.002	
Vascular	391 (39)	274 (52)	<0.001	
Cardiac	300 (30)	216 (41)	<0.001	
Hypertension	389 (38)	237 (45)	0.015	
Diabetes mellitus	192 (19)	109 (21)	0.437	
History of CVA	46 (5)	64 (12)	<0.001	
Gastrointestinal	135 (13)	82 (16)	0.244	
Hepatic	20 (2)	5 (1)	0.129	
Urologic	34 (3)	36 (7)	0.002	
Dementia	5 (1)	24 (5)	<0.001	
Psychiatric	23 (2)	9 (2)	0.457	
Rheumatic disease	32 (3)	9 (2)	0.091	
Previously malignancy	147 (15)	108 (20)	0.003	137 (8)
Diagnostics				
Gastroscopy (yes)	1127 (100)	552 (100)	n.a.	
CT thorax/abdomen (yes)	967 (91)	395 (72)	<0.001	
FDG-PET/CT (yes)	240 (23)	73 (13)	<0.001	
Staging laparoscopy (yes)	294 (26)	34 (6)	<0.001	

Percentages may not add up to 100% due to rounding. ASA: American Society of Anesthesiologists, BMI: Body Mass Index; CT: Computed Tomography; CVA: cerebrovascular accident; FDG-PET/CT: fluorodeoxyglucose positron emission tomography with CT; WHO: World Health Organization; n.a. not applicable, n.r. no resection

Factors associated with refraining from surgery

In univariable logistic regression analysis, many factors were associated with refraining from surgery (Table 5). Multivariable logistic regression revealed that variables independently associated with refraining from surgery included age ≥80 years (OR 4.77, [95%CI 2.27-10.06], p< 0.001), low Social-Economic-Status (OR 2.68 [95%CI 1.31-5.46], p=0.007), WHO

Table 2. Tumor characteristics of 1679 patients who were diagnosed with potentially curable gastric cancer

	Resection n = 1127	No resection n = 552	*p*-value	Missing values (%)
Tumor characteristics				
cT-stage			<0.001	0 (0)
T1	78 (7)	8 (1)		
T2	453 (40)	175 (32)		
T3	287 (26)	89 (16)		
T4	46 (4)	17 (3)		
Tx	263 (23)	263 (48)		
cN-stage			<0.001	0 (0)
N0	720 (64)	252 (46)		
N1	238 (21)	83 (15)		
N2	101 (9)	49 (9)		
N3	10 (1)	10 (2)		
Nx	57 (5)	158 (29)		
Differentiation			0.218	478 (28)
Well	28 (3)	10 (4)		
Moderate	309 (34)	76 (27)		
Poor	584 (63)	192 (69)		
Undifferentiated	2 (<1)	0 (0)		
Lauren classification			<0.001	0 (0)
Intestinal type	492 (44)	156 (28)		
Diffuse type	426 (38)	211 (38)		
Mixed type	41 (4)	11 (2)		
Unclassified	168 (15)	174 (32)		
Tumor location			<0.001	0 (0)
Fundus	42 (4)	13 (2)		
Corpus	273 (24)	127 (23)		
Antrum	443 (39)	199 (36)		
Pylorus	102 (9)	29 (5)		
Lesser curvature	37 (3)	13 (2)		
Greater curvature	10 (1)	5 (1)		
Overlapping*	163 (15)	117 (21)		
Not otherwise specified	57 (5)	49 (9)		

Percentages may not add up to 100% due to rounding. *Overlapping tumors consisted of linitis plastic (29%), signet ring cell carcinomas (19%), diffuse type (15%) and intestinal type tumors (14%), adenocarcinoma not otherwise specified (15%), tubular adenocarcinomas (4%) and mixed types (3%).

performance status 3-4 (OR 10.48 [95%CI 2.41-45.73], p=0.002), pulmonary comorbidities (OR 2.53, [95%CI 1.11-5.76], p=0.027), vascular comorbidity (OR 0.21, [95%CI 0.06-0.81], p=0.023), history of CVA (OR 6.33, [95%CI 1.70-23.61], p=0.006), previous malignancy (OR 2.24, [95%CI 1.03-4.92], p=0.043), unclassified Lauren classification (OR 3.93 [95%CI 1.61-9.56], p=0.003) and overlapping/diffuse tumors (OR 3.51, [95%CI 1.54-8.05], p=0.003).

Survival

The 1- and 3-year overall survival was 24% and 6% in the nRG and 84% and 56% in the RG. Median survival in the nRG was 4.9 months overall, 7.1 months after chemotherapy, and 4.3

Table 3. Treatment characteristics of 1679 patients who were diagnosed with potentially curable gastric cancer

	Resection n = 1127	No resection n = 552	*p*-value	Missing values (%)
Treatment characteristics				
Systemic treatment			<0.001	0 (0)
None	478 (42)	468 (85)		
Neoadjuvant chemotherapy	246 (22)	60 (11)[$]		
Perioperative chemotherapy	379 (34)	n.a.		
Adjuvant chemotherapy	24 (2)	n.a.		
Palliative chemotherapy	n.a.	24 (4)[$]		
Chemoradiotherapy	31 (3)	0 (0)		
Radiotherapy (yes)	83 (7)	64 (12)	0.004	0 (0)
Targeted therapy (yes)	2 (<1)	3 (1)	0.196	0 (0)
Explorative surgery	7 (1)[¥]	30 (5)	<0.001	0 (0)
Resection type		n.a.	n.a.	0 (0)
EMR/ESD*	66 (6)	.		
Total gastrectomy	404 (36)	.		
Subtotal gastrectomy	653 (58)	.		
Other[#]	4 (<1)	.		

Percentages may not add up to 100% due to rounding. *In 17 patients, a surgical tumor resection took place after the EMR/ESD; #Surgery, not otherwise specified (n=3) of which 1 patient received perioperative chemotherapy; local tumor destruction, such as electrocauterization, cryosurgery, radiofrequency ablation (n=1). ¥Although invasion into adjacent structures (n=2) or distant metastases were found (n=2) during explorative surgery, a resection was performed. $Intent of chemotherapy is not registered in NCR, so this subdivision is based on chemotherapy regimen, whereby curative treatment consisted of a chemotherapeutic regimen compared to the MAGIC or FLOT-4 trial.

Table 4. Reasons to refrain from surgery in 552 patients who were diagnosed with potentially curable gastric cancer

	No. (%)				*p*-value
Reasons to refrain from resection	All n = 552	2015 n = 157	2016 n = 220	2017 n = 175	
Refusal / patient's or family's wish	138 (25)	43 (27)	48 (22)	47 (27)	0.370
Performance status / physical fitness	126 (23)	39 (25)	43 (20)	44 (25)	0.326
Comorbidities	54 (10)	17 (11)	25 (11)	12 (7)	0.284
Extent of disease / tumor progression*	55 (10)	23 (15)	25 (11)	7 (4)	0.004
Age	22 (4)	8 (5)	9 (4)	5 (3)	0.579
Short life expectancy	11 (2)	0 (0)	7 (3)	4 (2)	0.088
Social context	1 (<1)	0 (0)	1 (1)	0 (0)	0.470
Other	53 (10)	14 (9)	27 (12)	12 (7)	0.182
Unknown	92 (17)	13 (8)	35 (16)	44 (25)	<0.001

Percentages may not add up to 100% due to rounding. *24 out of 55 patients underwent explorative surgery, who were assumed resectable / non-metastasized during previously performed staging laparoscopy

without chemotherapy. In the RG, median survival was 41.4 months without chemotherapy, the median survival overall and with chemotherapy was not reached.

Table 5. Uni- and multivariable logistic regression analyses on the influence of patient and tumor characteristics on refraining from surgical resection

	Refraining from resection					
	Univariable			Multivariable		
	OR	[95% CI]	*p*-value	OR	[95% CI]	*p*-value
Age (>80 years)	7.80	[6.18-9.84]	<0.001	4.77	[2.27-10.06]	<0.001
Social-Economic-Status						
Low	1.30	[1.04-1.64]	0.024	2.68	[1.31-5.46]	0.007
Medium	Ref			Ref		
High	0.75	[0.57-1.00]	0.046	1.24	[0.50-3.05]	0.643
ASA				.	.	.
I-II	Ref			.	.	.
III-V	1.39	[0.72-2.70]	0.332	.	.	.
WHO performance status						
0-1	Ref			Ref		
2	4.74	[3.11-7.22]	<0.001	2.37	[0.90-6.25]	0.080
3-4	13.43	[6.83-26.42]	<0.001	10.48	[2.41-45.73]	0.002
Anemia* (yes)	2.48	[1.97-3.12]	<0.001	0.76	[0.38-1.52]	0.434
Hypoalbuminemia# (yes)	3.24	[2.48-4.23]	<0.001	1.29	[0.63-2.63]	0.490
Pulmonary comorbidity	1.54	[1.17-2.03]	0.002	2.53	[1.11-5.76]	0.027
Cardiac comorbidity	1.64	[1.32-2.04]	<0.001	3.40	[0.91-12.67]	0.068
Vascular comorbidity	1.71	[1.38-2.11]	<0.001	0.21	[0.06-0.81]	0.023
Hypertension	1.30	[1.05-1.16]	0.015	1.51	[0.78-2.92]	0.225
History of CVA	2.89	[1.95-4.29]	<0.001	6.33	[1.70-23.61]	0.006
Urologic comorbidity	2.10	[1.30-3.40]	0.002	0.70	[0.11-4.37]	0.701
Dementia	9.58	[3.63-25.26]	<0.001	6.88	[0.31-149.99]	0.220
Previous malignancy	1.51	[1.15-2.00]	0.003	2.24	[1.03-4.92]	0.043
Tumor stage						
<cT3	Ref			.	.	.
≥cT3	0.92	[0.70-1.22]	0.572	.	.	.
Nodal stage						
N0	Ref			Ref		
N+	1.26	[1.21-1.31]	<0.001	1.10	[0.97-1.26]	0.135
Tumor differentiation						
Well/moderate	Ref			Ref		
Poor/undifferentiated	1.28	[0.96-1.71]	0.088	1.72	[0.74-3.98]	0.205
Lauren classification						
Intestinal type	Ref			Ref		
Diffuse type	1.56	[1.22-1.99]	<0.001	2.06	[0.90-4.75]	0.088
Mixed type	0.85	[0.43-1.69]	0.635	0.54	[0.05-5.57]	0.605
Unclassified	3.27	[2.47-4.31]	<0.001	3.93	[1.61-9.56]	0.003
Tumor location						
Proximal	Ref			Ref		
Distal	0.96	[0.75-1.22]	0.732	0.74	[0.35-1.57]	0.434
Overlapping	1.65	[1.22-2.23]	0.001	3.51	[1.54-8.05]	0.003

ASA: American Society of Anesthesiologists; CVA: cerebrovascular accident; OR: odds ratio; [95% CI]: 95% confidence interval; WHO: World Health Organization. *Anemia: Hb <7.5 in case of women, Hb <8.5 in case of men. #Hypoalbuminemia: albumin <35 g/L. Outcomes of <0.200 through univariable analysis were included in multivariable analysis.

DISCUSSION

In this Western population-based study, 33% of potentially curable patients did not undergo a resection. The most common reasons for refraining from surgery were patient refusal and performance status. Factors independently associated with refraining from surgery were higher age, lower Social-Economic-Status, worse WHO performance status and accompanying comorbidities and poor tumor characteristics.

Literature on overall non-resection rates of the general gastric cancer population is scarce. The National Oesophago-Gastric Cancer Audit of the U.K. reported that 19% of patients with a curable gastric carcinoma did not undergo a resection in 2018[9], wherein in approximately 11% records were not submitted, which might cause an underestimation of the non-resection rate. A study that compared treatment strategies between European countries, found non-resection rates of 33%, 42% and 46% of curable patients in Belgium, Denmark and Sweden, respectively[6]. These differences between countries might possibly be explained by hospital policies and possibilities for shared decision-making, cultural backgrounds and patient characteristics, such as age.

Since the beginning of this century, after a U.S. publication of the Institute of Medicine in 2001 proposing patient centered care as a basic principle[12], shared decision-making has become increasingly popular. Shared decision-making is defined as a process in which both health care professionals and patients make care decisions together. In this process, the health care professionals depend on medical and clinical knowledge, scientific evidence and experience, whereas patients take preferences, social and comfort aspects into consideration[13-15]. As yet, surgical resection for gastric cancer is the only curative treatment option. The fact that in this study the most common reason for refraining from surgery was the patient's wish, indicates that patient's preference is an important factor in the process of shared decision-making. However, given the lower SES found in the nRG and it being an independently associated factor with refraining from surgery, specialists must ensure that the information they want to convey is understandable and clear to the patient. The higher age, higher number of comorbidities and poorer performance status found in the nRG, which represent the majority of the remaining reasons, are undoubtedly important factors that contribute to the patient's wish, although these

may be assessed more objectively by the health care professional. It should therefore be clearly stated by the health care professional in the case of gastric cancer that surgical resection is the only curative treatment, especially in the quarter of patients who refuse surgical resection. Often in elderly and comorbid patients, the tradeoff between quality of life and risk of postoperative complications is weighed during consultation. In specific, critically evaluated cases, resection should nevertheless be encouraged, especially keeping in mind the recent improvements in survival due to systemic chemotherapy (FLOT: fluorouracil plus leucovorin, oxaliplatin, and docetaxel), emerging role of immune therapy and improvement of surgical quality[4, 16-18]. Moreover, it should be conveyed that compared to a reference population, quality of life after surgical resection is relatively good[19].

Tools for improving patient's knowledge and input during the decision-making process include interactive multimedia or computer programs, written/online materials, and mobile applications amongst others[20]. A recent Cochrane review, including 105 studies involving 31.043 patients facing treatment or screening decisions, found that patients who were subjected to decision tools felt more well-informed, and chose an option in line with their values more often[13,21]. It was even suggested that shared decision-making can improve patient satisfaction[13,22] and might affect medical malpractice claims, by improving communication[13,23]. In the field of surgery, decision tools resulted in patients choosing a conservative treatment more often[21], which may not be desirable in case of gastric cancer. For several other diseases in the Netherlands, decision tools are already being used, for example for breast and prostate cancer in curative setting, and colon and esophageal cancer in palliative setting. Further research might focus on effects of decision tools on logistic aspects, treatment strategies and patient satisfaction in the field of gastric cancer.

While the decision on refraining from surgery may have been well-considered, interestingly, in 4-25% of patients the patient and tumor characteristics did not match with the registered reason to refrain from resection. For example, of all patients that refrained from resection due to comorbidity, 4% of patients had no comorbidity. Therefore, these patients might be considered surgical candidates. Reasons for not undergoing surgery might be attributed to practice variation between hospitals, such as differences in organizational structures, clinical pathways[8], consultation and referral policies. In this context, it was previously reported that patients

diagnosed in a high-volume center had a higher possibility for curative treatment, and better survival[8,24-26]. This emphasizes the importance of regional comprehensive cancer networks with uniform protocols and tumor-specific multidisciplinary team meetings, where all patients can be adequately discussed and where consultations can be made about how to inform the patient.
Extent of disease / tumor progression was found to be a frequent reason in 2015 and gradually decreased in 2016 and 2017 as reason to refrain from surgery. This may have several reasons: first, due to a reduced number of patients with advanced tumors revealing after initial staging, possibly due to improved staging possibilities (FDG-PET/CT and staging laparoscopy). Second, more patients are resected due to evolving surgical capabilities, such as increased visual and technical possibilities in minimally invasive surgery, and centralization of gastric cancer care in the Netherlands during the past decade resulting in specialized multidisciplinary teams. Only those hospitals that achieve at least 20 gastrectomies a year are allowed to perform these procedures, which allows for more dedicated and experienced surgeons. A third reason could be that the registration of the reasons for not receiving surgery was added to NCR during the study period, therefore, data managers had to get used to registering this item which could have effect on the registration practices over time.

The study was limited by the fact that the reason for refraining from resection has only been registered since 2015, limiting the number of patients included, long-term follow-up and an adequate evaluation of changes in the reasons of refraining from surgery longer than 3 years. Furthermore, some patients with tumor progression may have been unintentionally excluded from this study. For instance, patients with interval metastases between diagnosis and treatment could have been incorrectly staged as cM1. However, this group will most likely be very small as a recent published study demonstrated detection in solely 1% of neoadjuvant treated patients[27]. Last, it is challenging for data managers to record the reason for not undergoing surgery from a patient file as this decision is most probably based on a combination of arguments.

CONCLUSION

This study shows that 33% of patients with potentially curable gastric cancer did not undergo a resection, mostly due to patient refusal, worse performance status and comorbidity. These results may reflect shared decision-making and practice variation between hospitals, but may also highlight the importance of adequate selection of surgical patients.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer 2018;103:356–87.
2. Integraal Kankercentrum Nederland. Diagnostiek, behandeling en follow-up van het maagcarcinoom 2016 2016:1–7. http://www.oncoline.nl/uploaded/docs/Maagcarcinoom/Richtlijn maagcarcinoom.pdf.
3. Cunningham D, Allum WH, Stenning SP, et al. Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. N Engl J Med 2007:11–20.
4. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ra. Lancet 2019;393:1948–57.
5. Smyth E, Schöder H, Strong VE, et al. A prospective evaluation of the utility of 2-deoxy-2-[18 F] fluorodeoxyglucose positron emission tomography and computed tomography in staging locally advanced gastric cancer. Cancer 2012;118:5481–8.
6. Claassen YHM, Dikken JL, Hartgrink HH, et al. North European comparison of treatment strategy and survival in older patients with resectable gastric cancer: A EURECCA upper gastrointestinal group analysis. Eur J Surg Oncol 2018;44:1982–9.
7. Nelen SD, Verhoeven RHA, Lemmens VEPP, et al. Increasing survival gap between young and elderly gastric cancer patients. Gastric Cancer 2017;20:919–28.
8. Van Putten M, Verhoeven RHA, Van Sandick JW, et al. Hospital of diagnosis and probability of having surgical treatment for resectable gastric cancer. Br J Surg 2016;103:233–41.
9. National Oesophago-Gastric Cancer Audit N. An audit of the care received by people with Oesophago-gastric Cancer in England and Wales 2018.
10. International Union Against Cancer. TNM: Classification of Malignant Tumors 7th edition. 2009.
11. International Union Against Cancer. TNM: Classification of Malignant Tumors 8th edition 2016.
12. National Research Council. Crossing the quality chasm: a new health system for the 21st century. 2001.
13. Schrager S, Phillips G, Burnside E. Shared decision making in cancer screening. Fam Pract Manag 2017;24:5–10.
14. Barry MJ, Edgman-Levitan S. Shared decision making - The pinnacle of patientcentered care. N Engl J Med 2012;366:780–1.
15. Steffensen KD, Vinter M, Crüger D, et al. Lessons in Integrating Shared Decision-Making Into Cancer Care. J Oncol Pract 2018;14:229–35.
16. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, et al. Early outcomes from the Dutch Upper Gastrointestinal Cancer Audit. Br J Surg 2016;103:1855–63.
17. Earle CC, Maroun J, Zuraw L, et al. Neoadjuvant or adjuvant therapy for resectable gastric cancer? A practice guideline. Can J Surg 2002;45:438–46.
18. Wang X, Tang S, Cui X, et al. Cytokine-induced killer cell/dendritic cell–cytokine-induced killer cell immunotherapy for the postoperative treatment of gastric cancer: A systematic review and meta-analysis. Med (United States) 2018;97:1–9.
19. Brenkman HJF, Tegels JJW, Ruurda JP, et al. Factors influencing health-related quality of life after gastrectomy for cancer. Gastric Cancer 2018;21:524–32.
20. O'Connor AM, Fiset V, DeGrasse C, et al. Decision aids for patients considering options affecting cancer outcomes: evidence of efficacy and policy implications. J Natl Cancer Inst Monogr 1999:67–80.
21. Stacey D, Légaré F, Lewis K, Mj B, Cl B, Kb E, et al. Decision aids for people facing health treatment or screening decisions (Review). Cochrane Database Syst Rev 2017:1–242.
22. Keevil J, Leaf M, Zelenski A. Patient survey results after use of integrated EHF decision tool. 2015.
23. Durand MA, Moulton B, Cockle E, et al. Can shared decisionmaking reduce medical malpractice litigation? A systematic review. BMC Health Serv Res 2015;15:1–11.

24. van Putten M, Verhoeven RHA, Koëter M, et al. Ziekenhuis van diagnose beïnvloedt kans op curatieve behandeling voor slokdarm- en maagkanker. Ned Tijdschr Geneeskd 2018;162:D1970.
25. Bachmann MO, Alderson D, Peters TJ, et al. Influence of specialization on the management and outcome of patients with pancreatic cancer. Br J Surg 2003;90:171–7.
26. Bachmann MO, Alderson D, Edwards D, et al. Cohort study in South and West England of the influence of specialization on the management and outcome of patients with oesophageal and gastric cancers. Br J Surg 2002;89:914–22.
27. Gertsen EC, Jongh C De, Brenkman HJF, et al. The additive value of restaging-CT during neoadjuvant chemotherapy for gastric cancer. Eur J Surg Oncol 2020.

Chapter 10

The introduction of minimally invasive surgery for distal and total gastrectomy: a population-based study

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ABSTRACT

Background: Minimally invasive gastrectomy has been introduced in Western populations during the last decade. As minimally invasive distal gastrectomy (MIDG) versus total gastrectomy (MITG) are procedures with a different complexity, outcomes may differ. The aim of this population-based cohort study was to evaluate the safety of MIDG and MITG.

Methods: All patients who underwent potentially curative gastrectomy for gastric adenocarcinoma were included from the Dutch Upper GI Cancer Audit (2011–2016). Propensity score matching was applied to create comparable groups of patients receiving open distal gastrectomy (ODG) versus MIDG and open total gastrectomy (OTG) versus MITG, using patient and tumor characteristics. Postoperative outcomes and short-term oncological outcomes were appraised.

Results: Of the 1970 eligible patients, 1138 underwent distal gastrectomy and 832 underwent total gastrectomy. For distal gastrectomy, 390 ODG were matched to 288 MIDG patients. Although overall postoperative morbidity and mortality were similar, patients who underwent MIDG encountered less intra-abdominal abscesses (4% vs. 1%, $p = 0.039$) and wound complications (6% vs. 2%, $p = 0.021$). The median hospital stay was shorter after MIDGs (9 vs. 7 days, $p < 0.001$). For total gastrectomy, 323 OTG patients were matched to 258 MITG patients. Overall postoperative morbidity, mortality and hospital stay were similar, whereas the anastomotic leakage rate was higher after MITGs (11% vs. 17%, $p = 0.030$). Short-term oncological outcomes between both groups were equal for distal and total gastrectomy.

Conclusion: Benefits of MIG during the early introduction were demonstrated for distal gastrectomy but not for total gastrectomy. An increased anastomotic leakage rate was encountered for MITG.

BACKGROUND

Gastric cancer is the fifth most common type of malignancy worldwide and the third leading cause of cancer-related death[1]. In the Netherlands, approximately 1200 new gastric cancer patients are identified yearly, of which nearly 500 undergo curative treatment[2,3].

Gastrectomy with lymphadenectomy is the cornerstone of curative treatment for gastric cancer, potentially combined with perioperative chemotherapy[4,5] . Open gastrectomy is the standard surgical procedure worldwide[3,6]. Several Asian trials have demonstrated benefits of minimally invasive gastrectomy, including decreased postoperative morbidity and shorter hospital stay[7]. Minimally invasive gastrectomy has been performed increasingly in the Netherlands, representing 58% of all gastrectomies in 2016[8]. Recently, it was demonstrated by a Dutch research group that in a Western population-based cohort study, overall morbidity and mortality occurring after minimally invasive gastrectomy were similar with open gastrectomy, but minimally invasive gastrectomy embraced the additional advantages of fewer wound complications and shorter hospitalization[9].

In Western countries, total gastrectomy and distal gastrectomy are the most frequently performed types of gastric resection[3]. It is known that total gastrectomy is a more extensive and difficult procedure compared to distal gastrectomy, resulting in longer operative time, more estimated blood loss and a higher risk of postoperative complications[10-13]. Because most Western studies did not make a distinction between distal and total gastrectomy[14,15], the aim of the present study is to evaluate the safety of the introduction of minimally invasive distal gastrectomy (MIDG) and minimally invasive total gastrectomy (MITG) in the Netherlands.

METHODS

Study design

This population-based cohort study included data from the Dutch Upper GI Cancer Audit (DUCA), a prospective nationwide registration of all patients undergoing surgery with the intention of resection for gastroesophageal cancer. The DUCA is part of the Dutch Institute for Clinical Auditing (DICA) that organizes national audits in a uniform format. It does so by requiring hospitals that perform gastric cancer surgery (varying from 36 hospitals in 2011 to 22 hospitals

in 2016, due to centralization), to annually provide data which include patient and tumor characteristics, items regarding processes of care and clinical and pathological outcomes of surgery. An independent team of data managers performed an in-depth quality investigation on a random data sample, which showed a complete and reliable data entry in all participating hospitals[3]. This study was approved by the scientific committee of the DUCA and no ethical approval or informed consent was required under Dutch law.

Patient population

All patients who underwent elective gastrectomy with curative intent for gastric adenocarcinoma (cT1-4a-x, N0-3-x, M0-x) in the period 2011–2016 were included from the DUCA. Patients in which no lymphadenectomy was performed or no Roux-en Y or Billroth reconstruction was created, were excluded, as were the patients with registered data not compatible with gastrectomy. Patients were staged and treated according to the Dutch national guidelines[4]. Staging consists of gastroscopy and computed tomography (CT) of the thorax and abdomen[16]. Before its recent implementation in the nationwide guidelines in July 2016[16], ^{18}F-fluordeoxyglucose (FDG) positron emission tomography (PET)/CT and staging laparoscopy were not routinely performed. Treatment with curative intent was defined as gastrectomy and lymphadenectomy, with or without perioperative chemotherapy, which was only offered to patients with an advanced tumor (cT2+ or N+) deemed fit enough to tolerate chemotherapy according or comparable to the MAGIC trial[5,17]. As recommended in the Dutch national guidelines, the surgical procedure consisted of (sub)total gastrectomy with, if deemed necessary (in case of advanced stage), a modified D2 lymphadenectomy (without pancreaticosplenectomy), according to the Japanese Gastric Cancer Treatment Guidelines[18]. Subtotal gastrectomies consisted of distal gastrectomies with the exception of a few. Tumors were classified according to the 7th edition of the American Joint Committee on Cancer TNM staging system[19].

Outcomes

Patient, tumor and hospital characteristics were appraised. Postoperative outcomes (e.g. morbidity, re-interventions, mortality and recovery) and histopathological characteristics were analyzed. Overall morbidity was divided into four groups: i) intra-abdominal complications including anastomotic leakage; ii) wound complications including infection/abscess and fascia

dehiscence; iii) non-surgical complications including pulmonary, cardiac, thromboembolic, neurologic and urologic complications; iv) other complications (Tables 3 and 4). All complications were scored according to the standards of the DUCA, provided via online information[20].

Statistical analysis

A propensity score matched analysis was used to balance observed covariates between open and minimally invasive surgery for both the distal and total gastrectomy group. To enhance matching, missing patient and treatment-related characteristics were imputed. Missing data were considered at random and handled using imputation with the iterative Markov chain Monte Carlo method (5 iterations)[21]. The frequency of missing values per variable before imputation is presented in Tables 1 and 2.

In the current study, the propensity score was the conditional probability to undergo open or minimally invasive surgery based on all the patient and treatment-related characteristics mentioned in Table 1. Propensity scores were calculated for all patients using a non-parsimonious multivariable logistic regression model. First 1:1 nearest-neighbor matching without replacement was performed within a caliper width of 0.25 multiplied by the standard deviation of the logit propensity score. Then a second-level match (1:2) was added among the remaining patients. Balance in patient and treatment-related characteristics was measured using the standardized mean difference; differences of less than 10% represent adequate balance[22].

IBM SPSS Statistics version 23.0 (IBM, Armonk, New York, USA) and R 3.1.2 open-source software (http://www.R-project.org; 'MatchIt' and 'optmatch' packages) were used for statistical analysis. To identify differences in postoperative and histopathological outcomes, categorical parameters were compared using the Chi-square test, and the student's t-test was used for continuous variables. Logarithmic transformation was applied for variables with a non-parametric distribution. Statistical significance was acknowledged when the p-value was below 0.05.

RESULTS

Study population

During the study period, 2154 patients underwent a gastrectomy with curative intent for gastric adenocarcinoma in the Netherlands. Of these patients, 184 patients were excluded, because no lymphadenectomy was performed (n = 72) or no Roux-en Y or Billroth reconstruction was made (n = 99). In addition, patients who were registered as minimally invasive thoracic surgery were excluded (n = 3), as were the patients of whom it was unclear or deviant where the anastomosis was located (n = 10). Of the 1970 remaining patients, 1138 underwent distal and 832 underwent total gastrectomy. After propensity score matching, 390 ODG patients were matched to 288 MIDG patients (Table 1). In the total gastrectomy group, 581 patients remained after PSM, 323 receiving OTG and 258 receiving MITG (Table 2).

In both the distal and total gastrectomy group, most of the patients were male and had an ASA II classification. The most common cT-stage was cT3 tumor, the majority of the patients was staged as N0-stage, and around 50% of patients in both groups was treated with neoadjuvant chemotherapy.

Postoperative outcomes

For *distal gastrectomy*, the postoperative outcomes of the original and the PSM cohort of the patients are shown in Table 3. Results are henceforth given from the propensity score analysis. In 24 patients (9%) conversion of MIDG to ODG occurred, due to extent of the tumor (18%), limited accessibility (73%) or intraoperative complications (9%). Although overall postoperative morbidity (37% vs. 34%, p=0.422) and mortality (both 3%, p=0.817) were similar, patients who underwent MIDG encountered less intra-abdominal abscesses (4% vs. 1%, p=0.039), chyle leakage (2% vs. <1%, p=0.036), wound infections (6% vs. 2%, p=0.021) and fascia dehiscence (2% vs. 0%, p=0.034). In addition, significant less neurological complications (i.e. delirium) were found in the MIDG group (5% vs. 2%, p=0.041). The anastomotic leakage rate (3% vs. 3%) and number of re-interventions (12% vs. 11%) were equal between the groups. The median hospital stay was shorter after MIDG (9 vs. 7 days, p<0.001), whereas the median ICU stay was equal (both 0 days).

Table 1. Baseline characteristics of the original and propensity score matched cohort of patients who underwent distal gastrectomy

	Original cohort (n = 1138)			Missing	PSM cohort [a] (n = 678)		
	ODG	MIDG	*SMD*	values (%)	ODG	MIDG	*SMD*
	n = 761 (%)	n = 377 (%)			n = 390 (%)	n = 288 (%)	
Baseline characteristics							
Age, years (mean ± SD)	70.6 ± 11.0	69.8 ± 11.0	7.0	0 (0)	70.4 ± 10.9	70.4 ± 10.7	0.5
BMI, kg/m^2 (mean ± SD)	25.3 ± 4.2	25.3 ± 4.3	0.4	35 (3)	25.3 ± 4.1	25.4 ± 4.2	0.7
Gender			7.7	0 (0)			0.4
Male	465 (61)	216 (57)			243 (62)	176 (61)	
Female	296 (39)	161 (43)			147 (38)	112 (39)	
ASA-classification			4.2	14 (1)			1.6
I	91 (12)	41 (11)			49 (13)	36 (13)	
II	404 (54)	217 (58)			213 (55)	160 (56)	
III	246 (33)	110 (30)			121 (31)	88 (31)	
IV	10 (1)	5 (1)			7 (2)	4 (1)	
Comorbidities				0 (0)			
Cardiac	259 (34)	119 (32)	5.3		130 (33)	99 (34)	3.4
Vascular	312 (41)	180 (48)	13.5		164 (42)	135 (47)	5.9
Diabetes	126 (17)	81 (22)	12.0		67 (17)	58 (20)	3.8
Pulmonary	131 (17)	59 (16)	4.3		70 (18)	50 (17)	<0.1
cT-stage			1.2	307 (27)			4.7
T1	56 (10)	37 (13)			36 (9)	42 (15)	
T2	201 (37)	94 (33)			153 (39)	87 (30)	
T3	268 (49)	141 (50)			184 (47)	150 (52)	
T4	24 (4)	10 (4)			17 (4)	9 (3)	
cN-stage			1.0	162 (14)			<0.1
N0	438 (68)	219 (67)			261 (69)	196 (70)	
N1	170 (26)	76 (23)			99 (26)	63 (22)	
N2	35 (5)	27 (8)			18 (5)	18 (6)	
N3	6 (1)	5 (2)			3 (1)	4 (1)	
Neoadjuvant treatment				0 (0)			
None	379 (50)	169 (45)	10.0		177 (45)	137 (48)	7.0
Chemotherapy	379 (50)	203 (54)	8.1		212 (54)	150 (52)	7.0
Chemoradiotherapy	2 (<1)	5 (1)	9.2		1 (<1)	1 (<1)	<0.1
Year of surgery				0 (0)			
2011	127 (17)	13 (3)	40.4		24 (6)	13 (5)	7.2
2012	152 (20)	4 (1)	184.4		10 (3)	4 (1)	3.4
2013	178 (23)	30 (8)	57.0		57 (15)	30 (10)	1.9
2014	142 (19)	91 (24)	12.8		137 (35)	85 (30)	4.0
2015	93 (12)	105 (28)	34.8		93 (24)	82 (29)	1.9
2016	69 (9)	134 (36)	55.2		69 (18)	74 (26)	4.4
Volume			55.1	0 (0)			4.3
0-20	476 (63)	136 (36)			167 (43)	113 (39)	
>20	285 (38)	241 (64)			223 (57)	175 (61)	

Percentages may not add up to 100% due to rounding. *Dataset after imputation. ASA: American Society of Anesthesiologists, BMI: Body Mass Index, MIDG: Minimally Invasive Distal Gastrectomy, ODG: Open Distal Gastrectomy, PSM: Propensity Score Matched, SMD: Standardized Mean Difference

For *total gastrectomy*, Table 4 presents the postoperative outcomes of the original and the PSM cohort. Conversions occurred in 11% of patients undergoing MITG, caused by extent of the tumor (41%), limited accessibility (44%) or intraoperative complications (15%). After PSM, overall postoperative morbidity (45% vs. 47%, p=0.643) and mortality (6% vs. 8%, p=0.291)

Table 2. Baseline characteristics of the original and propensity score matched cohort of patients who underwent total gastrectomy

	Original cohort (n = 1138)			Missing	PSM cohort [a] (n = 678)		
	OTG	MITG	*SMD*	values (%)	OTG	MITG	*SMD*
	n = 518 (%)	n = 314 (%)			n = 323 (%)	n = 258 (%)	
Baseline characteristics							
Age, years (mean ± SD)	65.9 ± 12.4	66.0 ± 12.0	0.3	3 (<1)	66.2 ± 12.1	65.9 ± 12.1	0.3
BMI, kg/m^2 (mean ± SD)	25.4 ± 4.5	25.5 ± 4.8	4.2	13 (2)	25.6 ± 4.7	25.6 ± 5.0	0.3
Gender			21.5	0 (0)			0.8
Male	357 (69)	183 (58)			214 (66)	164 (64)	
Female	161 (31)	131 (42)			109 (34)	94 (36)	
ASA-classification			15.7	3 (<1)			0.3
I	100 (19)	45 (14)			57 (18)	44 (17)	
II	296 (58)	182 (58)			188 (58)	153 (59)	
III	117 (23)	84 (27)			77 (24)	60 (23)	
IV	2 (<1)	3 (1)			1 (<1)	1 (<1)	
Comorbidities				0 (0)			
Cardiac	139 (27)	94 (30)	6.8		87 (27)	68 (26)	1.7
Vascular	190 (37)	122 (39)	4.5		131 (41)	102 (40)	1.2
Diabetes	66 (13)	54 (17)	11.8		40 (12)	39 (15)	6.2
Pulmonary	75 (15)	60 (19)	11.8		52 (16)	41 (16)	0.5
cT-stage			12.1	184 (22)			2.4
T1	33 (8)	12 (5)			24 (7)	14 (5)	
T2	98 (25)	53 (21)			84 (26)	60 (23)	
T3	234 (59)	170 (68)			186 (58)	169 (66)	
T4	30 (8)	18 (7)			29 (9)	15 (6)	
cN-stage			0.6	124 (15)			2.0
N0	241 (56)	143 (51)			163 (53)	127 (51)	
N1	128 (30)	91 (33)			98 (32)	80 (32)	
N2	51 (12)	37 (13)			41 (13)	36 (14)	
N3	8 (2)	9 (3)			7 (2)	8 (3)	
Neoadjuvant treatment				1 (<1)			
None	168 (33)	86 (27)	11.7		107 (33)	73 (28)	0.9
Chemotherapy	335 (65)	219 (70)	11.0		206 (64)	177 (69)	1.7
Chemoradiotherapy	14 (3)	9 (3)	1.0		10 (3)	8 (3)	2.3
Year of surgery				0 (0)			3.6
2011	81 (16)	0 (0)	n.a.		0 (0)	0 (0)	n.a.
2012	95 (18)	9 (3)	92.6		15 (5)	9 (4)	3.5
2013	116 (22)	53 (17)	14.7		89 (28)	53 (21)	9.8
2014	90 (17)	94 (30)	27.4		89 (28)	69 (27)	3.0
2015	65 (13)	80 (26)	29.6		63 (20)	61 (24)	3.6
2016	71 (14)	78 (25)	25.7		67 (21)	66 (26)	6.7
Volume			39.7	0 (0)			1.2
0-20	342 (66)	145 (46)			163 (51)	124 (48)	
>20	176 (34)	169 (54)			160 (50)	134 (52)	

Percentages may not add up to 100% due to rounding. *Dataset after imputation. ASA: American Society of Anesthesiologists; BMI: Body Mass Index; MIDG: Minimally Invasive Distal Gastrectomy; ODG: Open Distal Gastrectomy; PSM: Propensity Score Matched; SMD: Standardized Mean Difference.

were similar between OTG and MITG, whereas the anastomotic leakage rate was higher after MITG (11% vs. 17%, p=0.030). On the other hand, less chyle leakage was seen in the MITG group (5% vs. 1%, p=0.016). Wound complications, medical complications and re-interventions were similar between the OTG and MITG group. Although the length of hospital stay was similar

Table 3. Postoperative outcomes of the original and propensity score matched cohort of patients who underwent distal gastrectomy

	Original cohort (n = 1138)			PSM cohort [a] (n = 678)		
	ODG	MIDG	*p*-value	ODG	MIDG	*p*-value
	n = 761 (%)	n = 377 (%)		n = 390 (%)	n = 288 (%)	
Postoperative outcomes						
Conversions	-	33 (9)	-	-	24 (9)	-
Morbidity	269 (35)	127 (34)	0.580	143 (37)	97 (34)	0.422
Intra-abdominal complications						
Anastomotic leakage†	25 (3)	16 (4)	0.414	10 (3)	10 (3)	0.490
Abscess	30 (4)	7 (2)	0.062	16 (4)	4 (1)	0.039
Bleeding	11 (1)	5 (1)	0.872	5 (1)	4 (1)	0.904
Pancreatitis, leakage or fistula	1 (<1)	2 (1)	0.217	1 (<1)	1 (<1)	0.829
Chyle leakage	14 (2)	2 (1)	0.077	9 (2)	1 (<1)	0.036
Trauma of the gut	6 (1)	7 (2)	0.110	4 (1)	4 (1)	0.665
Wound complications						
Infection/abscess	36 (5)	6 (2)	0.008	22 (6)	6 (2)	0.021
Fascia dehiscence	15 (2)	0 (0)	0.006	6 (2)	0 (0)	0.034
Non-surgical complications						
Pulmonary*	97 (13)	42 (11)	0.436	45 (12)	35 (12)	0.806
Cardiac‡	44 (6)	19 (5)	0.606	22 (6)	15 (5)	0.806
Thromboembolic¶	5 (1)	7 (2)	0.062	1 (<1)	4 (1)	0.088
Neurologic#	34 (5)	11 (3)	0.207	20 (5)	6 (2)	0.041
Urologic§	24 (3)	20 (5)	0.076	15 (4)	15 (5)	0.394
Other	89 (33)	45 (35)	0.645	37 (26)	35 (36)	0.090
Re-interventions††	96 (13)	50 (13)	0.758	46 (12)	32 (11)	0.783
Mortality**	34 (5)	12 (3)	0.300	11 (3)	9 (3)	0.817
Recovery						
ICU stay (median, IQR)	0 (0 – 54)	0 (0 – 40)	<0.001	0 (0 – 44)	0 (0 – 56)	<0.001
Hospital stay (median, IQR)	9 (1 – 124)	7 (2 – 164)	<0.001	9 (3 – 124)	7 (2 – 164)	<0.001
Readmissions‡‡	72 (10)	44 (12)	0.246	38 (10)	31 (11)	0.664

*Dataset after imputation. ICU: Intensive Care Unit, IQR: interquartile range, MIDG: Minimally Invasive Distal Gastrectomy, ODG: Open Distal Gastrectomy, PSM: Propensity Score Matched. †Any clinically or radiologically proven anastomotic leakage *Pneumonia, pleural effusion, respiratory failure, pneumothorax and/or acute respiratory distress syndrome (ARDS). ‡Supra- and ventricular arrhythmia, myocardial infarction and/or heart failure. ¶Pulmonary embolism, deep venous thrombosis and/or cerebro vascular accident. #Acute delirium. §Acute renal insufficiency, acute kidney failure requiring dialysis, urine tract infection and/or urine retention. ††Re-intervention (radiological / endoscopic / surgical). **Death during initial hospital admission or within 30 days after surgery. ‡‡Readmission to hospital within 30 days after initial discharge.

between both groups (both 10 days, p=0.608), the median ICU stay was shorter in the MITG group (1 day vs. 0 days, p=0.001).

Surgical and histopathological outcomes

For *distal gastrectomy* (Supplementary file S1), the median lymph node yield was 19 nodes after ODG and 21 nodes after MIDG (p=0.214). A radical resection was realized in 93% after ODG and 94% after MIDG (p=0.634). After *total gastrectomy* (Supplementary file S2), the median lymph node yield was similar between OTG and MITG (21 vs. 22 nodes, p=0.425). In 89% of the patients in both groups, a radical resection was achieved (p=0.911).

Table 4. Postoperative outcomes of the original and propensity score matched cohort of patients who underwent total gastrectomy

	Original cohort (n = 832)			PSM cohort [a] (n = 581)		
	OTG	MITG	*p*-value	OTG	MITG	*p*-value
	n = 518 (%)	n = 314 (%)		n = 323 (%)	n = 258 (%)	
Postoperative outcomes						
Conversions	-	34 (11)		-	27 (11)	-
Morbidity	219 (42)	145 (46)	0.272	144 (45)	120 (47)	0.643
Intra-abdominal complications						
Anastomotic leakage†	53 (10)	48 (15)	0.030	34 (11)	43 (17)	0.030
Abscess	26 (5)	16 (5)	0.961	14 (4)	14 (5)	0.541
Bleeding	4 (1)	4 (1)	0.472	1 (<1)	3 (1)	0.217
Pancreatitis, leakage or fistula	3 (1)	2 (1)	0.917	3 (1)	2 (1)	0.842
Chyle leakage	17 (3)	3 (1)	0.034	15 (5)	3 (1)	0.016
Trauma of the gut	8 (2)	4 (1)	0.751	5 (2)	3 (1)	0.692
Wound complications						
Infection/abscess	17 (3)	4 (1)	0.073	10 (3)	4 (2)	0.227
Fascia dehiscence	4 (1)	3 (1)	0.779	2 (1)	3 (1)	0.481
Non-surgical complications						
Pulmonary*	89 (17)	63 (20)	0.297	58 (18)	52 (20)	0.502
Cardiac‡	33 (6)	17 (5)	0.574	27 (8)	13 (5)	0.116
Thromboembolic¶	8 (2)	9 (3)	0.191	4 (1)	7 (3)	0.195
Neurologic#	23 (4)	17 (5)	0.524	13 (4)	14 (5)	0.425
Urologic§	13 (3)	9 (3)	0.756	6 (2)	5 (2)	0.944
Other	46 (21)	35 (24)	0.496	33 (23)	27 (23)	0.912
Re-interventions††	91 (18)	72 (23)	0.059	60 (19)	59 (23)	0.203
Mortality**	26 (5)	22 (7)	0.233	18 (6)	20 (8)	0.291
Recovery						
ICU stay (median, IQR)	1 (0 – 93)	0 (0 – 66)	0.001	1 (0 – 93)	0 (0 – 66)	0.001
Hospital stay (median, IQR)	10 (1 – 207)	9 (2 – 197)	0.001	10 (1 – 132)	10 (2 – 197)	0.608
Readmissions‡‡	66 (13)	40 (13)	0.999	44 (14)	34 (13)	0.876

*Dataset after imputation. ICU: Intensive Care Unit, IQR: interquartile range, MIDG: Minimally Invasive Distal Gastrectomy, ODG: Open Distal Gastrectomy, PSM: Propensity Score Matched. †Any clinically or radiologically proven anastomotic leakage *Pneumonia, pleural effusion, respiratory failure, pneumothorax and/or acute respiratory distress syndrome (ARDS). ‡Supra- and ventricular arrhythmia, myocardial infarction and/or heart failure. ¶Pulmonary embolism, deep venous thrombosis and/or cerebro vascular accident. #Acute delirium. §Acute renal insufficiency, acute kidney failure requiring dialysis, urine tract infection and/or urine retention. ††Re-intervention (radiological / endoscopic / surgical). **Death during initial hospital admission or within 30 days after surgery. ‡‡Readmission to hospital within 30 days after initial discharge.

DISCUSSION

This is the first population-based cohort study to evaluate the safety of minimally invasive surgery for distal and total gastrectomy in a Western population. MIDG was associated with less intra-abdominal abscesses and wound complications and a shorter hospital stay compared to ODG. After MITG, the anastomotic leakage rate was significantly higher in comparison with OTG. Remarkably, the frequently reported shorter hospitalization after minimally invasive surgery was not demonstrable for MITG. Overall postoperative morbidity, mortality, radicality and lymph node yield were similar between minimally invasive and open surgery for both distal and total gastrectomy. Finally, this study demonstrates a diminished rate of chyle leakage after minimally

invasive surgery for both distal and total gastrectomy, and less neurological complications after MIDG compared with ODG.

Due to its greater complexity, total gastrectomy is more often associated with a higher risk of complications, especially concerning anastomotic complications[12,13]. This is probably caused by a more technically challenging anastomotic technique involving the esophagus, combined with a different anatomical position and vascularization. This difference stresses the importance of separate analysis for distal and total gastrectomy.

The surgical safety and oncologic outcomes of MIDG compared with conventional ODG were previously evaluated in two large Asian trials. In the CLASS-01 trial, a Chinese multicenter trial of 1039 patients with advanced cancer, the overall postoperative morbidity rate was comparable between the MIDG (15.2%) and ODG (12.9%) group. Moreover, no significant differences were reported for anastomotic leakage (1.9% vs. 0.6%), postoperative mortality (0.4% vs. 0%) or short-term oncological outcomes. However, patients that underwent MIDG had a shorter postoperative hospital stay. Results of the KLASS-01 trial, a Korean multicenter trial including 1384 patients with early cancer, demonstrate a lower postoperative morbidity rate (13.7% vs. 18.9%) and shorter hospitalization (7.2 vs. 8.0 days) after MIDG. No difference in anastomotic leakage (0.7% vs. 1.0%) or postoperative mortality (0.6% vs. 0.3%) was reported. However, the lymph node yield was less favorable for MIDG in this trial (40.5 vs. 43.3 lymph nodes). In comparison to both Asian trials, the current study found similar postoperative morbidity and mortality rates between MIDG and ODG (with advantages of MIDG in wound complications and abscesses), and a shorter postoperative hospital stay in favor of MIDG. Fortunately, in contrast to the KLASS-01 trial, the current study found a similar lymph node yield between the two procedures. On the other hand, compared to the Asian trials, the postoperative morbidity and mortality rates were higher in our study[7,23]. Firstly, these discrepancies with the CLASS-01 trial might be clarified by differences in patient characteristics between populations (with more comorbidities and overweight found in the Western population), whereas the discrepancies with the KLASS-01 trial might be explained by differences in tumor characteristics (less advanced tumors in the Korean population)[24]. Secondly, population-based studies frequently reflect other populations compared to randomized trials. Furthermore, Asian centers tend to see a substantially higher number of cases annually due to a higher incidence of gastric cancer. This

allows for dedicated specialized gastric surgeons to become more experienced in performing gastrectomies. The shorter postoperative hospital stay compared to the CLASS-01 trial might be explained by the Enhanced Recovery After Surgery (ERAS) program, which most patients were subjected to in the current study[25].

The evidence for the safety, feasibility and benefits of MITG is scarce, in contrast to MIDG. Only a few retrospective, mostly Asian, studies have reported that MITG is safe and feasible[12,13,26,27]. However, the current study shows less advantages of MITG. The frequently reported benefits of minimally invasive surgery, such as less wound infection, less intra-abdominal abscesses and shorter hospital stay were not demonstrated for MITG. Moreover, a higher rate of anastomotic leakage was found. These findings were also described in a previous study that demonstrated a significantly higher anastomotic leakage rate and a tendency to a higher incidence of re-interventions after MITG[13]. The current findings could be explained by a less steep and more extensive learning curve for MITG compared to MIDG. Minimally invasive gastrectomy has only been introduced in the Netherlands in the past decade and since its introduction, surgeons have been adapting these procedures and are suspected to be halfway through the learning curve. Minimally invasive gastrectomy has been progressively performed with 4% being accomplished in 2011, increasing to 58% in 2016. The findings on MITG imply that more caution should be exercised when performing this procedure. Furthermore, it might be appropriate to organize more dedicated trainings for MITG, especially considering that a previous study concluded that approximately 100 MITGs should be performed to complete the learning curve[28]. In the Netherlands, training of minimally invasive gastrectomy consists of a hands-on course, which is preceded by lectures reviewing anatomy, operative technique and perioperative management for minimally invasive gastrectomy. This course has been adopted as an official European Society of Surgical Oncology Course (ESSO)[29]. After that, a structured proctoring program is offered by expert surgeons starting with a case observation and followed by proctoring on site during the first surgical procedures[30]. There is much discrepancy on the number of procedures required for completion of the learning curve and Western studies on this topic are scarce[26,29].

Following the example of Asian centers and studies, the results of this study might call for further centralization of gastric cancer surgery in the West. In the Netherlands, centers performing gastrectomy should achieve a minimum of 20 gastrectomies a year, but herein no distinction is

made between total and distal gastrectomy. Bearing in mind the possible longer learning curve for MITG, it might be justifiable to further increase the annual minimum number of gastrectomies overall per center, or to set a minimum number of annual total gastrectomies per center as well.

As in some other studies, the current study also shows less frequent chyle leakage after MIDG and MITG compared to open resection, which might be explained by the improved visibility during minimally invasive gastrectomy[9,30]. Relating to the higher number of neurological complications (i.e. delirium) following ODG, the explanation might be found in the significantly higher rates of wound complications and higher pain scores associated with open gastrectomy[31,32,33].

The current study may have some limitations as selection bias or residual confounding, for which PSM cannot adjust, may have affected the results. Furthermore, the current study was not able to report data on anastomosis techniques, surgeon volume, disease progression and survival, as these were lacking from the DUCA.

CONCLUSION

Benefits of minimally invasive gastrectomy during the early introduction can be demonstrated for distal but not for total gastrectomy. Especially, a higher anastomotic leakage rate was found after MITG compared with OTG.

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; 136:359-386.
2. Integraal Kankercentrum Nederland. Diagnostiek: Cijfers over kanker; 2014: https://www.iknl.nl/cijfers/cijfers-over-kanker
3. Busweiler L.A.D., Wijnhoven B.P.L., van Berge Henegouwen M.I., et. al.: Early outcomes from the Dutch upper gastrointestinal cancer audit. Br J Surg 2016; 103:1855-1863.
4. Vereniging Integrale Kankercentra : Richtlijn Diagnostiek, behandeling en follow-up van het maagcarcinoom 2009.
5. Cunningham D., Allum W.H., Stenning S.P., et. al.: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2007;11-20.
6. Brenkman H.J.F., Haverkamp L., Ruurda J.P., Van Hillegersberg R.: Worldwide practice in gastric cancer surgery. World J Gastroenterol 2016; 22:4041-4048.
7. Kim W., Kim H.H., Han S.U., et. al.: Decreased morbidity of laparoscopic distal gastrectomy compared with open distal gastrectomy for stage I gastric cancer: short-term outcomes from a multicenter randomized controlled trial (KLASS-01). Ann Surg 2016;263:28-35.
8. Dutch Upper GI Cancer Audit : DUCA Jaarrapportage 2016.2017. http://dica.nl/jaarrapportage-2016/duca
9. Brenkman H.J.F., Gisbertz S.S., Slaman A.E., et. al.: Postoperative outcomes of minimally invasive gastrectomy versus open gastrectomy during the early introduction of minimally invasive gastrectomy in The Netherlands. Ann Surg 2017;266:831-838.
10. Li Z., Ji G., Bai B., et. al.: Laparoscopy-assisted distal gastrectomy versus laparoscopy-assisted total gastrectomy with D2 lymph node dissection for middle-third advanced gastric cancer. Surg Endosc Other Interv Tech 2017;0:1-8.
11. Chen K., Zhai S.-T., Pan J.-H., et. al.: Short-term outcomes of laparoscopic total gastrectomy for gastric cancer: a comparative study with laparoscopic distal gastrectomy at a high-volume center. Minim Invasive Ther Allied Technol 2017;0:1-7.
12. Lee S.E., Ryu K.W., Nam B.H., et. al.: Technical feasibility and safety of laparoscopy-assisted total gastrectomy in gastric cancer: a comparative study with laparoscopy-assisted distal gastrectomy. J Surg Oncol 2009;100:392-395.
13. Kodera Y., Yoshida K., Kumamaru H., et. al.: Introducing laparoscopic total gastrectomy for gastric cancer in general practice: a retrospective cohort study based on a nationwide registry database in Japan. Gastric Cancer 2018;
14. Haverkamp L., Ruurda J.P., van der Sluis P.C., van Hillegersberg R.: Chirurgische behandeling van maagcarcinoom: focus op centralisatie en laparoscopische resecties. Ned Tijdschr Geneeskd 2013;157:1-6.
15. Kelly K.J., Selby L., Chou J.F., et. al.: Laparoscopic versus open gastrectomy for gastric adenocarcinoma in the West: a case–control study. Ann Surg Oncol 2016;22:3590-3596.
16. Vereniging Integrale Kankercentra : Diagnostiek, behandeling en follow-up van het maagcarcinoom 2016.1-7. http://www.oncoline.nl/uploaded/docs/Maagcarcinoom/Richtlijn maagcarcinoom.pdf
17. Cunningham D., Starling N., Rao S., et. al.: Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008;358:36-46.
18. Sano T., Kodera Y.: Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011;14:113-123.
19. Washington K.: 7th edition of the AJCC cancer staging manual: Stomach. Ann Surg Oncol 2010;17:3077-3079.
20. Dutch Upper GI Cancer Audit : Data dictionairy. 2016
21. Donders A.R.T., van der Heijden G.J.M.G., Stijnen T., Moons K.G.M.: Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59:1087-1091.
22. Austin P.C.: An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399-424.

23. Hu Y., Huang C., Sun Y., et. al.: Morbidity and mortality of laparoscopic versus open D2 distal gastrectomy for advanced gastric cancer: a randomized controlled trial. J Clin Oncol 2016;34:1350-1357.
24. Griffin S.M.: Gastric cancer in the East: same disease, different patient. Br J Surg 2005; 92:1055-1056.
25. Mortensen K., Nilsson M., Slim K., et. al.: Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery after Surgery (ERAS) Society recommendations. Br J Surg 2014;101:1209-1229.
26. Usui S., Yoshida T., Ito K., et al.: Laparoscopy-assisted total gastrectomy for early gastric cancer. Surg Laparosc Endosc Percutan Tech 2005;15:309-314.
27. Haverkamp L., Weijs T.J., Van Der Sluis P.C., et al.: Laparoscopic total gastrectomy versus open total gastrectomy for cancer: a systematic review and meta-analysis. Surg Endosc Other Interv Tech 2013;27:1509-1520.
28. Jung D.H., Son S.-Y., Park Y.S., et. al.: The learning curve associated with laparoscopic total gastrectomy. Gastric Cancer 2016;19:264-272.
29. ESSO course on minimally invasive ESOPHAGECTOMY and gastrectomy.Partnership with University Medical Center Utrecht Utrecht (NL), 15th to 16th March 2018.
30. Brenkman H.J.F., Correa-Cote J., Ruurda J.P., van Hillegersberg R.: A step-wise approach to total laparoscopic gastrectomy with jejunal pouch reconstruction: how and why we do it. J Gastrointest Surg 2016;20:1908-1915.
31. Jeong O., Ryu S.Y., Choi W.Y., et al: Risk factors and learning curve associated with postoperative morbidity of laparoscopic total gastrectomy for gastric carcinoma. Ann Surg Oncol 2014;21:2994-3001.
32. Lu J., Wei Z.-Q., Huang C.-M., et. al.: Small-volume chylous ascites after laparoscopic radical gastrectomy for gastric cancer: results from a large population-based sample. World J Gastroenterol 2015;21:2425-2432.
33. Lee J.H., Han H.S.: A prospective randomized study comparing open vs laparoscopy-assisted distal gastrectomy in early gastric cancer: early results. Surg Endosc 2005;19: 168-173.

SUPPLEMENTARY FILES

Supplementary Table S1. Histopathological characteristics of the original and propensity score matched cohort of patients who underwent distal gastrectomy

	Original cohort (*n*= 1138)			**PSM cohort* (*n*= 678)**		
	ODG	MIDG	*p*-value	ODG	MIDG	*p*-value
	n = 761 (%)	n = 377 (%)		n = 390 (%)	n = 288 (%)	
Histopathological characteristics						
Lauren classification			0.156			0.341
Intestinal	368 (48)	182 (48)		192 (49)	141 (49)	
Diffuse	189 (25)	122 (32)		104 (27)	92 (32)	
Mixed	50 (7)	23 (6)		30 (8)	17 (6)	
Unknown	154 (20)	50 (13)		38 (13)	38 (13)	
Tumor differentiation			0.093			0.358
Well/moderate	285 (38)	118 (31)		159 (41)	99 (34)	
Poor/ undifferentiated	368 (48)	193 (51)		191 (49)	139 (48)	
Unknown	108 (14)	66 (18)		40 (10)	50 (17)	
pT-stage			0.203			0.447
T0	23 (3)	21 (6)		19 (5)	14 (5)	
Tis	8 (1)	3 (1)		5 (1)	3 (1)	
T1	146 (19)	80 (21)		84 (22)	67 (23)	
T2	136 (18)	69 (18)		70 (18)	59 (21)	
T3	297 (39)	132 (35)		145 (37)	94 (33)	
T4	141 (19)	72 (19)		67 (17)	51 (18)	
Tx	10 (1)	-		-	-	
pN-stage			0.305			0.677
N0	377 (50)	173 (46)		196 (50)	139 (48)	
N1	137 (18)	81 (22)		77 (20)	60 (21)	
N2	129 (17)	63 (17)		60 (15)	44 (15)	
N3	105 (14)	58 (16)		57 (15)	45 (16)	
Nx	13 (2)	2 (1)		-	-	
pM-stage			0.393			0.680
M0	743 (98)	371 (98)		377 (97)	280 (97)	
M1	18 (2)	6 (2)		13 (3)	8 (3)	
Additional resections	61 (8)	21 (6)	0.133	30 (8)	17 (6)	0.365
Radicality of the resection			0.370			0.634
R0	703 (92)	354 (94)		362 (93)	270 (94)	
R+	57 (8)	23 (6)		28 (7)	18 (6)	
Lymph node yield (median, IQR)	18 (0 – 72)	22 (0 – 80)	<0.001	19 (0 – 64)	21 (0 – 80)	0.214
≥ 15 Lymph nodes in the specimen	493 (67)	294 (80)	<0.001	279 (72)	224 (78)	0.066
Positive lymph nodes (median, IQR)	0 (0 – 38)	1 (0 – 29)	0.206	0 (0 – 32)	1 (0 – 29)	0.589

*Dataset after imputation. IQR: interquartile range, MIDG: Minimally Invasive Distal Gastrectomy, ODG: Open Distal Gastrectomy, PSM: Propensity Score Matched

Supplementary Table S2. Histopathological characteristics of the original and propensity score matched cohort of patients who underwent total gastrectomy

	Original cohort (*n*= 832)			**PSM cohort* (*n*= 581)**		
	ODG	MIDG	*p*-value	ODG	MIDG	*p*-value
	n = 518 (%)	n = 314 (%)		n = 323 (%)	n = 258 (%)	
Histopathological characteristics						
Lauren classification			0.235			0.404
Intestinal	176 (34)	123 (39)		117 (36)	101 (39)	
Diffuse	214 (41)	117 (37)		142 (44)	95 (37)	
Mixed	21 (4)	17 (5)		15 (5)	11 (4)	
Unknown	107 (21)	57 (18)		49 (15)	51 (20)	
Tumor differentiation			0.014			0.017
Well/moderate	122 (24)	101 (32)		76 (24)	84 (33)	
Poor/ undifferentiated	316 (61)	175 (56)		202 (63)	141 (55)	
Unknown	80 (15)	38 (12)		45 (14)	33 (13)	
pT-stage			0.507			0.296
T0	21 (4)	18 (6)		12 (4)	17 (7)	
Tis	2 (<1)	1 (<1)		2 (1)	1 (<1)	
T1	59 (12)	31 (10)		34 (11)	26 (10)	
T2	64 (12)	49 (16)		42 (13)	39 (15)	
T3	232 (45)	132 (42)		150 (46)	112 (43)	
T4	126 (24)	75 (24)		83 (27)	63 (24)	
Tx	14 (3)	8 (3)				
pN-stage			0.370			0.393
N0	222 (43)	121 (39)		145 (45)	101 (39)	
N1	95 (18)	63 (20)		52 (16)	51 (20)	
N2	74 (14)	49 (16)		44 (14)	42 (16)	
N3	117 (23)	73 (23)		82 (25)	64 (25)	
Nx	10 (2)	8 (3)				
pM-stage			0.134			0.066
M0	492 (95)	305 (97)		304 (94)	251 (97)	
M1	26 (5)	9 (3)		19 (6)	7 (3)	
Additional resections	64 (12)	36 (12)	0.702	47 (15)	29 (11)	0.240
Radicality of the resection			0.803			0.911
R0	459 (89)	280 (89)		287 (89)	230 (89)	
R+	59 (11)	34 (11)		36 (11)	28 (11)	
Lymph node yield (median, IQR)	20 (2 – 71)	22 (1 – 85)	0.009	21 (2 – 71)	22 (2 – 62)	0.425
≥ 15 Lymph nodes in the specimen	381 (74)	265 (84)	<0.001	258 (80)	220 (85)	0.091
Positive lymph nodes (median, IQR)	1 (0 – 49)	1 (0 – 68)	0.634	1 (0 – 46)	1 (0 – 40)	0.776

*Dataset after imputation. IQR: interquartile range, MIDG: Minimally Invasive Distal Gastrectomy, ODG: Open Distal Gastrectomy, PSM: Propensity Score Matched

Chapter 11

Minimally invasive surgery for large gastric gastrointestinal stromal tumors

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ABSTRACT

Background: Gastrointestinal stromal tumors (GISTs) frequently present as a large exophytically growing mass in the stomach, for which open partial gastrectomy is standard of care. The aim of this study was to evaluate the safety and feasibility of minimally invasive gastric resection (MIG) of large (>5 cm) GIST.

Methods: All patients who underwent MIG for a GIST in the University Medical Center Utrecht between 2011 and 2019 were included. Postoperative course and oncological outcomes were analyzed.

Results: Twenty-two patients with gastric GIST, median size 53 mm [20–175 mm], underwent MIG. In 4 patients, preoperative imatinib was given, aiming for tumor regression. Conversion from laparoscopic to open surgery occurred once (5%). An additional resection was performed in 3 patients (14%). In 2 patients (9%), an intraoperative complication occurred, consisting of tumor rupture in 1 patient (5%), and 6 patients (27%) developed postoperative complications. Median hospital stay was 5 days [3–7 days]. R0 resection was achieved in 96%. In 4 patients, adjuvant treatment was indicated. The median follow-up was 31 months, and 1-, 3- and 5-year disease-free survival were 94, 74 and 74%, respectively. One patient presented with local recurrence 2 years after the index resection.

Conclusion: MIG for large GIST up to 17.5 cm in diameter is safe, feasible, and oncologically sound, allowing for a controlled resection and reduced patient morbidity.

BACKGROUND

Gastrointestinal stromal tumors (GISTs) are the most common type of mesenchymal tumors in the gastrointestinal tract[1] and most frequently occur in the stomach (50–60%), followed by the small intestines (20–30%) and rectum (10%)[2]. In the Netherlands, gastric GIST had an annual incidence of 130 cases for the entire population (17 million) but appears to be increasing[3]. Radical surgical resection with prevention of rupture is the cornerstone of curative treatment for GIST ≥2 cm[4,5].

Minimally invasive gastric surgery (MIG) has gained popularity in surgical oncology since it embraces benefits such as reduced postoperative morbidity and shorter length of hospital stay[6,7]. In addition, since MIG appears to cause less operative trauma compared to traditional open surgery, more frail patients may be considered for resection. However, previously reported contraindications for MIG are tumor size, invasion into adjacent organs, and a tumor near the gastroesophageal junction[1,8]. Opinions differ on whether MIG is feasible and safe for "large" GIST (those exceeding 5 cm in size). To date, guidelines advise that GIST exceeding 5 cm in size should only be treated by open resection[5]. Few studies report on laparoscopic resection being superior to open surgery for gastric GIST[1,9-11]. However, most of these studies were conducted in an Asian population with different patient and tumor characteristics, such as lower BMI and smaller sized tumors, compared to the Western population. Consequently, the aim of this study was to evaluate the safety and feasibility of MIG for large gastric GIST in a Western population.

METHODS

Study population

This descriptive, single-center, retrospective study included all patients who underwent MIG for a GIST between January 2011 and December 2019 from the University Medical Center Utrecht (UMC Utrecht). In the regional Comprehensive Cancer Network Utrecht (population: 1.2 million), surgical treatment of upper gastrointestinal tumors is centralized in the UMC Utrecht, and approximately 130 upper gastrointestinal cancer patients are operated annually, varying from wedge resections of GIST to robot-assisted minimally invasive thoracolaparoscopic esophagectomy. Since 2006, MIG is the standard procedure for gastric GIST in the UMC Utrecht.

Patients were diagnosed via gastroscopy with biopsies or EUS with fine needle aspiration and CT of the thorax and abdomen. If indicated, preoperative treatment with imatinib was given, and surgical wedge resection or partial gastrectomy was performed. No lymphadenectomy was performed, since gastric GISTs have a very low risk of dissemination to the lymph nodes[1,5,8,9]. Data on all upper gastrointestinal procedures were prospectively registered in the Upper-GI database of the Department of Surgery. The resection specimens were collected from the pathology archives and re-evaluated by an experienced gastrointestinal pathologist (L.A.A.B.) to reassess pathological characteristics. In case of a high-grade tumors with high risk of progressive disease according to the NCCN Guidelines, adjuvant imatinib was given[5]. According to the Medical Ethical Committee and the Medical Research Involving Human Subjects Act (WMO), informed consent requirement was waived.

Surgical techniques

All patients were positioned in the supine position. A 12 mm balloon trocar was placed and 4 additional ports were used: 2 working ports (each 5 mm), an assisting port (5 mm), and a port through which the liver retractor could be introduced (12 mm). The lesser omentum was opened. Then, the tumor was located and approached carefully, and in case of a dorsally located tumor, the bursa was opened through the gastrocolic ligament. As preservation of the vagus nerve is important to achieve good functional outcome, these were preserved. If a wedge excision was sufficient, a local resection of the tumor was performed, using a barbed suture to close the defect anatomically. In case no hand-sewn anatomical reconstruction could be performed (e.g., in case of a tumor near the gastroesophageal junction), the EndoGIA (60 mm) was used to perform the wedge resection. In case of a tumor location near the gastroesophageal junction, a gastroduodenoscopy was used intraoperatively to assess the patency and diameter of the lumen. If a partial gastrectomy was necessary, this was performed laparoscopically as described previously[12]. The resected specimen was removed through a mini-laparotomy, which was intraoperatively infiltrated with bupivacaine and located according to the surgeon's insight. A ring wound retractor that enlarges the wound was used to extract large tumors. If required, a Roux-en-Y gastroenterostomy was created. Supplementary file (see online supplementary file 1; see www.karger.com/doi/10.1159/000510386 for all online supplementary material)

demonstrates a video of a minimally invasive partial gastrectomy for a large GIST (13.9 × 8.6 cm).

Study outcomes

Patient and tumor characteristics, intraoperative surgical parameters, postoperative outcomes, histopathological characteristics, and follow-up were prospectively collected and assessed (Tables 1-5).

RESULTS

Study population

Between 2011 and 2019, 22 consecutive patients underwent surgical gastric resection for a GIST. The mean age was 70.4 years, and mean BMI was 27.9 kg/m2 (Table 1). Most of the patients were female (59%) and had an ASA II classification, where cardiac and vascular comorbidities were most common (both accounting for almost 50%). c-KIT expression was found in the biopsies of 19 patients (86%), and 4 patients received preoperative imatinib. In 2 patients, the effect of preoperative imatinib on the tumor was objectively assessed by a re-staging CT abdomen, which showed a size reduction to 9.2 cm in 1 patient (original size 13.9 cm) and to 2.0 cm in another patient (original size 7.0 cm). In the other 2 patients, persistent bleedings occurred during imatinib treatment, resulting in resection before completion of the imatinib.

Intraoperative parameters

Intraoperative parameters are shown in Table 2. The majority of patients underwent a wedge resection (86%). In case of partial gastrectomy (3 patients, 14%), a gastrojejunostomy was created. Conversion from laparoscopic to open surgery occurred in 1 patient, due to invasion of the GIST in the pancreas and spleen, resulting in an additional partial resection of the pancreas and splenectomy. In another 2 patients, an additional resection was performed beyond the GIST to ensure en bloc oncological resection: resection of diaphragm and an edge of the spleen and resection of part of the transverse mesocolon. All additional resections took place during the index operation. A cruroplasty was performed intraoperatively in 2 patients (9%).

Table 1. Baseline characteristics of the patients who underwent minimally invasive surgery for gastrointestinal stromal cell tumor.

	GIST n = 22 (%)
Baseline characteristics	
Age, years (mean ± SD)	70.4 ± 10.0
BMI, kg/m^2 (mean ± SD)	27.9 ± 5.5
Gender (% female)	13 (59)
ASA-classification	
I	0 (0)
II	13 (62)
III	7 (33)
IV	1 (5)
Comorbidities	
Cardiac	9 (41)
Vascular	11 (50)
Diabetes	3 (14)
Pulmonary	3 (14)
c-KIT expression	19 (86)
Neoadjuvant treatment	
Yes (Imatinib)	4 (18)

Percentages may not add up to 100% due to rounding. ASA: American Society of Anesthesiologists, BMI: Body Mass Index

Table 2. Surgical outcomes of the patients who underwent minimally invasive surgery for gastrointestinal stromal cell tumor.

	GIST n = 22 (%)
Surgical outcomes	
Conversion	1 (5)
Type of resection	
Partial gastrectomy[a]	3 (14)
Wedge	19 (86)
Additional resection	3 (14)
Diaphragm + spleen	1 (5)
Spleen + pancreas	1 (5)
(Meso)Colon	1 (5)
Cruroplasty	2 (9)
Operation time (min; mean ± SD)	107 (48)
Operation time (min; median, IQR)	103 [72 – 138]
Intraoperative complication	3 (14)
Bowel injury	2 (9)
Spill due to tumor rupture	1 (5)

Percentages may not add up to 100% due to rounding. ASA: American Society of Anesthesiologists, BMI: Body Mass Index

In 3 patients (14%), an intraoperative complication occurred: in 2 patients, a bowel injury occurred (requiring suturing), and in 1 patient, who was operated in an emergency setting because of bleeding, a small tumor perforation occurred at extraction, without spill (macroscopically no tumor was left behind). The mean overall operating time was 107 min.

Postoperative outcomes

In total, 6 patients (27%) developed postoperative complications (Table 3). In 1 patient, a re-operation was needed with surgical drainage and repair of a leakage at the sutured defect following a wedge resection. In this patient, the defect was located near the pylorus at the lesser curve and closed with a barbed suture. Two patients developed a hospital-acquired pneumonia, 1 patient had cardiac complications (supraventricular fibrillation combined with a troponin rise), and 1 patient had a urologic complication (replacement of a bladder catheter due to retention). There was no postoperative mortality. Median ICU stay was 0 [0–0] days and hospital stay was 5 days [3–7 days].

Histopathological outcomes

Table 4 shows histopathological outcomes. The median size of the GIST was 53 mm (range 20–175 mm), and mitotic rate was ≤5 per 5 mm2 in the majority of patients (Figure 1). Based on the WHO classification and Risk Stratification of Primary GIST by Mitotic Index, Size and Site table[5, 13], 15 patients (68%) had a low risk of progressive disease, 2 patients (9%) had a moderate risk, and 5 patients (23%) had a high risk of progressive disease. R0 resection was performed in all but 1 patient (96%). In 1 patient with a dorsally located GIST, the tumor had a close relationship with the mesocolon and retroperitoneum. In this patient, tumor cells were found in the stapler edge, resulting in R1 resection. c-KIT expression was found in 19 patients (86%) by immunohistochemistry. c-KIT mutation analysis was performed in 9 patients (41%), of whom 4 patients were treated with preoperative imatinib.

Follow-up

Table 5 summarizes follow-up data. Postoperative therapy with imatinib was administered in 4 patients (18%, of whom 3 patients also received preoperative imatinib), as soon as this was permitted by the physical condition and postoperative recovery of the patient. The median follow-up was 31 months, and 1-, 3- and 5-year disease-free survival were 94, 76, and 76%, respectively. Overall survival rates were 94, 86, and 86% (1, 3, and 5 years, respectively). To date, the patient in whom an R1 resection was performed did not present with recurrence.

Table 3. Postoperative outcomes of the patients who underwent minimally invasive surgery for gastrointestinal stromal cell tumor.

	GIST n = 22 (%)
Postoperative outcomes	
Morbidity	6 (27)
Intra-abdominal complications	
Anastomotic leakage[a]	0 (0)
Perforation at suturing site	1 (5)
Abscess	0 (0)
Bleeding	0 (0)
Pancreatitis, leakage or fistula	0 (0)
Chyle leakage	0 (0)
Trauma of the gut	0 (0)
Gastroparesis	0 (0)
Wound complications	0 (0)
Non-surgical complications	
Pulmonary[b]	2 (9)
Cardiac[c]	1 (5)
Thromboembolic[d]	0 (0)
Neurologic[e]	0 (0)
Urologic[f]	1 (5)
Other	1 (5)
Re-interventions	1 (5)
Mortality	0 (0)
Recovery	
ICU stay (median, IQR)	0 [0 – 0]
Hospital stay (median, IQR)	5 [3 – 7]
Readmissions	0 (0)

Percentages may not add up to 100% due to rounding. ICU: Intensive Care Unit, IQR: interquartile range. a. Any clinically or radiologically proven anastomotic leakage; b. pneumonia, pleural effusion, respiratory failure, pneumothorax and/or acute respiratory distress syndrome (ARDS); c. supra- and ventricular arrhythmia, myocardial infarction and/or heart failure; d. pulmonary embolism, deep venous thrombosis and/or cerebrovascular accident; e. acute delirium; f. acute renal insufficiency, acute kidney failure requiring dialysis, urine tract infection and/or urine retention.

Table 4. Histopathological outcomes of the patients who underwent minimally invasive surgery for gastrointestinal stromal cell tumor.

	GIST n = 22 (%)
Histopathological outcomes	
Size (mm; mean ± SD)	57 (35)
Size (mm; median, ranges)	53 (20 – 175)
Mitotic rate ≤5 / 5 mm^2 [a]	17 (77)
Risk of progressive disease[b]	
Low risk (WHO I, II, IIIa-IV)	15 (68)
Moderate risk (WHO IIIb, V)	2 (9)
High risk (WHO VIa-VIb)	5 (23)
c-Kit mutation analysis	9 (41)
Radicality of the resection	
R0	21 (96)
R1	1 (5)
Lymph node resection (yes, %)	5 (23)
Lymph node yield (median, IQR)	2 [2 – 11]
Positive lymph nodes (median, IQR)	0 [0 – 0]

IQR: interquartile range. a. if a patient received preoperative treatment with Imatinib it is questionable whether or not MAI count is reliable due to therapeutic changes (e.g. fibrosis) of the tumor, b. According to the NCCN Guidelines

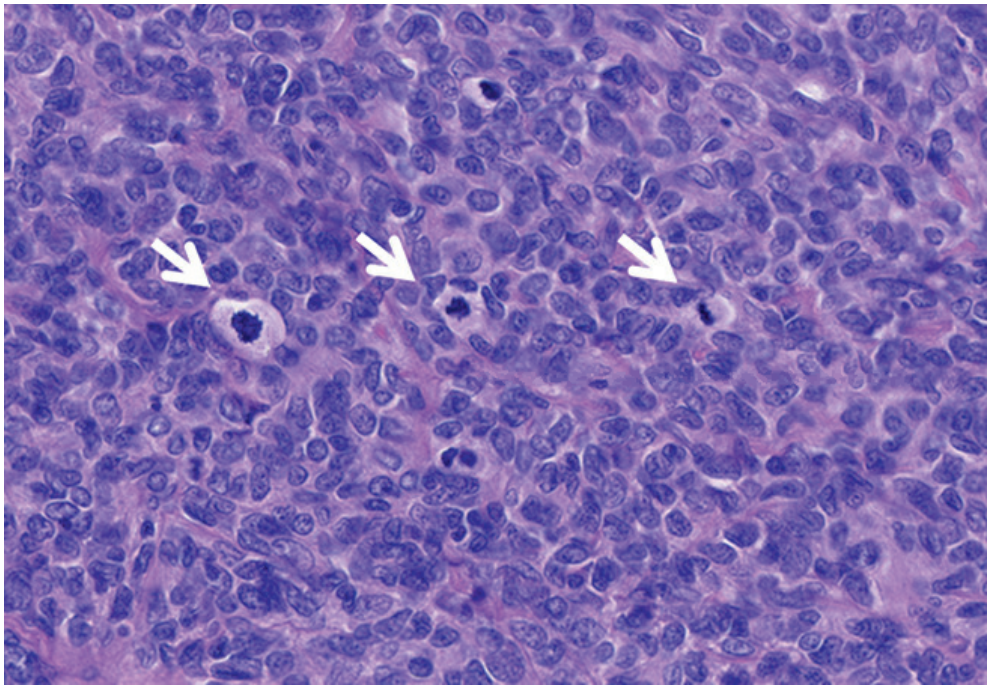

Figure 1. Three mitoses per HPF in a patient with a high-graded GIST

Two years after surgery, another patient presented with local recurrence with hepatogenic and peritoneal metastases. In this patient, with an initial tumor of 5.5 cm, mitotic index of >5 mitoses per HPF, WHO risk category 6a and R0 resection, postoperative imatinib was stopped after 2 months due to toxicity. As yet, there are no patients with postoperative gastric stenosis.

Table 5. Follow-up data on the patients who underwent minimally invasive surgery for gastrointestinal stromal cell tumor.

	GIST n = 22 (%)
Stenosis	
Adjuvant treatment	57 (35)
Follow-up (months; median, IQR)	53 (20 – 175)
Overall survival	17 (77)
1-year	
3-year	
5-year	
Recurrence*	
Disease free survival	15 (68)
1-year	
3-year	
5-year	

IQR: interquartile range. *Two years after surgery, patient presented with local recurrence with hepatogenic and peritoneal metastases

DISCUSSION

This study demonstrates that minimally invasive surgery for gastric GIST up to 17.5 cm in diameter can be performed safely and oncologically effective with excellent long-term results. In patients in whom an irresectable tumor with c-KIT expression is suspected, preoperative imatinib resulted in adequate tumor regression, allowing for MIG.

GISTs are the most common type of mesenchymal tumors in the gastrointestinal tract and require surgical resection once over 2 cm, with clear margins because of its malignant potential. No lymphadenectomy is necessary due to the very low risk of dissemination to the lymph nodes[1,5,8,9]. Since the reports on improved patient outcomes following laparoscopic gastrectomy, MIG for GIST has gained popularity[2,13,14]. Several studies have reported on safety and feasibility of MIG for small gastric GIST[1,8,9,15-19]. In addition to the safety and feasibility, MIG has many other benefits, as reviewed by Chen et al[9]. In their systematic review and meta-analysis, 1,166 gastric GISTs were included, and benefits such as reduced blood loss, earlier first flatus day and oral intake, fewer postoperative complications, shorter hospitalization, and lower recurrence risk were described. Koh et al.[1] performed a similar study a year before with roughly the same results; however, the larger tumor size was mostly approached by open surgery.

Unfortunately, no systematic reviews or meta-analyses have been conducted for a Western population. De Vogelaere et al.[8] were one of the first to describe MIG for GIST in a Western population (31 patients) with a mean tumor size of 4.4 cm and range 0.4–11.0 cm. A low morbidity rate was reported (1 patient [3.2%] suffered from hemorrhage postoperatively) and no spill was reported[8]. Bischof et al.[19] performed a propensity score matched analysis on 248 Western patients with a mean tumor size of 3.9 cm (range 2.3–5.2 cm) in the MIG group and found a postoperative grade 3+ (Clavien-Dindo) morbidity rate of 3.2% in the MIG group and 13.7% in the open surgery group. They reported a spill rate of 1.6% during minimally invasive surgery and 0.8% during open surgery. A study by Melstrom et al.[17] also comparing laparoscopic versus open surgery for GIST in 17 patients with a mean tumor size of 4.3 cm (range 1.5–9.1 cm) reported 100% radical resections and 11.8% postoperative complications. In the current study, much larger tumors (mean 5.7 cm, range up to 17.5 cm) in patients with less favorable characteristics (higher age and high BMI) could be treated laparoscopically. In this study, a higher

number of patients required subtotal gastrectomy, which may explain the higher overall morbidity rate (27%) and possibly higher rate of spill (5%). Other Western studies report similar overall postoperative morbidity rates of 33%, despite including younger patients with smaller tumors: 3.6 cm (0.7–7.8 cm) and 5.5 cm (2.5–12 cm)[16,20].

In comparison with results from DeMatteo et al.[2], a higher R0 resection rate was found (81 vs. 96%). Compared to De Vogelaere et al.[8], a shorter hospital stay (8.4 vs. 5 days) was found in the current study. Bischof et al.[19] and Melstrom et al.[17] reported a longer operation time (157 vs. 135 vs. 108 min in the current study). These differences might be caused by centralization of gastric cancer care in the Netherlands, starting of 2009, which results in more experienced surgeons in high-volume centers (>20 gastrectomies per year per center required in the Netherlands).

The literature is scarce regarding long-term survival after MIG for large GIST. In the study of Karakousis et al., disease-free survival was 90%, whereas Bischof et al.[19] reported a recurrence-free survival of 79.5% at the 5-year follow-up. Likewise, the current study demonstrated a 5-year disease-free survival of 76%.

Although this study has several strengths, such as the prospective data collection with complete data registry of patient and tumor characteristics, intra- and postoperative parameters (including recovery and follow-up data), and the preference for MIG regardless of the tumor size, a few limitations should be addressed. The current results are based on an observational study design and data of 2 experienced surgeons in a single university hospital; generalization of these results might therefore not be possible. In addition, the small sample size is potentially limiting.

CONCLUSION

MIG for large gastric GIST up to 17.5 cm in diameter is safe and feasible in a Western population with advanced GIST. The laparoscopic approach could be considered the standard of care for gastric GIST regardless of tumor size.

REFERENCES

1. Koh Y, Chok A, Zheng H, Tan C. A Systematic Review and Meta-Analysis Comparing Laparoscopic Versus Open Gastric Resections for Gastrointestinal Stromal Tumors of the Stomach. Gastrointest Oncol 2013:3549–60.
2. Dematteo RP, Lewis JJ, Leung D, Mudan SS. Two Hundred Gastrointestinal Stromal Tumors. Ann Surg 2000;231:51–8.
3. Nederlandse Kankerregistratie. Incidence of gastric GISTs 2019:2018–20. https://www.cijfersoverkanker.nl/selecties
4. Casali PG, Abecassis N, Bauer S, et al. Gastrointestinal stromal tumours: ESMO – EURACAN Clinical Practice Guidelines for diagnosis , treatment Clinical Practice Guidelines. Ann Oncol 2018;29:68–78.
5. Demetri GD, Benjamin RS, Blanke CD, et al. NCCN Task Force Report: Optimal Management of Patients with Gastrointestinal Stromal Tumor (GIST)—Update of the NCCN Clinical Practice Guidelines. vol. 5. 2007.
6. Kim W, Kim HH, Han SU, et al. Decreased morbidity of laparoscopic distal gastrectomy compared with open distal gastrectomy for stage I gastric cancer: Short-term outcomes from a multicenter randomized controlled trial (KLASS-01). Ann Surg 2016;263:28–35.
7. Brenkman HJF, Gisbertz SS, Slaman AE, et al. Postoperative Outcomes of Minimally Invasive Gastrectomy Versus Open Gastrectomy during the Early Introduction of Minimally Invasive Gastrectomy in the Netherlands. Ann Surg 2017;266:831–8.
8. De Vogelaere K, Van Loo I, Peters O, et al. Laparoscopic resection of gastric gastrointestinal stromal tumors (GIST) is safe and effective, irrespective of tumor size. Surg Endosc 2012:2339–45.
9. Chen Q, Pan Y, Cai J, et al. Laparoscopic versus open resection for gastric gastrointestinal stromal tumors: an updated systematic review and meta-analysis. World J Surg Oncol 2014:1–13.
10. Otani Y, Furukawa T, Yoshida M, et al. Operative indications for relatively small (2-5 cm) gastrointestinal stromal tumor of the stomach based on analysis of 60 operated cases. Surgery 2006;139:484–92.
11. Dressler JA, Palazzo F, Berger AC, et al. Long-term functional outcomes of laparoscopic resection for gastric gastrointestinal stromal tumors. Surg Endosc 2016;30:1592–8.
12. Haverkamp L, Brenkman HJF, Seesing MFJ, et al. Laparoscopic versus open gastrectomy for gastric cancer, a multicenter prospectively randomized controlled trial (LOGICA-trial). BMC Cancer 2015;15:1–7.
13. Fletcher CDM, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 2002;33:459–65.
14. Miettinen M, El-Rifai W, Sobin L, Lasota J. Evaluation of malignancy and prognosis of gastrointestinal stromal tumors: A review. Hum Pathol 2002.
15. Huang C, Chen Q, Lin J, et al. Can laparoscopic surgery be applied in gastric gastrointestinal stromal tumors located in unfavorable sites? Medicine (Baltimore) 2017;96:1–8.
16. Karakousis GC, Singer S, Zheng J, et al. Laparoscopic versus open gastric resections for primary gastrointestinal stromal tumors: a size-matched comparison. Ann Surg Oncol 2011;18:1588–605.
17. Melstrom LG, Phillips JD, Bentrem DJ, Wayne JD. Laparoscopic Versus Open Resection of Gastric Gastrointestinal Stromal Tumors. Am J Clin Oncol 2012;35:451–4.
18. Xiong Z, Wan W, Zeng X, et al. Laparoscopic Versus Open Surgery for Gastric Gastrointestinal Stromal Tumors: a Propensity Score Matching Analysis. J Gastrointest Surg 2019 epub ahead of print.
19. Bischof DA, Kim Y, Dodson R, et al. Open versus minimally invasive resection of gastric gist: A multi-institutional analysis of short- and long-term outcomes. Ann Surg Oncol 2014;21:2941–8.
20. Masoni L, Gentili I, Maglio R, et al. Laparoscopic resection of large gastric GISTs: feasibility and long-term results. Surg Endosc 2014;28:2905–10.

SUPPLEMENTARY FILES

Video S1: Laparoscopic procedure with English narration

https://karger.figshare.com/articles/dataset/Supplementary_Material_for_Minimally_Invasive_Resection_of_Large_Gastric_Gastrointestinal_Stromal_Tumors/13005326

Chapter 12

Identification of the clinically most relevant postoperative complications after gastrectomy: a population-based cohort study

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ABSTRACT

Background: Postoperative complications frequently occur after gastrectomy for gastric cancer and are associated with poor clinical outcomes, such as mortality and reoperations. The aim of this study was to identify the clinically most relevant complications after gastrectomy, using the population-attributable fraction (PAF).

Methods: Between 2011-2017, all patients who underwent potentially curative gastrectomy for gastric adenocarcinoma were included from the Dutch Upper GI Cancer Audit. Postoperative outcomes (morbidity, mortality, recovery and hospitalization) were evaluated. The prevalence of postoperative complications (e.g. anastomotic leakage and pneumonia) and of the study outcomes were calculated. The adjusted relative risk and Confidence Interval (CI) for each complication-outcome pair were calculated. Subsequently, the PAF was calculated, which represents the percentage of a given outcome occurring in the population, caused by individual complications, taking both the relative risk and the frequency in which a complication occurs into account.

Results: In total, 2176 patients were analyzed. Anastomotic leakage and pulmonary complications had the greatest overall impact on postoperative mortality (PAF: 29.2% [95%CI: 19.3-39.1] and 21.6% [95%CI: 10.5-32.7], respectively) and prolonged hospitalization (PAF: 12.9% [95%CI: 9.7-16.0] and 14.7% [95%CI: 11.0-18.8], respectively). Anastomotic leakage had the greatest overall impact on re-interventions (PAF: 25.1% [95%CI: 20.5-29.7]) and reoperations (PAF: 30.3% [95%CI: 24.3-36.3]). Intra-abdominal abscesses had the largest impact on readmissions (PAF: 7.0% [95%CI: 3.2-10.9]). Other complications only had a small effect on these outcomes.

Conclusion: Surgical improvement programs should focus on preventing or managing anastomotic leakage and pulmonary complications, since these complications have the greatest overall impact on clinical outcomes after gastrectomy.

BACKGROUND

Gastrectomy with lymphadenectomy is the cornerstone of curative treatment for patients diagnosed with adenocarcinoma of the stomach[1] and, if deemed fit enough, patients will also receive perioperative chemotherapy[2]. Gastrectomy is associated with a high risk of postoperative complications (up to 40%)[3], of which pulmonary complications, anastomotic leakage and wound complications occur most frequently[4-9]. These complications have a negative influence on postoperative outcomes, such as mortality, length of hospital stay, number of re-operations and re-admissions[10,11]. The effects of various complications on deteriorated postoperative outcomes also result in a significant increase in healthcare costs[12,13].

Identification of complications that have the most effect on outcomes after gastrectomy is important for efficient allocation of healthcare resources. Yet, few studies have explicitly measured the population-burden of complications on outcomes after gastrectomy. In this context, the population-attributable fraction (PAF) is a useful measure, because it represents the anticipated percentage reduction of a given outcome in case a certain complication would be completely prevented[14]. The strength of the association of a complication with an outcome is represented by the relative risk (RR). However, the RR does not reckon with the frequency in which a complication occurs, whereas the PAF takes both frequency and the relative risk into account[15,16]. The introduction of centralization of specialized care across several countries in Europe has led to an overall reduction in the number of complications[17-21]. Using the PAF to describe the impact of postoperative complications will be of direct relevance for prioritizing research agendas and acquirement of appropriate funding, primary prevention efforts, and resource allocation to enhance reduction of postoperative complications after gastrectomy. Consequently, the aim of the current study was to assess the impact of relevant postoperative complications on predefined outcomes and to subsequently identify the clinically most relevant postoperative complications after gastrectomy for gastric cancer as measured by the PAF.

METHODS

Study design

This population-based cohort study included data from a prospective nationwide registration of all patients that underwent a surgical resection for gastroesophageal cancer, the Dutch Upper GI Cancer Audit (DUCA). All hospitals that perform gastric surgery in the Netherlands are obliged to annually provide data on patient and tumor characteristics, items regarding processes of care and clinical and pathological outcomes of surgery. Being part of the Dutch Institute for Clinical Auditing (DICA) that organizes national audits in a uniform format, DUCA provides complete and reliable registered data, as was reported by an independent team of data managers that performed an in-depth quality investigation[3]. The scientific committee of the DUCA approved the current study, and no ethical approval or informed consent was required under Dutch law.

Outcomes

Between 2011-2017 all patients with gastric adenocarcinoma (cT1-4a-x, N0-3-x, M0-x) who underwent elective (sub)total gastrectomy with curative intent were selected from the DUCA. Curative treatment consisted of a (sub)total gastrectomy with, in case of an advanced disease stage, a modified D2 (D1+) lymphadenectomy (without pancreaticosplenectomy and corresponding lymph node station 10), according to the Japanese Gastric Cancer Treatment Guidelines[22]. According to these guidelines, lymph node stations 1, 3, 4d, 4sb, 5-9, 11p and 12a are dissected in case of distal gastrectomy and lymph node stations 1-3, 4d, 4sa, 4sb, 5-9, 11p, 11d and 12a are dissected during total gastrectomy. Furthermore, if patients with an advanced tumor (cT2+ or cN+) were considered fit enough, perioperative chemotherapy according or comparable to the MAGIC trial regimen was offered[2,23]. If during surgery no Roux-en-Y or Billroth reconstruction was created, or no lymphadenectomy was performed, patients were excluded. According to the Dutch national guidelines, patients were staged using gastroscopy and computed tomography (CT) of the thorax and abdomen[24] and, since their recent implementation in July 2016, with ^{18}F-fluordeoxyglucose (FDG) positron emission tomography (PET)/CT and staging laparoscopy in case of an advanced tumor (cT3-4, cN+)[1]. Tumors were classified according to the 7th edition of the American Joint Committee on Cancer TNM staging system[25].

Predictors and study outcomes

Postoperative morbidity was appraised and divided into four groups: intra-abdominal complications (including anastomotic leakage, abscesses and bleeding), wound complications, non-surgical complications (including pulmonary, cardiac, thromboembolic, neurological, and urological complications) and other complications. Definitions of the abovementioned complications are given in Table 2. The study outcomes included mortality (defined as death during the initial hospital stay or within 30 days after surgery), prolonged hospitalization (defined as hospital stay that exceeds the 75th percentile value), re-interventions (consisting of radiological/endoscopic/ surgical interventions), reoperation (defined as a postoperative surgical procedure under general anesthesia) and readmission (within 30 days after initial discharge). All complications were scored according to the standards of the DUCA, provided via online information[26].

Statistical analysis

Patient and treatment-related characteristics are described as mean ± standard deviations (SD) and categorical data are presented as frequencies (percentages). Missing information of patients for one or more variables were imputed with the iterative Markov chain Monte Carlo method (5 iterations)[27]. The frequency of initial missings per variable are presented in Table 1. All statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY) and R language environment (version 3.3.1, http://www.R-project.org, 'geeglm', 'sandwich', 'mice', 'AF' packages). Significance was set at $p < 0.05$.

Population-attributable fraction (PAF)

As stated in the introduction, the PAF is a useful measure to present the impact of a complication, as it takes both frequency and the relative risk of a certain outcome into account[15,16]. To determine the PAF, first the prevalence of complications and study outcomes were calculated. The adjusted relative risk (aRR) and Confidence Interval (CI) for each complication-outcome pair were calculated using multivariable Poisson regression models with log link and robust error variance. The PAF was calculated with the AF package in R software which allows for confounder-adjusted estimation of PAFs for cohort studies[28]. The models were adjusted for patient and treatment-related characteristics (i.e. age, gender, Body Mass Index, American Society of Anesthesiologists (ASA) score, comorbidities, previous abdominal or thoracic surgery, use of

immunosuppressant drugs, open or minimally invasive surgery, total or partial gastrectomy, conversions, cTN-stage and neoadjuvant treatment) and for all complications with a significant association with the study outcome (to adjust for simultaneous occurrence of coexisting complications and thereby prevent overestimation of the individual contribution of a specific complication). The severity of a complication (as assessed by the Clavien Dindo classification) was not integrated in the analysis, since this would have incorporated the outcomes of our study (which indirectly define the severity of the complication, e.g. re-intervention, mortality) into our determinants (i.e. complications).

In this study the risk-adjusted PAF represents the anticipated percentage reduction of a given outcome (i.e. mortality, prolonged hospital stay, reoperation, and readmission) in case a certain complication would be completely prevented in our study population.

RESULTS

Study population

In the Netherlands, 2304 patients underwent an elective (sub)total gastrectomy with curative intent for primary gastric adenocarcinoma during the study period. Some 128 of these patients were excluded as no lymphadenectomy was performed or no Roux-Y or Billroth reconstruction was made. Of the remaining 2176 patients, 1343 (62%) were male and the mean age was 68.6 (± 11.7) years. The majority of patients had an ASA score of 2 (56%), and hypertension (35%) and diabetes mellitus (17%) were the most common comorbidities. Most patients had a cT3 tumor (54%), cN0-stage (59%) and were treated with neoadjuvant therapy (62%). Patient and treatment-related characteristics are presented in Table 1.

Postoperative outcomes

All postoperative complications and clinical outcomes are shown in Table 2. Pulmonary complications (15%), anastomotic leakage (7%) and cardiac complications (6%) were the most common complications. Postoperative mortality occurred in 118 patients (5%), prolonged hospitalization in 484 patients (22%), reoperations in 247 patients (11%) and 259 patients (12%)

were readmitted. Ileus occurred in 4% of patients, but was only scored in DUCA since 2016, and therefore not shown in Table 2.

The risk-adjusted associations between the postoperative complications and subsequent clinical outcomes are described in Tables 3-7. Anastomotic leakage and bowel injury were associated with the greatest relative risk of both postoperative mortality and reoperations (aRR: 6.32 [95%CI: 4.18-9.49] and aRR: 8.56 [95%CI: 6.46-11.3] for anastomotic leakage, respectively, and aRR: 5.27 [95%CI: 2.27-10.67] and aRR 8.03 [95%CI: 5.03-12.30] for bowel injury, respectively). Anastomotic leakage was associated with the greatest relative risk for prolonged hospitalization (aRR: 3.94 [95%CI: 3.12-4.93]), followed by intra-abdominal abscess (aRR: 3.57 [95%CI: 2.67-4.69]). In fact, all postoperative complications were significantly associated with prolonged hospitalization. All postoperative complications, except urological complications were associated with re-interventions, with anastomotic leakage (aRR: 7.25 [95%CI: 5.70-9.21]) and intra-abdominal abscesses (aRR: 6.22 [95%CI: 4.73-8.12]) having the highest association. Intra-abdominal abscesses and bowel injury were associated with the greatest risk of hospital readmission (aRR: 3.24 [95%CI: 2.16-4.70] and 2.93 [95%CI: 1.38-5.45], respectively).

The risk-adjusted population-attributable fractions (PAF) of each complication-outcome pair are presented in Tables 3-7. The PAF embodies the percentage reduction of a given outcome that is expected if that complication would be completely prevented (see also Supplementary File: Figure 1a-e). Anastomotic leakage and pulmonary complications had the greatest overall impact on both postoperative mortality and prolonged hospitalization (PAF: 29.2% [95%CI: 19.3-39.1] and 12.9% [95%CI: 9.7-16.0] for anastomotic leakage, respectively, and PAF: 21.6% [95%CI: 10.5-32.7] and 14.7% [95%CI: 11.0-18.8] for pulmonary complications, respectively). Elimination of anastomotic leakage and intra-abdominal abscesses would have resulted in a reduction of re-interventions of 25.1% [95%CI: 20.5-29.7] and 11.5% [95%CI: 8.2-14.8], respectively. Again, anastomotic leakage, together with wound infections, had the greatest overall impact on reoperations (PAF: 30.3% [95%CI: 24.3-36.3] and 10.6% [95%CI: 6.5-14.8, respectively). Intra-abdominal abscesses and wound infections were the complications with the greatest overall impact on hospital readmission (PAF: 7.0% [95%CI: 3.2-10.9] and 5.1% [95%CI: 1.5-8.8], respectively).

Table 1. Baseline characteristics of 2176 patients who underwent elective, intentionally curative gastrectomy for gastric cancer

	No. (%)	Initial missing values (%)
Patient characteristics		
Age, years (mean ± SD)	68.6 ± 11.7	1 (<1%)
BMI, kg/m^2 (mean ± SD)	25.2 ± 4.5	44 (2%)
Gender (% male)	1343 (62)	0 (0%)
ASA-classification		10 (1%)
I	303 (14)	
II	1225 (56)	
III	627 (29)	
IV	21 (1)	
Comorbidities		0 (0%)
Asthma / COPD	270 (12)	
Coronary artery disease†	253 (12)	
History of myocardial infarction	175 (8)	
History of arrhythmia	302 (14)	
Hypertension	763 (35)	
Peripheral vascular disease	101 (5)	
Diabetes mellitus	368 (17)	
History of CVA	103 (5)	
History of thromboembolic events	157 (7)	
Endocrine disorder	131 (6)	
Previous abdominal or thoracic surgery	868 (40)	0 (0%)
Tumor characteristics		
cT-stage		515 (23%)
T1	202 (9)	
T2	675 (31)	
T3	1169 (54)	
T4	130 (6)	
cN-stage		235 (11%)
N0	1287 (59)	
N1	583 (27)	
N2	192 (9)	
N3	44 (2)	
Nx	70 (3)	
Treatment characteristics		
Neoadjuvant treatment	1339 (62)	3 (<1%)
Resection type		0 (0%)
Total gastrectomy	905 (42)	
Subtotal gastrectomy	1271 (58)	
Surgical approach (% open procedure)	1352 (62)	0 (0%)
Conversion	87 (4)	0 (0%)
Tumor location		53 (2%)
Fundus	165 (8)	
Corpus	691 (32)	
Antrum	959 (44)	
Pylorus	189 (9)	
Whole stomach	98 (5)	
Other	74 (3)	

Percentages may not add up to 100% due to rounding. ASA: American Society of Anesthesiologists, BMI: Body Mass Index, COPD: Chronic Obstructive Pulmonary Disease, CVA: Cerebrovascular accident. †Patients with a history of angina pectoris, percutaneous transluminal coronary angioplasty (PTCA) and/or coronary artery bypass graft (CABG).

Table 2. Postoperative complications and clinical outcomes after elective gastrectomy of 2176 patients.

	No. (%)	Initial missing values¶¶
Postoperative complications		
Pulmonary complication*	321 (15)	0
Anastomotic leakage†	154 (7)	0
Cardiac complication‡	122 (6)	0
Acute delirium	103 (5)	0
Abscess	85 (4)	0
Wound infection	93 (4)	0
Urological complication§	80 (4)	0
Thromboembolic complication¶	32 (2)	0
Chyle leakage	38 (2)	0
Post-operative bleeding	35 (2)	0
Bowel injury	26 (1)	0
Pancreatitis	10 (<1)	0
Clinical outcomes		
Postoperative mortality#	118 (5)	0
Duration of hospital stay (days)**	9 (7-13)	17
Prolonged hospitalization††	484 (22)	17
Re-intervention‡‡	344 (16)	0
Re-operation§§	247 (11)	0
Hospital readmission##	259 (12)	0

Values in parentheses are percentages unless indicated otherwise. Data shown in Table represent the dataset after imputation. *Pneumonia, pleural effusion, respiratory failure, pneumothorax and/or acute respiratory distress syndrome (ARDS). †Any clinically or radiologically proven anastomotic leakage. ‡Supra- and ventricular arrhythmia, myocardial infarction and/or heart failure. §Acute renal insufficiency, acute kidney failure requiring dialysis, urine tract infection and/or urine retention. ¶Pulmonary embolism, deep venous thrombosis and/or cerebro vascular accident. #Death during initial hospital admission or within 30 days after surgery. **Data are depicted as median (IQR). ††Length of hospital stay ≥75th percentile (for each surgical approach). ‡‡ Re-intervention (radiological / endoscopic / surgical). §§Postoperative surgical procedure under general anesthesia. ##Readmission to hospital within 30 days after initial discharge. ¶¶Number of missing values for each variable before imputation.

Table 3. Risk-adjusted associations and population attributable fraction between postoperative mortality* and complications after elective resection for gastric cancer.

Postoperative complication	No. died / survived (% died)	Risk-adjusted association†		Risk-adjusted PAF‡	
		Adjusted relative risk (95%CI)	*p*-value	PAF% (95%CI)	*p*-value
Pulmonary complication	49/272 (15)	3.02 (2.06-4.41)	<0.001	21.6 (10.5-32.7)	<0.001
Anastomotic leakage	45/109 (29)	6.32 (4.18-9.49)	<0.001	29.2 (19.3-39.1)	<0.001
Cardiac complication	25/97 (21)	3.10 (1.91-4.87)	<0.001	8.9 (1.1-1.7)	0.025
Acute delirium	14/89 (14)	1.71 (0.92-2.95)	0.054	-	-
Abscess	11/74 (13)	2.30 (1.15-4.16)	0.003	0.3 (-5.2-5.9)	0.902
Wound infection	10/83 (11)	1.64 (0.79-3.02)	0.119	-	-
Urological complication	8/72 (10)	1.41 (0.62-2.76)	0.362	-	-
Thromboembolic complication	5/27 (16)	2.82 (0.97-6.49)	0.034	0.2 (-3.7-4.1)	0.921
Chyle leakage	2/36 (5)	0.93 (0.15-2.97)	0.911	-	-
Post-operative bleeding	7/28 (20)	3.53 (1.47-7.20)	<0.001	2.7 (-1.1-6.6)	0.162
Bowel injury	8/18 (31)	5.27 (2.27-10.67)	<0.001	4.2 (0.2-8.2)	0.036

* Death during initial hospital admission or within 30 days after surgery. PAF: population-attributable fraction. † Multivariable Poisson regression; ‡ logistic regression-based estimates of confounder-adjusted attributable fractions.

Table 4. Risk-adjusted associations and population attributable fraction between prolonged hospitalization* and complications after elective resection for gastric cancer.

Postoperative complication	No. with/without prolonged stay (% prolonged)	Risk-adjusted association†		Risk-adjusted PAF‡	
		Adjusted relative risk (95%CI)	*p*-value	PAF% (95%CI)	*p*-value
Pulmonary complication	162/159 (50)	2.78 (2.29-3.38)	<0.001	14.7 (11.0-18.8)	<0.001
Anastomotic leakage	112/42 (73)	3.94 (3.12-4.93)	<0.001	12.9 (9.7-16.0)	<0.001
Cardiac complication	62/60 (51)	2.22 (1.67-2.91)	<0.001	2.8 (0.4-5.2)	0.021
Acute delirium	52/51 (51)	2.26 (1.66-3.01)	<0.001	2.6 (0.6-4.4)	0.008
Abscess	59/26 (69)	3.57 (2.67-4.69)	<0.001	5.3 (3.2-7.5)	<0.001
Wound infection	58/35 (62)	2.96 (2.20-3.89)	<0.001	4.6 (2.8-6.9)	<0.001
Urological complication	31/49 (39)	1.59 (1.08-2.26)	0.003	1.3 (-0.3-2.9)	0.121
Thromboembolic complication	17/15 (53)	2.63 (1.54-4.17)	<0.001	0.8 (-0.2-1.8)	0.145
Chyle leakage	17/21 (45)	2.16 (1.27-3.42)	<0.001	1.6 (0.4-2.8)	0.006
Post-operative bleeding	19/16 (54)	2.29 (1.39-3.53)	<0.001	1.4 (0.2-2.6)	0.015
Bowel injury	18/8 (69)	2.98 (1.78-4.68)	<0.001	1.2 (0.0-2.3)	0.052

* Length of hospital stay ≥75th percentile (for each surgical approach). PAF: population-attributable fraction. † Multivariable Poisson regression; ‡ logistic regression-based estimates of confounder-adjusted attributable fractions.

Table 5. Risk-adjusted associations and population attributable fraction between re-interventions* and complications after elective resection for gastric cancer.

Postoperative complication	No. with/ without re-intervention (% re-intervention)	Risk-adjusted association†		Risk-adjusted PAF‡	
		Adjusted relative risk (95%CI)	*p*-value	PAF% (95%CI)	*p*-value
Pulmonary complication	119/202 (37)	2.72 (2.15-3.42)	<0.001	11.3 (7.2-15.5)	<0.001
Anastomotic leakage	129/25 (84)	7.25 (5.70-9.21)	<0.001	25.1 (20.5-29.7)	<0.001
Cardiac complication	46/76 (38)	2.36 (1.69-3.23)	<0.001	1.6 (-0.8-4.0)	0.206
Acute delirium	37/66 (36)	2.29 (1.58-3.21)	<0.001	1.7 (-0.6-3.9)	0.153
Abscess	72/13 (85)	6.22 (4.73-8.12)	<0.001	11.5 (8.2-14.8)	<0.001
Wound infection	57/36 (61)	4.28 (3.15-5.73)	<0.001	6.9 (4.4-9.9)	<0.001
Urological complication	20/60 (25)	1.50 (0.92-2.32)	0.050	-	-
Thromboembolic complication	13/19 (41)	2.61 (1.41-4.40)	<0.001	0.2 (-0.6-0.9)	0.674
Chyle leakage	13/25 (34)	2.28 (1.23-3.83)	<0.001	1.5 (0.2-2.9)	0.029
Post-operative bleeding	26/9 (74)	4.60 (2.99-6.79)	<0.001	4.1 (2.0-6.3)	<0.001
Bowel injury	25/1 (96)	6.02 (3.85-9.01)	<0.001	3.6 (1.8-5.5)	<0.001

* Re-intervention (radiological / endoscopic / surgical). PAF: population-attributable fraction. † Multivariable Poisson regression; ‡ logistic regression-based estimates of confounder-adjusted attributable fractions.

Table 6. Risk-adjusted associations and population attributable fraction between reoperation* and complications after elective resection for gastric cancer.

Postoperative complication	No. with/ without reoperation (% reoperation)	Risk-adjusted association†		Risk-adjusted PAF‡	
		Adjusted relative risk (95%CI)	*p*-value	PAF% (95%CI)	*p*-value
Pulmonary complication	85/236 (27)	2.62 (1.98-3.43)	<0.001	10.3 (4.8-15.9)	<0.001
Anastomotic leakage	102/52 (66)	8.56 (6.46-11.3)	<0.001	30.3 (24.3-36.3)	<0.001
Cardiac complication	33/89 (27)	2.37 (1.59-3.42)	<0.001	2.2 (-0.1-5.7)	0.224
Acute delirium	24/79 (23)	2.04 (1.29-3.08)	<0.001	0.4 (-2.6-3.5)	0.787
Abscess	41/44 (48)	4.75 (3.32-6.66)	0.003	5.9 (2.5-9.4)	<0.001
Wound infection	49/44 (53)	5.13 (3.64-7.11)	<0.001	10.6 (6.5-14.8)	<0.001
Urological complication	15/65 (19)	1.60 (0.90-2.63)	0.067	-	-
Thromboembolic complication	12/20 (38)	3.68 (1.93-6.38)	<0.001	1.5 (0.5-3.0)	0.042
Chyle leakage	6/32 (16)	1.48 (0.58-3.06)	0.318	-	-
Post-operative bleeding	24/11 (69)	5.52 (3.49-8.33)	<0.001	5.7 (2.9-8.5)	<0.001
Bowel injury	24/2 (92)	8.03 (5.03-12.30)	<0.001	5.8 (3.1-8.6)	<0.001

* Postoperative surgical procedure under general anesthesia. PAF: population-attributable fraction. † Multivariable Poisson regression; ‡ logistic regression-based estimates of confounder-adjusted attributable fractions.

Table 7. Risk-adjusted associations and population attributable fraction between hospital readmissions* and complications after elective resection for gastric cancer.

Postoperative complication	No. with/without readmission (% readmission)	Risk-adjusted association†		Risk-adjusted PAF‡	
		Adjusted relative risk (95%CI)	*p*-value	PAF% (95%CI)	*p*-value
Pulmonary complication	53/268 (17)	1.39 (1.01-1.88)	0.026	3.0 (-2.9-8.9)	0.315
Anastomotic leakage	32/122 (21)	1.68 (1.12-2.43)	0.005	2.3 (-2.2-6.7)	0.319
Cardiac complication	19/103 (16)	1.20 (0.72-1.89)	0.405	-	-
Acute delirium	20/83 (19)	1.52 (0.92-2.37)	0.044	1.1 (-2.1-4.3)	0.508
Abscess	31/54 (37)	3.24 (2.16-4.70)	<0.001	7.0 (3.2-10.9)	<0.001
Wound infection	27/66 (29)	2.70 (1.75-3.99)	<0.001	5.1 (1.5-8.8)	0.006
Urological complication	10/70 (13)	0.97 (0.48-1.74)	0.912	-	-
Thromboembolic complication	6/26 (19)	1.45 (0.57-3.01)	0.300	-	-
Chyle leakage	5/33 (13)	1.14 (0.40-2.49)	0.762	-	-
Post-operative bleeding	9/26 (26)	2.15 (1.02-3.97)	0.010	1.4 (-0.6-3.5)	0.172
Bowel injury	9/17 (35)	2.93 (1.38-5.45)	<0.001	1.4 (-0.6-3.4)	0.164

* Readmission to hospital within 30 days after initial discharge. PAF: population-attributable fraction. † Multivariable Poisson regression; ‡ logistic regression-based estimates of confounder-adjusted attributable fractions.

A large part of the causes of the study outcomes (grouped under 'other' factors in Supplementary File: Figure 1a-e) cannot be specified, due to variation in the data that cannot be explained by patient and/or treatment characteristics and complications. Interestingly, these 'other' factors, also contributed to all clinical postoperative outcomes in large numbers, accounting for 32.9% of postoperative mortality, 50.8% of prolonged hospitalization, 32.5% of re-interventions, 27.3% of reoperations and 78.7% of hospital readmissions.

DISCUSSION

In this population-based study, the clinically most relevant complications after gastrectomy for gastric cancer were evaluated in a Western population using the PAF. Anastomotic leakage and pulmonary complications were demonstrated to have the greatest overall impact on postoperative mortality, prolonged hospitalization, re-interventions, and reoperations. Intra-abdominal abscesses and wound infections also had a high impact on re-interventions, reoperations and hospital readmissions.

The PAF is a measure with which the contribution of specific postoperative complications on a subsequent clinical outcome can be quantified[14-16]. It provides a perspective of prevention of disease actions considering the risk of disease in exposed individuals and the prevalence of exposure in the population. Thus, high risk of disease in exposed individuals can have low

population impact if the risk factors associated to it are rare, whereas low risk may impact public health when exposures are frequent. In colorectal and esophageal cancer surgery, it already has been shown useful and helps to guide surgical quality improvement initiatives[14,16]. For instance, an American study that assessed the PAF of complications after colorectal cancer surgery pointed out that the continued focus of federal quality initiatives on specific outcomes (e.g. urinary tract infections) had to be changed, illustrated by an estimated PAF of less than 10%, which indicates that its effect on the population is relatively minor[14].

The significance of complications such as anastomotic leakage and pulmonary complications after gastrectomy has previously been acknowledged in literature[4,7-9]. However, by using the PAF the current study allows us to confirm the impact of these complications for the first time. Pulmonary complications, being the most common complication in our study (15%), indeed demonstrated to be an important driver of postoperative mortality and prolonged hospitalization. General advises to prevent pulmonary complications include abstinence of smoking before surgery, preoperative pulmonary rehabilitation and adequate pain management (using epidural analgesia and a transversus abdominis plane block). Also, Enhanced Recovery After Surgery (ERAS) programs could help to prevent pulmonary complications after major surgery[10,29]. Future studies should focus on factors to prevent these complications as this will reduce deteriorated outcomes with the PAFs mentioned in the current study.

Although centralization of gastric cancer surgery has led to a reduction in the anastomotic leakage rate in the Netherlands[18-20], manifestation of anastomotic leakage remains a frequently occurring and significant problem. At the same time, this study demonstrated that anastomotic leakage is a major driver of postoperative mortality, re-interventions, and reoperations. Our study indicates that preventing or managing anastomotic leakage should receive priority when developing or adapting surgical quality improvement programs. Initiatives to reduce the anastomotic leakage rate may include further centralization and adequate proctoring programs with hands-on courses for new surgeons[30]. A proctoring program, that allows beginning surgeons to operate together with an experienced surgeon during a reasonable amount of cases, can be a starting point for going through the learning curve of gastric cancer surgery. Data on the number of procedures required for completion is scarce and vary, with studies reporting between 10 to 100 procedures to complete the learning curve, depending on the outcome under

investigation[31,32]. In addition, pre-operative evaluation of a patients' condition, for instance the vascular status[33], may contribute to select and treat patient who are prone for developing anastomotic leakage. Moreover, if an adequate oncologic resection is possible, subtotal gastrectomy should be preferred over total gastrectomy as the former results in a lower risk of postoperative complications and better quality of life[34,35]. Last, special intraoperative attention should be paid to the perfusion of and tension on the anastomosis and its staple-line technique (hand sewn vs. stapler and linear vs. circular) and reinforcement to avoid leakage and support the healing process[36,37].

Both wound infections and abscesses had a high impact on re-interventions and reoperations, which highlights the importance of preventing these complications as well. The occurrence of wound infections is counteracted by preoperative prophylactic administration of antibiotics. Furthermore, minimally invasive surgery could play a role in decreasing wound infections and pain[38], thereby also resulting in shorter hospitalization. In addition, centralization of gastric cancer surgery and completion of the learning curve also play an important role, since intra-abdominal abscesses are often an expression of anastomotic leakage or caused by other perioperative complications.

This study demonstrated that a large part of postoperative outcomes can be attributed to postoperative complications. However, approximately one third of the outcomes could not be attributed to patient and treatment related characteristics or postoperative complications. For example, 78.7% of hospital readmissions could not be attributed to the well-defined complications or patients' demographics. This finding indicates that further research is warranted to identify these other drivers that attribute to outcomes after gastric cancer surgery. This knowledge could then be used to modify these factors and thereby reduce the clinical deteriorated outcomes.

Although this is the first study to evaluate the clinically most relevant postoperative complication after gastrectomy, a few limitations should be discussed. Firstly, unknown confounders and time-varying perioperative care may have affected the associations between postoperative complications and the clinical outcomes. Second, DUCA only registers data up to discharge and 30 days postoperative, lacks data on long-term survival and makes no distinction in the different locations where anastomotic leakage can occur, although it would have been interesting to

evaluate different anastomotic sites. Moreover, unfortunately no cost aspect could be included in this study, since data on costs are not registered in DUCA. However, previous studies have shown that postoperative complications are the main drivers of costs of cancer surgery[39]. As such, extrapolation of this knowledge to the current study indicates that pulmonary complications and anastomotic leakage are probably the main drivers of costs after gastrectomy. Lastly, factors to prevent complications could not be evaluated in this study as the DUCA lacks significant data to perform these multivariable analyses.

CONCLUSION

By using the PAF for the first time in gastric cancer surgery, this population-based study identified anastomotic leakage and pulmonary complications as major attributors to clinical outcomes after gastrectomy. Surgical quality improvement programs that can successfully reduce these complications will have the greatest potential to reduce deteriorated outcomes.

REFERENCES

1. Vereniging Integrale Kankercentra. Diagnostiek, behandeling en follow-up van het maagcarcinoom 2016 2016:1–7.
2. Cunningham D, Allum WH, Stenning SP, et al. Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. N Engl J Med 2007:11–20.
3. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, et al. Early outcomes from the Dutch Upper Gastrointestinal Cancer Audit. Br J Surg 2016;103:1855–63.
4. Brenkman HJF, Gisbertz SS, Slaman AE, et al. Postoperative Outcomes of Minimally Invasive Gastrectomy Versus Open Gastrectomy during the Early Introduction of Minimally Invasive Gastrectomy in the Netherlands. Ann Surg 2017;266:831–8.
5. Haverkamp L, Weijs TJ, Van Der Sluis PC, et al. Laparoscopic total gastrectomy versus open total gastrectomy for cancer: A systematic review and meta-analysis. Surg Endosc Other Interv Tech 2013;27:1509–20.
6. [6] Chen K, Zhai S-T, Pan J-H, Yu W-H, Pan Y, Chen Q-L, et al. Short-term outcomes of laparoscopic total gastrectomy for gastric cancer: a comparative study with laparoscopic distal gastrectomy at a high-volume center. Minim Invasive Ther Allied Technol 2017;0:1–7. doi:10.1080/13645706.2017.1350718.
7. Hu Y, Huang C, Sun Y, et al. Morbidity and mortality of laparoscopic versus open D2 distal gastrectomy for advanced gastric cancer: A randomized controlled trial. J Clin Oncol 2016;34:1350–7.
8. Kodera Y, Yoshida K, Kumamaru H, et al. Introducing laparoscopic total gastrectomy for gastric cancer in general practice: a retrospective cohort study based on a nationwide registry database in Japan. Gastric Cancer 2018.
9. Kelly KJ, Selby L, Chou JF, et al. Laparoscopic Versus Open Gastrectomy for Gastric Adenocarcinoma in the West: A Case–Control Study 2016;22:3590–6.
10. Mortensen K, Nilsson M, Slim K, et al. Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery after Surgery (ERAS) Society recommendations. Br J Surg 2014;101:1209–29.
11. Varadhan KK, Neal KR, Dejong CHC, et al. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: A meta-analysis of randomized controlled trials. Clin Nutr 2010;29:434–40.
12. Short MN, Aloia TA, Ho V. The influence of complications on the costs of complex cancer surgery. Cancer 2014;120:1035–41.
13. Dimick JB, Pronovost PJ, Cowan JA, et al. Complications and costs after high-risk surgery: Where should we focus quality improvement initiatives? J Am Coll Surg 2003;196:671–8.
14. Scarborough JE, Schumacher J, Kent KC, et al. Associations of specific postoperative complications with outcomes after elective colon resection: A procedure-targeted approach toward surgical quality improvement. JAMA Surg 2017;152:1–7.
15. Poole C. A history of the population attributable fraction and related measures. Ann Epidemiol 2015;25:147–54.
16. Goense L, Meziani J, Ruurda JP, et al. The impact of postoperative complications on outcomes after esophagectomy for cancer: results of a nationwide cohort study. 2018:1–26.
17. Wouters MWJM, Jansen-Landheer MLEA, Van De Velde CJH. The quality of cancer care initiative in the Netherlands. Eur J Surg Oncol 2010;36:S3–13.
18. Tegels JJW, De Maat MFG, Hulsewé KWE, et al. Improving the outcomes in gastric cancer surgery. World J Gastroenterol 2014;20:13692–704.
19. Jensen LS, Nielsen H, Mortensen PB, et al. Enforcing centralization for gastric cancer in Denmark. Eur J Surg Oncol 2010;36:S50–4.
20. Nelen SD, Heuthorst L, Verhoeven RHA, et al. Impact of Centralizing Gastric Cancer Surgery on Treatment, Morbidity, and Mortality. J Gastrointest Surg 2017;21:2000–8.
21. Pasquer A, Renaud F, Hec F, et al. Is centralization needed for esophageal and gastric cancer patients with low operative risk? A nationwide study. Ann Surg 2016;264:823–30.

22. Sano T, Kodera Y. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011;14:101–12.
23. Cunningham D, Starling N, Rao S, et al. Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer. N Engl J Med 2008;358:36–46.
24. Vereniging Integrale Kankercentra. Richtlijn Diagnostiek, behandeling en follow-up van het maagcarcinoom 2009.
25. Washington K. 7th edition of the AJCC cancer staging manual: Stomach. Ann Surg Oncol 2010;17:3077–9.
26. Dutch Upper GI Cancer Audit. Data Dictionairy. 2016.
27. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393–b2393.
28. Dahlqwist E, Zetterqvist J, Pawitan Y, et al. Model-based estimation of the attributable fraction for cross-sectional, case–control and cohort studies using the R package AF. Eur J Epidemiol 2016;31:575–82.
29. Gustafsson UO, Scott MJ, Schwenk W, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced recovery after surgery (ERAS®) society recommendations. World J Surg 2013;37:259–84.
30. ESSO Course On Minimally Invasive ESOPHAGECTOMY and Gastrectomy In partnership with University Medical Center Utrecht Utrecht (NL), 15th to 16th March 2018.
31. Brenkman HJF, Ruurda JP, Verhoeven RHA, et al. Safety and feasibility of minimally invasive gastrectomy during the early introduction in the Netherlands: short-term oncological outcomes comparable to open gastrectomy. Gastric Cancer 2017;20:853–60.
32. Jung DH, Son S-Y, Park YS, et al. The learning curve associated with laparoscopic total gastrectomy. Gastric Cancer 2016;19:264–72.
33. Goense L, Van Rossum PSN, Weijs TJ, et al. Aortic Calcification Increases the Risk of Anastomotic Leakage after Ivor-Lewis Esophagectomy. Ann Thorac Surg 2016;102:247–52.
34. Gertsen EC, Brenkman HJF, Seesing MFJ, et al. Introduction of minimally invasive surgery for distal and total gastrectomy: a population-based study. Eur J Surg Oncol 2018.
35. Brenkman HJF, Tegels JJW, Ruurda JP, et al. Factors influencing health-related quality of life after gastrectomy for cancer. Gastric Cancer 2018;21:524–32.
36. Pavlidis E, Vousvouki M, Pavlidis T. Prevention of Anastomotic Leakage in Gastrointestinal Tract: A Brief Literature Review. Br J Med Med Res 2015;5:633–7.
37. Phillips BR. Reducing gastrointestinal anastomotic leak rates: Review of challenges and solutions. Open Access Surg 2016;9:5–14.
38. Sluis PC Van Der, Horst S Van Der, May AM, et al. Robot-assisted Minimally Invasive Thoracolaparoscopic Esophagectomy Versus Open Transthoracic Esophagectomy for Resectable Esophageal Cancer. Ann Surg 2018;XX:1–10.
39. Goense L, van Dijk WA, Govaert JA,et al. Hospital costs of complications after esophagectomy for cancer. Eur J Surg Oncol 2017;43:696–702.

SUPPLEMENTARY FILES

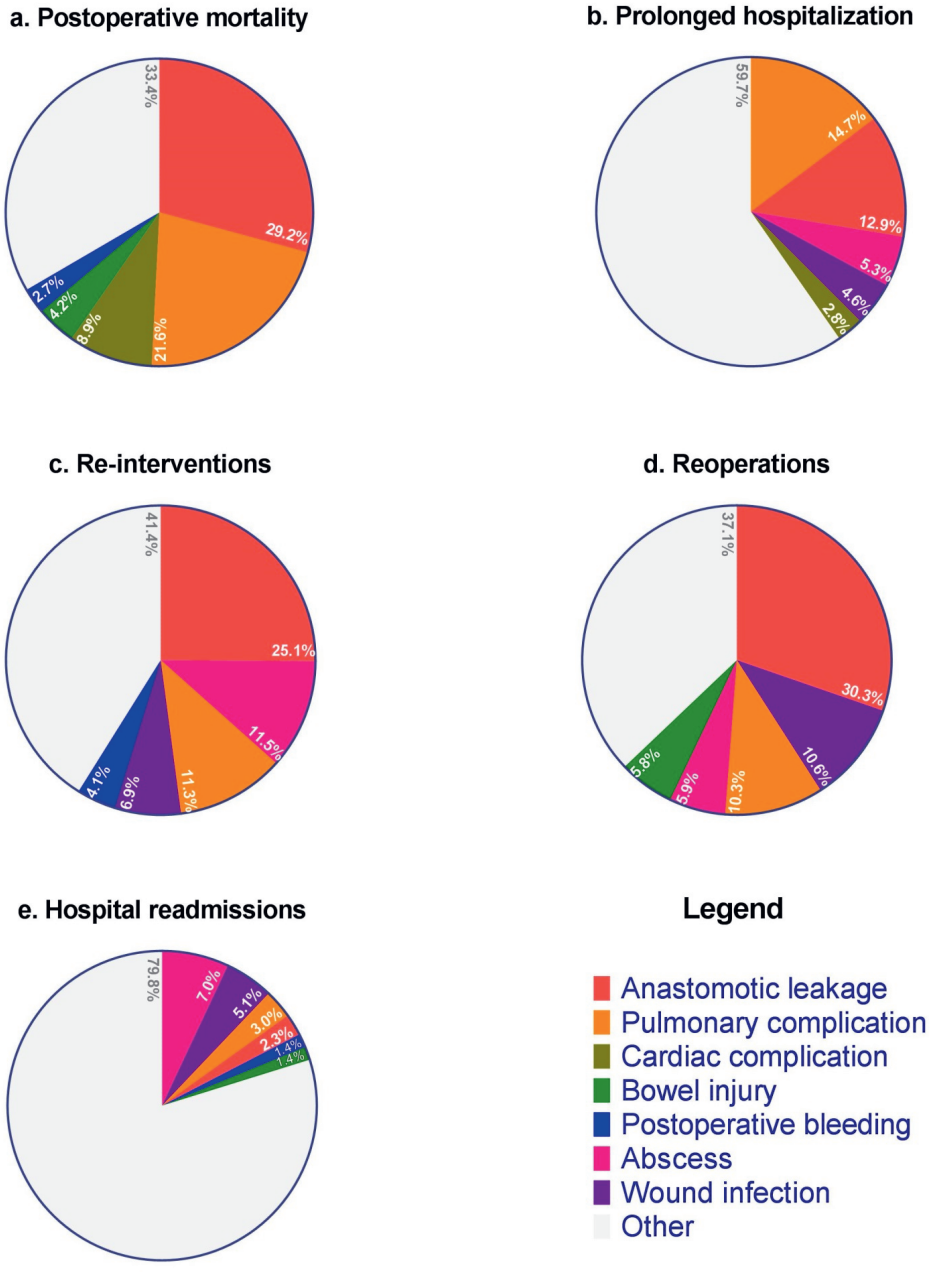

Figure 1. Risk-adjusted population-attributable fractions (PAF) for the complications per outcome: **a** postoperative mortality; **b** prolonged hospitalization; **c** re-interventions; **d** reoperations; **e** hospital readmissions

Chapter 13

Non-curative gastrectomy for advanced gastric cancer does not result in additional postoperative risks compared to curative gastrectomy

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ABSTRACT

Background: Non-curative gastrectomy (nCG) for gastric cancer can be considered in selected cases to relieve symptoms. The aim of this study was to evaluate postoperative morbidity and mortality in patients who underwent nCG and compare these results with an intended curative gastrectomy (CG).

Methods: All patients who underwent both nCG and CG in the Netherlands were included from the Dutch Upper GI Cancer Audit (2011-2016). In this population-based cohort study postoperative morbidity, mortality, readmissions and short-term oncological outcomes were appraised. Propensity score matching (PSM) was applied to create comparable groups of patients who underwent nCG versus CG, using patient and tumor characteristics.

Results: Of the 2202 eligible patients, 115 patients underwent nCG and 2087 underwent CG. After PSM, 115 nCG-patients were matched to 227 CG-patients. More conversions from laparoscopic to open surgery occurred during nCG (10.4 versus 2.6 per cent, p=0.007). Although postoperative mortality was higher after nCG in the original cohort (9.6 versus 4.8 per cent, p=0.026), after PSM there was no difference between groups (9.6 versus 7.0 per cent, p=0.415). Postoperative morbidity, re-interventions and readmission rates did not differ significantly between groups. Resection of additional organs (30.4 versus 11.5 per cent, p<0.001) and R+ resections (65.2 versus 12.3 per cent, p<0.001) occurred more frequently during nCG.

Conclusion: nCG does not lead to additional postoperative risks compared to CG in patients with similar characteristics, and may be considered in fit patients with advanced gastric cancer. However, randomized trials evaluating potential (survival) benefits of nCG should be awaited.

BACKGROUND

Gastric cancer is in fifth place on the list of most common types of malignancies worldwide and the third leading cause of cancer-related death[1]. In the Netherlands, approximately 500 out of 1200 newly diagnosed gastric cancer patients undergo curative treatment each year[2,3]. Curative treatment consists of gastrectomy with lymphadenectomy, preferably combined with perioperative chemotherapy[4,5]. Due to evolving preoperative staging modalities, such as 18F-fluorodeoxyglucose positron emission tomography with computed tomography and staging laparoscopy, metastatic or irresectable disease might become an increasing entity. Patients with non-resectable or metastasized gastric cancer generally do not undergo surgical resection[6], but receive palliative systemic chemotherapy or best supportive care, leading to a median survival of 8 months[4,7]. In selected cases, non-curative gastrectomy (nCG) is considered to relieve symptoms, such as obstruction, pain or bleeding. In contrast to asymptomatic patients, symptom relief may outweigh the surgical risks in symptomatic patients. Some retrospective studies suggest that nCG increases survival compared to palliative chemotherapy, whereas a recent Asian trial (REGATTA), which randomly assigned asymptomatic patients with a single non-curable factor (metastasis to liver, peritoneum or para-aortic lymph nodes) to either solely chemotherapy or gastrectomy (without resection of metastases) followed by chemotherapy, found no benefit of gastrectomy[7–9,10]. However, it is well known that the Asian gastric cancer population differs from the Western population, as the latter present with more advanced tumors and less favorable patient characteristics, such as overweight, making it difficult to extrapolate these results. To date, the effect of nCG on long-term survival for Western patients is unknown. Moreover, nCG is known for its high mortality and morbidity rates and before making firm statements on long-term outcomes, it is relevant to evaluate short-term outcomes, such as mortality.

Little is known about the safety of non-curative resections compared to curative resections. The aim of this study is to investigate whether the postoperative outcomes differ between non-curative and curative gastrectomy (CG) to contribute to the existing literature supporting that nCG could be considered a valid option for selected patients suffering from advanced gastric cancer.

METHODS

Study design

In this population-based study, data of all patients undergoing surgery for gastric cancer were included from the Dutch Upper GI Cancer Audit (DUCA), which is a prospective nationwide registration. The DUCA is part of the Dutch Institute for Clinical Auditing (DICA), performing national audits in a uniform format. Hospitals are required to annually provide data that include patient and tumor-related characteristics, items regarding processes of care and clinical and pathological outcomes of surgery. A complete and reliable data entry was demonstrated by an independent team of data managers which performed an in-depth quality investigation[3]. This study was approved by the scientific committee of the DUCA and no ethical approval or informed consent was required under Dutch law.

Study population

Between 2011-2016 all patients who underwent elective gastrectomy for gastric adenocarcinoma were extracted from the DUCA database. Tumors were classified according to the 7th edition of the American Joint Committee on Cancer TNM staging system[11]. Patients in which a prophylactic gastric resection was performed were excluded, as were patients in whom essential data were missing. According to the Dutch national guidelines, patients were staged with gastroscopy and computed tomography (CT) of the thorax and abdomen[12]. In patients with ≥cT2 or cN+, cM0 stage disease and who were deemed fit enough, curative treatment with perioperative chemotherapy equal or similar to the MAGIC trial regimen was started, followed by surgical resection[5,13]. Surgical resection consisted of (sub)total gastrectomy, with a modified D2 lymphadenectomy (without pancreaticosplenectomy) according to the Japanese Gastric Cancer Treatment Guidelines[14]. In case of non-curative treatment, (sub)total gastrectomy with limited lymphadenectomy was performed.

Definition

The DUCA registers the intent of surgery as determined by the surgical team at two time points: (1) before the start of surgery, and (2) at the end of surgery. To evaluate outcomes of non-curative gastrectomy from a clinical decision-making point of view, this study defined non-curative gastrectomy as surgery with non-curable intent at one or both time points: patients in

whom M1 disease or irresectability was preoperatively known or intraoperatively found. A curative gastrectomy was defined as not having the intent for non-curable surgery at both time points. At first, due to expected differences, three groups were created that consisted of (1) curative patients, (2) patients in whom cM1 disease was preoperatively known and (3) patients in whom irresectability or M1 disease was intraoperatively found. Since no significant differences were found between the non-curative groups, the two non-curable groups were merged for all analyses. As the DUCA registry lacks data on reasons for performing non-curative or palliative gastrectomy, it was chosen to name this latter group non-curative gastrectomy as palliative gastrectomy might imply treatment of symptoms.

Outcomes

Patient characteristics (age, Body Mass Index (BMI), sex, American Society of Anesthesiologists (ASA) classification and comorbidities), treatment characteristics (neoadjuvant treatment, type of procedure and type of resection), postoperative characteristics (morbidity, re-interventions, mortality and recovery) and tumor-specific characteristics (TNM stage, Lauren classification, tumor differentiation, additional resections, radicality of the resection, and lymph node yield) were appraised. The conversion rate was assessed in both groups and was defined as any minimally invasive intended procedure, that was converted to an open procedure. Postoperative complications that were assessed included intra-abdominal complications (anastomotic leakage, abscesses, bleeding, pancreatic complications, chyle leakage and trauma of the gut), wound complications (infection/abscess and fascia dehiscence), non-surgical complications (including pulmonary, cardiac, thromboembolic, neurologic and urologic complications) and other complications. The definition of postoperative mortality and readmissions were: death during the initial hospital stay or within 30 days after surgery and readmissions within 30 days after discharge, respectively. All complications were scored according to the definitions of the DUCA that were online provided for all registrars[15].

Statistical analysis

Propensity score matching (PSM) was used to balance observed preoperative covariates between curative versus non-curative gastrectomy. In order to perform matching, missing patient and treatment-related characteristics were imputed. Missing data regarding inclusion and exclusion criteria were not imputed, resulting in exclusion of patients. Missing data were

considered at random and handled using imputation with the iterative Markov chain Monte Carlo method (5 iterations)[16]. The frequency of missing values per variable before imputation are presented in Table 1.

A propensity score was calculated for each patient using a non-parsimonious multivariable logistic regression model based on all patient and treatment-related characteristics presented in Table 1 and 2. In this context, the propensity score represents the conditional probability to undergo non-curative or curative gastrectomy. First, 1-to-1 nearest-neighbor matching without replacement was performed – using a caliper width of 0.25 multiplied by the standard deviation of the logit propensity score – to generate matched pairs of cases. Accordingly, a second level of matches (2:1) was added to the control group (curative gastrectomy). Balance in patient and treatment-related characteristics was assessed using the standardized difference of the mean; a differences of less than 10 per cent indicates adequate covariate balance[17].
IBM SPSS Statistics version 23.0 (IBM, Armonk, New York, USA) and R 3.1.2 open-source software (http://www.R-project.org; 'MatchIt' and 'optmatch' packages) were used for statistical analysis. Categorical parameters (postoperative and histopathological outcomes) were compared using the Chi-square test (or Fisher's Exact test in case of cell counts less than 5), and for continuous variables the student's t-test was used. For variables with a non-parametric distribution logarithmic transformation was applied. A p-value below 0.05 was considered statistically significant.

RESULTS

Study population

Between 2011-2016, 2237 patients underwent elective (sub)total gastrectomy for gastric adenocarcinoma in the Netherlands. Patients were excluded (n = 35), in case prophylactic or unknown resection was performed (n = 6) or when essential data was missing (n = 29). A total of 2087 patients underwent curative gastrectomy, whereas 115 patients underwent non-curative resection. Locations of the primary tumor in the original cohort were as follows: fundus (7.7 per cent), corpus (30.9 per cent), antrum (41.0 per cent), pyloric (8.8 per cent), whole stomach (5.7 per cent), residual stomach (4.1 per cent) and unknown (2.0 per cent). In general, the CG group

Table 1. Baseline characteristics of the patients who underwent elective gastrectomy for gastric cancer

	Original cohort (n = 2202)				PSM cohort [a] (n = 342)		
	Curative gastrectomy n = 2087 (%)	Non-curative gastrectomy n = 115 (%)	*SMD*	Missing values (%)	Curative gastrectomy n = 227 (%)	Non-curative gastrectomy n = 115 (%)	*SMD*
Baseline characteristics							
Age, years (mean ± SD)	68.5 ± 11.6	71.1 ± 11.4	22.4	3 (0.1)	71.5 ± 11.0	71.0 ± 11.4	4.5
BMI, kg/m^2 (mean ± SD)	25.4 ± 4.4	25.0 ± 4.4	9.0	51 (2.3)	25.2 ± 4.8	25.0 ± 4.3	4.3
Gender (male, %)	1309 (62.7)	71 (61.7)	2.1	0 (0.0)	136 (59.9)	71 (61.7)	4.1
ASA-classification			28.1	21 (0.9)			0.0
I-II	1455 (69.7)	65 (56.5)			129 (56.8)	66 (57.4)	
III-IV	613 (29.4)	48 (41.7)			98 (43.2)	49 (42.6)	
Comorbidities				0 (0.0)			
Cardiac	645 (30.9)	32 (27.8)	6.5		65 (28.6)	32 (27.8)	2.2
Vascular	844 (40.4)	39 (33.9)	12.2		80 (35.2)	39 (33.9)	2.1
Diabetes	355 (17.0)	21 (18.3)	2.7		42 (18.5)	21 (18.3)	2.6
Pulmonary	341 (16.3)	15 (13.0)	8.2		28 (12.3)	15 (13.0)	3.0
cT-stage			53.8	550 (25.0)			3.6
T1-2	603 (28.9)	11 (9.6)			22 (9.7)	11 (9.6)	
T3-4	962 (46.1)	76 (66.1)			153 (67.4)	76 (66.1)	
Tx	522 (25.0)	28 (24.3)			52 (22.9)	28 (24.3)	
cN-stage			56.6	344 (15.6)			9.5
N0	1082 (51.8)	30 (26.1)			70 (30.8)	30 (26.1)	
N+	757 (36.2)	66 (57.4)			124 (54.6)	66 (57.4)	
Nx	248 (11.9)	19 (16.5)			33 (14.5)	19 (16.5)	
cM-stage			248.1	101 (4.6)			102.9
cM0	1986 (95.2)	78 (67.8)			227 (100.0)	78 (67.8)	
cM1	0 (0.0)	37 (32.2)			0 (0.0)	37 (32.2)	
cMx	101 (4.8)	0 (0.0)			n.a.	n.a.	
Neoadjuvant chemotherapy[a]			44.9	4 (0.2)			2.1
Yes	1229 (58.9)	41 (35.7)			83 (36.6)	41 (35.7)	
No	821 (39.3)	72 (62.6)			144 (63.4)	72 (62.6)	
Type of procedure (open, %)	1361 (65.2)	81 (70.4)	12.6	0 (0.0)	162 (71.4)	82 (71.3)	0.0
Type of resection			10.1	0 (0.0)			2.0
Total gastrectomy	901 (43.2)	44 (38.3)			88 (38.8)	44 (38.3)	
Distal gastrectomy	1186 (56.8)	71 (61.7)			139 (61.2)	71 (61.7)	

Percentages may not add up to 100% due to rounding. *Dataset after imputation. SMD of more than 10% indicate inadequate covariate balance. ASA: American Society of Anesthesiologists, BMI: Body Mass Index, n.a. not applicable, MIG: Minimally Invasive Gastrectomy, SMD: Standardized Mean Difference. a. In both groups <2% received neoadjuvant chemoradiotherapy.

consisted of fitter patients (lower age, ASA classification and tumor stages) of whom the majority underwent neoadjuvant chemotherapy. In the CG group, 50 per cent completed neoadjuvant chemotherapy, in the nCG this percentage was only 25 per cent. Using PSM, 227 curative gastrectomy patients were matched to the 115 non-curative gastrectomy patients (Table 1). After PSM the balance among the two treatment groups improved substantially, creating two groups with comparable, nevertheless more frail patients. Regarding clinical M-stage, PSM was unable to create a balance, due to the fact that the curative group did not consist of M1 patients. The 67.8% M0 patients in the nCG were patients preoperatively known with a cT4b tumor or patients in whom irresectable or metastatic disease was intraoperatively found.

Postoperative outcomes

In Table 2 postoperative outcomes of both the original and the PSM cohort of patients are demonstrated. In the PSM cohort, conversion occurred in 10.4 per cent of non-curative patients versus 2.6 per cent in the curative group (p=0.007), either caused by irresectability (in the majority of cases; 58.2 per cent), accessibility or intraoperative complications. Regarding intra-abdominal and non-surgical complications, re-interventions, readmissions and hospital stay, no significant differences were found. A higher mortality rate was demonstrated after nCG compared to CG in the original cohort (9.6 versus 4.8 per cent, p=0.026), which was not found after PSM (9.6 versus 7.0 per cent, p=0.415).

Surgical and histopathological outcomes

Patients in the non-curative group had significantly more advanced disease, with more pT4 tumors and more pN+ stage disease, more diffuse tumors and more additional organs were resected (Table 3). During nCG more (partial) splenectomies (6.1 versus 1.8 per cent, p=0.002), hepatectomies (3.5 versus 1.2 per cent, p=0.061) pancreatectomies (10.4 versus 2.5 per cent, p<0.001) and resections of the mesocolon (7.8 versus 2.7 per cent, p=0.002) were performed, in comparison with CG. In addition, less favorable oncological outcomes (R+ resections, less lymph nodes) were found in the nCG group.

Table 2. Postoperative outcomes of the patients who underwent elective gastrectomy for gastric cancer

	Original cohort (n = 2202)			PSM cohort [a] (n = 342)		
	Curative gastrectomy n = 2087 (%)	Non-curative gastrectomy n = 115 (%)	*p*-value	Curative gastrectomy n = 227 (%)	Non-curative gastrectomy n = 115 (%)	*p*-value
Postoperative outcomes						
Conversions	68 (3·3)	12 (10·4)	<0·001	6 (2·6)	12 (10·4)	0·007
Morbidity	817 (39·1)	50 (43·5)	0·357	97 (42·7)	50 (43·5)	0·895
Intra-abdominal complications						
Anastomotic leakage[a]	149 (7·1)	10 (8·7)	0·530	17 (7·5)	10 (8·7)	0·696
Abscess	85 (4·1)	6 (5·2)	0·548	11 (4·8)	6 (5·2)	0·881
Bleeding	26 (1·2)	4 (3·5)	0·044	2 (0·8)	4 (3·5)	0·101
Pancreatitis, leakage or fistula	10 (0·5)	1 (0·9)	0·563	0 (0·0)	1 (0·9)	0·336
Chyle leakage	38 (1·8)	3 (2·6)	0·551	4 (1·8)	3 (2·6)	0·691
Trauma of the gut	30 (1·4)	1 (0·9)	0·615	2 (0·8)	1 (0·9)	0·999
Wound complications						
Infection/abscess	62 (3·0)	8 (6·9)	0·018	6 (2·6)	8 (6·9)	0·057
Fascia dehiscence	23 (1·1)	2 (1·7)	0·530	3 (1·3)	2 (1·7)	0·999
Non-surgical complications						
Pulmonary[b]	320 (15·3)	17 (14·8)	0·873	33 (14·5)	17 (14·8)	0·952
Cardiac[c]	126 (6·0)	5 (4·3)	0·456	14 (6·2)	5 (4·3)	0·488
Thromboembolic[d]	28 (1·3)	2 (1·7)	0·720	5 (2·2)	2 (1·7)	0·999
Neurologic[e]	88 (4·2)	3 (2·6)	0·399	12 (5·3)	3 (2·6)	0·253
Urologic[f]	70 (3·4)	6 (5·2)	0.287	8 (3.5)	6 (5.2)	0.455
Other	230 (11.0)	18 (15.7)	0.235	39 (17.2)	18 (15.7)	0.720
Re-interventions	340 (16.3)	22 (19.1)	0.443	37 (16.3)	22 (19.1)	0.513
Mortality	101 (4.8)	11 (9.6)	0.026	16 (7.0)	11 (9.6)	0.415
Recovery						
ICU stay (median, IQR)	0 (0 – 1)	0 (0 – 1)	0.917	0 (0 – 2)	0 (0 – 1)	0.826
Hospital stay (median, IQR)	9 (7 – 13)	10 (7 – 16)	0.197	10 (7 – 15)	10 (7 – 16)	0.644
Readmissions	243 (11.6)	16 (13.9)	0.500	30 (13.2)	16 (13.9)	0.858

Percentages may not add up to 100% due to rounding. *Dataset after imputation. Expected count less than 5: Fisher's Exact Test. ICU: Intensive Care Unit, IQR: interquartile range. a. Any clinically or radiologically proven anastomotic leakage. b. Pneumonia, pleural effusion, respiratory failure, pneumothorax and/or acute respiratory distress syndrome (ARDS). c. Supra- and ventricular arrhythmia, myocardial infarction and/or heart failure. d. Pulmonary embolism, deep venous thrombosis and/or cerebrovascular accident. e. Acute delirium. f. Acute renal insufficiency, acute kidney failure requiring dialysis, urine tract infection and/or urine retention.

Table 3. Histopathological characteristics of the patients who underwent elective gastrectomy for gastric cancer

	Original cohort (n = 2202)				PSM cohort [a] (n = 342)		
	Curative gastrectomy n = 2087 (%)	Non-curative gastrectomy n = 115 (%)	*SMD*	Missing values (%)	Curative gastrectomy n = 227 (%)	Non-curative gastrectomy n = 115 (%)	*SMD*
Histopathological characteristics							
Lauren classification			0·255	453 (20·6)			0.011
Intestinal	901 (54·3)	43 (48·3)			138 (60.8)	51 (44.3)	
Diffuse	643 (38·7)	36 (40·4)			75 (33.0)	51 (44.3)	
Mixed	116 (6·9)	10 (11·2)			14 (6.2)	13 (11.3)	
Tumour differentiation			0·035	331 (15·0)			0.111
Well/moderate	675 (38·2)	29 (27·9)			89 (39.2)	35 (30.4)	
Poor/ undifferentiated	1092 (61·7)	75 (72·1)			138 (60.8)	80 (69.6)	
pT-stage			<0·001	0 (0·0)			<0.001
T0	94 (4·5)	1 (0·8)			3 (1.3)	1 (0.8)	
Tis	16 (0·8)	0 (0·0)			0 (0.0)	0 (0.0)	
T1	325 (15·6)	2 (1·7)			23 (10.1)	2 (1.7)	
T2	342 (16·4)	5 (4·3)			35 (15.4)	5 (4.3)	
T3	827 (39·6)	38 (33·0)			107 (47.1)	40 (34.8)	
T4	439 (21·0)	66 (57·4)			59 (26.0)	67 (58.3)	
Tx	44 (2·1)	3 (2·6)			0 (0.0)	0 (0.0)	
pN-stage			<0·001	0 (0·0)			<0.001
N0	926 (44·4)	8 (7·0)			81 (35.7)	9 (7.8)	
N1	400 (19·2)	22 (19·1)			52 (22.9)	24 (20.9)	
N2	338 (16·2)	29 (25·2)			40 (17.6)	31 (27.0)	
N3	369 (17·7)	47 (40·9)			39 (17.2)	34 (29.6)	
Nx	54 (2·6)	9 (7·8)			0 (0.0)	0 (0.0)	
pM-stage			<0·001	151 (6·9)			<0.001
M0	1879 (96·6)	42 (39·6)			217 (95.6)	46 (40.0)	
M1	66 (3·4)	64 (60·4)			10 (4.4)	69 (60.0)	
Additional resections	212 (10·1)	35 (30·4)	<0·001	7 (0·3)	26 (11.5)	35 (30.4)	<0.001
Radicality of the resection			<0·001	45 (2·0)			<0.001
R0	1858 (90·8)	39 (34·4)			199 (87.7)	40 (34.8)	
R+	189 (9·2)	71 (64·5)			28 (12.3)	75 (65.2)	
Lymph node yield (median, IQR)	20 (14 – 28)	15 (10 – 22)	<0·001	63 (2·9)	19 (14 – 28)	15 (8 – 21)	<0.001
≥ 15 Lymph nodes in the specimen	1479 (73·0)	58 (56·2)	<0·001	63 (2·9)	163 (71.8)	63 (54.8)	0.002
Positive lymph nodes (median, IQR)	1 (0 –5)	6 (2 – 11)	<0·001	19 (0·8)	2 (0 – 7)	6 (2 – 10)	<0.001

Percentages may not add up to 100% due to rounding. *Dataset after imputation. IQR: interquartile range. The R+ of the PG group consisted of: 44% R1 resections and 21% R2 resections. In the PG group, R0 resections mean that even though the resection was non-curative, in 35% the local resection margins were clear.

DISCUSSION

This population-based study evaluated postoperative outcomes after non-curative gastrectomy for gastric cancer in a Western population in order to provide new information that could guide clinical decision-making. This study demonstrates that postoperative complications and length of hospitalization after nCG and CG are comparable in patients with similar baseline characteristics. Especially, no statistically significant difference in mortality was found between both groups.

Clinical decision-making on whether or not to perform nCG is based on the presence or absence of bothersome symptoms, their direct relation to quality of life (QoL), and the condition of the patient. Other important factors include the number of tumor sites[9,18], risk of postoperative morbidity and mortality and potential survival benefit of nCG.

One of the objectives in favor of performing nCG is that several studies have reported an improved QoL after reducing bothersome symptoms[7,18–22]. These symptoms occur in up to 35 per cent of patients and include obstruction causing nausea/vomiting, hemorrhage or pain[20,22]. In a single center study with 99 patients who underwent gastrectomy with incomplete removal of gross disease (R2 gastrectomy), it was demonstrated that gastrectomy improved bothersome symptoms in only 44 per cent of patients[22]. Another single center cohort study with 151 patients demonstrated that QoL improved for patients who underwent palliative gastrectomy, by means of increased ability to return to normal daily activities and to take oral intake, and less vomiting and gastro-intestinal hemorrhage[18]. Other studies report that severe tumor-related complications occur less frequently in the remaining lifespan of patients who underwent nCG. Also, prevention of further surgery or interventions due to severe tumor-related complications in patients not undergoing resection is desirable[23,24]. Although in the current study, unfortunately, no link could be made to whether patients were symptomatic, the results support that morbidity and mortality is acceptable and even similar to a comparable group with curative intent.

Reasons to refrain from nCG are the previously reported high mortality and morbidity rates[7,9,20,22,25–27], of which the latter often results in worsened recovery. In the original cohort,

mortality rates after nCG were higher compared to CG, general mortality rates[28,29] and the Asian REGATTA trial[10], which reflects the poor general condition of these patients. Other explanations could be that Western patients present with more advanced tumor stages, whereas no cT4 patients were included in the REGATTA trial. In addition, only patients with a single non-curative factor were included in the Asian study, whereas there might have been patients with multiple non-curative factors in the current study. Moreover, population screening programs in the East allow for more experienced surgeons due to the higher number of gastric cancer patients. Interestingly however, after PSM all complication and recovery rates of nCG-patients were similar to that of CG-patients. These results indicate that postoperative outcomes are not determined by the intent of the procedure, but more likely by the frailty of patients, which was demonstrated to be worse in patients undergoing nCG. The extent of disease was less likely to influence postoperative outcomes, as the pTNM stage was generally higher in the nCG group, while postoperative outcomes were comparable between nCG and CG. In general, a factor that could play a role in reducing postoperative morbidity after nCG is the more frequent implementation of minimally invasive gastrectomy, which was demonstrated to result in less postoperative complications and shorter hospitalization compared to open procedures[28–30].

Non-curative resection of the primary tumor with the aim of prolonging survival in asymptomatic patients is matter of debate and has not been proven in randomized clinical trials. In colorectal cancer a retrospective analysis of two phase III studies on metastatic colorectal carcinoma (CAIRO and CAIRO2) showed that resection of the primary tumor resulted in a significant survival benefit[31,32]. However, in both studies comparing different chemotherapeutic regimens, patients were selected after surgical resection of the primary tumor and therefore these results were not corrected for morbidity and mortality that occurred as a result of surgery. For that reason, the CAIRO4 study is conducted which randomly assigns asymptomatic patients for resection of the primary tumor followed by systemic therapy or systemic therapy without resection. Results of this trial are awaited.

For gastric cancer, many studies varying from randomized trials to retrospective cohort studies, demonstrated a survival benefit[7,8,35,9,14,18–20,22,33,34], which obviously could be a main argument in favor of performing nCG. Included herein is a meta-analysis that analyzed 14 observational studies with 3003 patients who reported a statistically significant improvement in overall survival of nCG (HR 0.56; 95%CI 0.39-0.80; $p<0.002$) compared to patients treated without resection[33].

Moreover, the German AIO-FLOT3 trial demonstrated survival benefit in patients with limited metastatic disease who received neoadjuvant chemotherapy and underwent surgery, compared to patients who were not suitable for surgical resection. Also, it is hypothesized that the tumor might respond to palliative (chemo)therapy better, after a significant portion has been resected[9]. On the other hand, the Asian randomized REGATTA-trial did not find a benefit of nCG over palliative chemotherapy in terms of survival. However, patients in the REGATTA-trial mostly suffered from peritoneal metastases, who may not benefit from nCG[10,20]. Currently, the Dutch COSTA-trial and the German RENAISSANCE trial[36] are evaluating potential benefits of nCG in selected patients and the results from these studies will have to be awaited.

The current study has some limitations, as the results are affected by inherent selection bias that could not be adjusted with PSM. Second, the reason for non-curative gastrectomy (e.g. bothersome symptoms) was not available in the dataset, nor was the location of metastases or number of metastatic sites, which precluded performing several relevant sub analyses. Moreover, emergency resections were excluded, which could have led to the exclusion of some nCG cases but allowed for a more homogeneous population. Last, no link could be made with survival data and QoL, since the DUCA lacks this kind of data.

CONCLUSION

A non-curative intent of surgery does not negatively impact postoperative outcomes compared to CG in patients with similar patient and tumor characteristics. As such, nCG might be considered in patients who are critically evaluated and deemed fit enough for surgery.

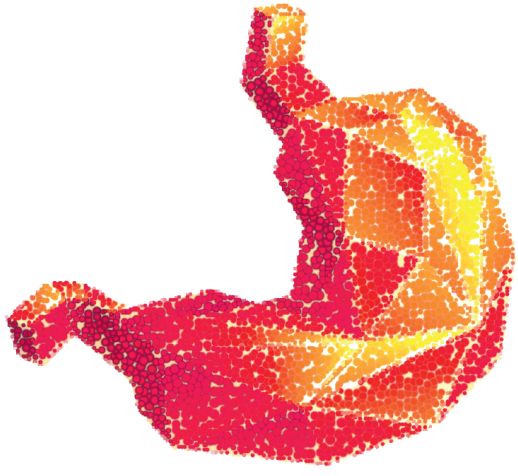
REFERENCES

1. Bray F, Ferlay J, Soerjomataram I. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. 2018:394-424.
2. IKNL. Cijfers over kanker. Ned Integr Kankercent. 2014. http://www.cijfersoverkanker.nl/selecties/Dataset_1/img51d171be67d58.
3. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, et al. Early outcomes from the Dutch Upper Gastrointestinal Cancer Audit. Br J Surg. 2016;103(13):1855-1863.
4. Integraal Kankercentrum Nederland. Diagnostiek, behandeling en follow-up van het maagcarcinoom 2016. http://www.oncoline.nl/uploaded/docs/Maagcarcinoom/Richtlijn maagcarcinoom.pdf. Published 2016.
5. Cunningham D, Allum WH, Stenning SP, et al. Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. N Engl J Med. 2007:11-20.
6. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(August):v38-v49.
7. Warschkow R, Baechtold M, Leung K, et al. Selective survival advantage associated with primary tumor resection for metastatic gastric cancer in a Western population. Gastric Cancer. 2017:1-14.
8. Bonenkamp JJ, Sasako M, Hermans J, van de Velde CJH. Tumor load and surgical palliation in gastric cancer. Hepatogastroenterology. 2001;48((41)):1219-1221.
9. Hartgrink HH, Putter H, Klein et al. Value of palliative resection in gastric cancer. Br J Surg. 2002;89(11):1438-1443.
10. Fujitani K, Yang HK, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): A phase 3, randomised controlled trial. Lancet Oncol. 2016;17(3):309-318.
11. Washington K. 7th edition of the AJCC cancer staging manual: Stomach. Ann Surg Oncol. 2010;17(12):3077-3079.
12. Integraal Kankercentrum Nederland. Richtlijn Diagnostiek, behandeling en follow-up van het maagcarcinoom 2009. 2009.
13. Cunningham D, Starling N, Rao S, et al. Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer. N Engl J Med. 2008;358(1):36-46.
14. Sano T, Kodera Y. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer. 2011;14(2):113-123.
15. Dutch Upper GI Cancer Audit. Data Dictionairy. https://documents.mrdm.nl/showcase/downloaden#. Published 2016.
16. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: A gentle introduction to imputation of missing values. J Clin Epidemiol. 2006;59(10):1087-1091.
17. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46(3):399-424.
18. Samarasam I, Chandran BS, Sitaram V, et al. Palliative gastrectomy in advanced gastric cancer: Is it worthwhile? ANZ J Surg. 2006;76(1-2):60-63.
19. Izuishi K, Mori H. Recent strategies for treating stage IV gastric cancer: Roles of palliative gastrectomy, chemotherapy, and radiotherapy. J Gastrointest Liver Dis. 2016;25(1):87-94.
20. Lasithiotakis K, Antoniou SA, Antoniou GA, et al. Gastrectomy for stage IV gastric cancer. A systematic review and meta-Analysis. Anticancer Res. 2014;34(5):2079-2086.
21. Kahlke V, Bestmann B, Schmid A, et al. Palliation of Metastatic Gastric Cancer: Impact of Preoperative Symptoms and the Type of Operation on Survival and Quality of Life. World J Surg. 2004;28(4):369-375.
22. Collins A, Hatzaras I, Schmidt C, et al. Gastrectomy in Advanced Gastric Cancer Effectively Palliates Symptoms and May Improve Survival in Select Patients. J Gastrointest Surg. 2014;18(3):491-496.

23. Chow LWC, Lim BH, Leung SY., et al. Gastric carcinoma with synchronous liver metastases: palliative gastrectomy or not? Aust N Z J Surg. 1995;65:719-723.
24. Ko KJ, Shim JH, Yoo HM, et al. The clinical value of non-curative resection followed by chemotherapy for incurable gastric cancer. World J Surg. 2012;36(8):1800-1805.
25. Saidi RF, ReMine SG, Dudrick PS, Hanna NN. Is there a role for palliative gastrectomy in patients with stage IV gastric cancer? World J Surg. 2006;30(1):21-27.
26. Kunisaki C, Makino H, Takagawa R, et al. Impact of Palliative Gastrectomy in Patients. Anticancer Res. 2008;28:1309-1316.
27. Jeong Y, Mahar AL, Coburn NG, et al. Outcomes of Non-curative Gastrectomy for Gastric Cancer: An Analysis of the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). Ann Surg Oncol. 2018.
28. Brenkman HJF, Gisbertz SS, Slaman AE, et al. Postoperative Outcomes of Minimally Invasive Gastrectomy Versus Open Gastrectomy during the Early Introduction of Minimally Invasive Gastrectomy in the Netherlands. Ann Surg. 2017;266(5):831-838.
29. Gertsen EC, Brenkman HJF, Seesing MFJ, Goense L, Ruurda JP, van Hillegersberg R. Introduction of minimally invasive surgery for distal and total gastrectomy: a population-based study. Eur J Surg Oncol. 2018.
30. Kim W, Kim HH, Han SU, et al. Decreased morbidity of laparoscopic distal gastrectomy compared with open distal gastrectomy for stage I gastric cancer: Short-term outcomes from a multicenter randomized controlled trial (KLASS-01). Ann Surg. 2016;263(1):28-35.
31. Venderbosch S, De Wilt JH, Teerenstra S, et al. Prognostic value of resection of primary tumor in patients with stage IV colorectal cancer: Retrospective analysis of two randomized studies and a review of the literature. Ann Surg Oncol. 2011;18(12):3252-3260.
32. 't Lam - Boer J, Mol L, Verhoef C, et al. The CAIRO4 study: the role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer – a randomized phase III study of the Dutch Colorectal Cancer Group (DCCG). BMC Cancer. 2014;14(1):741.
33. Sun J, Song Y, Wang Z, et al. Clinical significance of palliative gastrectomy on the survival of patients with incurable advanced gastric cancer: A systematic review and meta-analysis. BMC Cancer. 2013;13.
34. Omori H, Tanizawa Y, Makuuchi R, et al. Role of Palliative Resection in Patients with Incurable Advanced Gastric Cancer Who are Unfit for Chemotherapy. World J Surg. 2018.
35. Al-Batran S-E, Homann N, Pauligk C, et al. Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer The AIO-FLOT3 Trial. 2019;3(9):1237-1244.
36. Al-Batran SE, Goetze TO, Mueller DW, et al. The RENAISSANCE (AIO-FLOT5) trial: Effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III tri. BMC Cancer. 2017;17(1):1-7.

Part 3

Summary and general discussion



Chapter 14

Summary

SUMMARY

Gastric cancer annually affects over 1 million patients worldwide. Curative treatment usually comprises perioperative chemotherapy and surgical resection of the tumor, which is accompanied by high morbidity and mortality rates, while the 5-year overall survival rate in general remains poor. Prognosis mainly depends on tumour stage at diagnosis. The research presented in this thesis aimed to improve the preoperative staging process and evaluated several aspects of the surgical treatment of gastric cancer. Optimizing staging will allow for a more tailored treatment for patients with gastric cancer.

Part I. Staging

Chapter 2. PLASTIC-study: protocol

The initial staging process of gastric cancer consists of gastroscopy and CT, while other modalities such as FDG-PET/CT and staging laparoscopy may detect additional metastases or non-resectable disease. This chapter describes the protocol of the PLASTIC-study, a multicenter prospective observational study which evaluates the addition of FDG-PET/CT and staging laparoscopy to the staging process. It was hypothesized that adding both modalities would result in a more tailored treatment, accompanied by a better quality of life and a reduction of health care costs.

Chapter 3. Restaging CT during neoadjuvant chemotherapy

The additive value of restaging CT was evaluated after 2 out of 3 neoadjuvant chemotherapy cycles from the MAGIC regimen. A multicenter assessment of treatment alterations based on restaging CT showed that metastases and tumor progression were found in only 1% and 7% of patients, respectively, resulting in a change of treatment such as cancellation of surgical resection or an adaptation of chemotherapy regimen. In 3% of patients, distant interval metastases were not identified by the restaging CT, resulting in futile laparotomy. These findings indicate that a restaging CT has limited impact on clinical decision making.

Chapter 4. Implementation of FDG-PET/CT and staging laparoscopy

After having been included in the Dutch guidelines, the implementation of FDG-PET/CT and staging laparoscopy and their association with logistics and proportion of non-curative

procedures was studied. A nationwide comparison demonstrated that the use of FDG-PET/CT and staging laparoscopy increased from approximately 20% to 60% after introduction in the guidelines. Both modalities were associated with additional waiting time to the start of treatment but did not influence the number of non-curative procedures. These results show that the implementation of the use of both modalities has started successfully during the study period, but room for improvement remains regarding waiting times.

Chapter 5. PLASTIC-study: results

This chapter describes the results of the PLASTIC-study, of which the protocol was presented in chapter 2. The proportion of patients in whom the intent of treatment changed based on the addition of FDG-PET/CT and staging laparoscopy to the staging process was assessed. This multicenter prospective observational study found that FDG-PET/CT has limited additive value, only detecting distant metastases in 3% of patients but detects secondary findings in 20% of patients. On the other hand, staging laparoscopy adds considerably to accurate staging, by detecting metastatic or non-resectable disease in 19% of patients, thereby contributing significantly to changing treatment. Based on the results of this study, guidelines for staging advanced gastric cancer should include SL, whereas the routine use of FDG-PET/CT is not supported.

Part II. Surgical treatment

Chapter 6. Gastric cancer surgery worldwide

This cross-sectional international survey among surgeons analysed the worldwide status of gastric cancer surgery in 2019 and highlighted changes compared to a previous survey in 2014. In contrast to the previous survey, the majority of surgeons preferred a minimally invasive approach for early gastric cancer and continued to prefer an open approach in case of advanced cancer. Compared to the survey of 2014, perioperative chemotherapy and a D2 lymphadenectomy were more frequently favored. These results reflect worldwide trends in the treatment of gastric cancer.

Chapter 7. Treatment in diffuse type gastric cancer

Survival between patients with diffuse type gastric or gastroesophageal junction cancer undergoing either primary surgery or neoadjuvant chemo(radio)therapy plus surgery was compared. This nationwide cohort study found that neoadjuvant chemotherapy for both gastric and gastroesophageal junction cancer was associated with better survival when compared to surgery alone. Moreover, treatment of gastroesophageal junction cancer in high volume hospitals was associated with better outcomes. These findings indicate that neoadjuvant chemotherapy should be recommended and further centralization for treatment of these tumors is advised.

Chapter 8. Unplanned omission after neoadjuvant chemotherapy

Neoadjuvant chemotherapy is not without risk of complications. The results in this chapter show that 11% of patients who started neoadjuvant chemotherapy did not proceed to surgical resection. Disease progression and mortality during or within 30 days of ending chemotherapy were the most frequent reasons for omission from gastrectomy. This study stresses the importance of careful patient selection for neoadjuvant chemotherapy.

Chapter 9. Refraining from resection in potentially curable gastric cancer

Reasons for refraining from gastrectomy in potentially curable gastric cancer were assessed. This study found that 33% of patients with potentially curable gastric cancer do not undergo gastrectomy, for which the most common registered reasons were patient refusal, performance status, comorbidity and extent of disease. Moreover, higher age, lower socioeconomic status, and poor tumor characteristics were identified as associated factors. These results may reflect shared decision-making, patient selection, and practice variation between hospitals.

Chapter 10. Minimally invasive surgery: total and distal gastrectomy

The introduction of minimally invasive total and distal gastrectomy, two surgical procedures with different complexity, were evaluated. In this study with nationwide data, propensity score matched analyses showed that benefits of minimally invasive surgery were demonstrated for distal gastrectomy, but not for total gastrectomy. The results of this study suggest that further

centralization of gastric cancer surgery should be considered, as possible longer learning curves for minimally invasive total gastrectomy seem likely.

Chapter 11. Minimally invasive surgery: gastrointestinal stromal tumors

Safety and feasibility of minimally invasive resection of large (>5 cm) gastrointestinal stromal tumors of the stomach at the University Medical Center Utrecht were assessed. Intra- and postoperative complication rates were acceptable, and a R0-resection was achieved in 96%. These results indicate that minimally invasive surgery allows for controlled and oncologically complete resection of large gastrointestinal stromal tumors of the stomach.

Chapter 12. Minimally invasive surgery: clinically most relevant postoperative complications

A population-based study was conducted to identify the clinically most relevant complications after gastrectomy. By using the population-attributable fraction (PAF), anastomotic leakage and pulmonary complications were found to have the greatest overall impact on most of the predefined outcomes, such as mortality. Also, intra-abdominal abscesses and wound infections had a high impact. These results provide direction to what surgical quality improvement programs should focus on.

Chapter 13. Non-curative gastrectomy

Postoperative morbidity and mortality in patients who underwent non-curative gastrectomy were compared with an intended curative gastrectomy. After creating two comparable groups with propensity score matching, postoperative mortality, morbidity, re-interventions and readmission rates did not differ significantly between both groups. These findings suggest that, after critical evaluation, non-curative gastrectomy may be more frequently considered in fit patients.

Chapter 15

General discussion and conclusions

GENERAL DISCUSSION

In this thesis, several aspects of staging and surgical treatment were evaluated, in order to offer a more tailored treatment to patients with gastric cancer. In this final chapter, implications of the results for current and future clinical practice are discussed.

Staging

FDG-PET/CT

FDG-PET/CT was included in the Dutch national guidelines in 2016, after it was reported that its use led to detection of distant metastases in 1 out of 10 patients with locally advanced gastric cancer[1–3]. In this context, detection of metastatic disease prevents futile surgery and the accompanied high risk of postoperative complications after gastrectomy[4], thereby resulting in higher cost-effectiveness[2]. However, this thesis demonstrates that the additive value of FDG-PET/CT is only limited, and its use will almost certainly not be cost-effective in the Netherlands, due to the low detection rate of distant metastases and relatively high detection rate of secondary findings requiring additional examinations. A possible explanation for the low detection rate of FDG-PET/CT might be that during the set up and running time of the PLASTIC-study, new editions of the TNM classification system were introduced[5,6]. As a result, lower T-category tumors were included, as T3 and T4 tumors according to TNM-6 correspond to category T4a and T4b tumors according to TNM-7 and TNM-8.

Based on the results of the current thesis, it is advised that FDG-PET/CT will no longer be performed as standard of care in all patients with locally advanced gastric adenocarcinoma, and the Dutch national guidelines for patients with gastric cancer will likely be amended. There may, however, be subgroups of patients with specific tumor characteristics, such as large size or certain histological characteristics, for whom the use of FDG-PET/CT may be beneficial. The current thesis encourages research into certain molecular subtypes with a higher risk of distant metastases for which an FDG-PET/CT scan may be useful[7]. Moreover, improved techniques combining radiomics and artificial intelligence, or perhaps better radiotracers, may achieve greater gains[7–9]. Also, FDG-PET/CT may function as a modality to evaluate tumor response to chemotherapeutic treatment[10]. Future studies designed as part of this thesis will therefore focus

on identifying subgroups and techniques that achieve the greatest profit for staging of gastric cancer.

Staging laparoscopy

This thesis concluded that staging laparoscopy detects peritoneal disease or non-resectable tumors with ingrowth in other organs in 1 out of 5 patients. These numbers emphasize that laparoscopy is a good staging tool that adds considerably to the staging process of patients with gastric cancer, and likely will be a game changer for patients in whom metastatic disease is detected. In these patients, surgical resection is not considered beneficial, as this has no additive value oncologically and is accompanied by high morbidity rates[4,11,12]. The use of staging laparoscopy has a significant impact on patients, by reducing the number of futile surgical procedures. Patients in whom futile surgical resection is prevented are not exposed to the risks of perioperative complications and might have a better quality of life in their remaining life span. Additionally, preventing futile surgery will most likely lead to a high cost-effectiveness in the Netherlands, and the first results of the analysis carried out for this does indeed point in that direction. Moreover, staging laparoscopy leads to a more accurate assessment of peritoneal disease scored through the Peritoneal Cancer Index (PCI) than conventional imaging such as CT and FDG-PET/CT, which are known for their low sensitivity for detection of peritoneal disease[13]. For determining the PCI score, the abdomen is divided into 13 regions and a score of 1 to 3 is given to each region, based on the size of the peritoneal lesion. Many experimental studies evaluating survival benefits of hyperthermic intraperitoneal chemotherapy (HIPEC) with cytoreductive surgery, base their inclusion criteria on this PCI score. It has been suggested that the survival benefit achieved by HIPEC is greater than palliative systemic therapy alone, but this benefit is only valid up to certain PCI scores[14]. Also in other types of cancers, it is still being discussed whether MRI may be of benefit in accurately detecting peritoneal metastases[15]. In a broader sense, it would be interesting to investigate whether suggested peritoneal disease on imaging corresponds with findings during staging laparoscopy. For the time being and supported by this thesis, staging laparoscopy is reported as the most accurate modality for detecting peritoneal disease in gastric cancer patients. However, the role of imaging may change again in the future in view of the further improving imaging techniques and developments in the field of artificial intelligence for example. Moreover, little is known about differences in accuracy of scoring the PCI during staging laparoscopy when performed in centers with a high

volume of gastrectomies versus centers with a low volume of gastrectomies, and when performed by a surgical resident versus an experienced surgeon. Identifying the best, safest and most cost-effective detection modality to detect peritoneal metastases in the context of gastric cancer is something that future research should focus on.

One manifestation of peritoneal disease that cannot be detected by imaging but can be detected by staging laparoscopy is positive peritoneal cytology. According to the current TNM staging system[5,6], positive peritoneal cytology should be regarded as metastatic (M1) disease, and is associated with poor survival. Until now, it is not known what the treatment consequence of positive cytology is and whether these patients should be offered palliative treatment, or whether in some cases a curative treatment option should be offered. Another advantage of staging laparoscopy is that when combined with peritoneal lavage, it could potentially act as a restaging modality in patients with positive peritoneal cytology only. After neoadjuvant treatment, staging laparoscopy and peritoneal cytology can be used to evaluate whether the peritoneal disease has responded to chemotherapy. In those cases, it can be decided to still offer curative treatment by means of surgical resection, as it has been shown that these patients may have a survival benefit[16–18]. In patients with persistent positive peritoneal cytology or limited peritoneal disease, treatment with HIPEC and afterwards surgical resection can be offered, as some studies have suggested a survival benefit in these patients[19,20]. In these latter cases, it may be most efficient to perform the HIPEC treatment directly after the restaging laparoscopy, in the same session.

Staging laparoscopy has many advantages and can be deployed in many ways, with little post-procedural morbidity as demonstrated in this thesis. The role of staging laparoscopy may become even more important in the future and the use of laparoscopy should be further exploited, in the context of both staging and restaging. Laparoscopy can identify patients in whom futile surgery can be prevented and palliative care is best suited, as well as identify the patients who may still be able to undergo treatment aimed at curation. As a result, it will make an important contribution to clinical decision making and offering a more tailor-made treatment for patients with gastric cancer.

Perspectives

Before the revision of the Dutch national guidelines in 2016, staging of gastric cancer consisted of gastroscopy with biopsy and CT. As a result of a study with apparently compelling evidence, the guidelines were revised and FDG-PET/CT and staging laparoscopy were added to the Dutch guidelines. To evaluate the effect of addition of these modalities, the PLASTIC study was conducted. Theoretically, including these modalities in the guidelines meant that they could also be implemented immediately. However, during initiation visits in the start-up phase of the PLASTIC-study it appeared that implementation was not as smooth as thought initially, and that FDG-PET/CT, staging laparoscopy or both were not yet used routinely. Numerous wide-ranging hurdles for implementation of revised guidelines have been acknowledged, such as lack of awareness, agreement, outcome expectancy, and characteristics of the hospital setting[21,22]. Now that the results of the PLASTIC-study presented in this thesis are known, healthcare professionals in the Netherlands may face another challenge, namely to de-implement widespread use of FDG-PET/CT as effectively as possible. There may be a role for a follow-up study of the PLASTIC-study, in the form of a (de-)implementation study, in which the use of FDG-PET/CT will be stepped-wedged reduced, so that the collected data could also contribute to determining benefiting subgroups.

Surgical treatment

In general, surgical resection is the only curative treatment for gastric cancer. Perioperative chemo(radio)therapy can increase the chance of survival in patients undergoing surgery. Leading up to surgical treatment, it is important to weigh the pros and cons of surgical intervention together with the patient, and in particular to carefully consider the relatively high risk of complications. The physical condition and pre-existing comorbidities of the patient are important factors that should be taken into account when deciding whether or not to start with neoadjuvant therapy and whether or not to perform gastric resection. If the well-considered decision is made to start a curative treatment including perioperative chemotherapy and surgery, it is regrettable to find that 1 in 10 patients who started neoadjuvant therapy do not proceed with surgery, thereby not completing the preconceived treatment plan. In research presented in this thesis, it was found that 1 in 3 patients with a potentially curable gastric carcinoma refrained from surgery. Care must therefore be taken to ensure that patients are well enough informed

about the treatment options applicable to their situation. In hesitant patients with potentially curably disease, who are screened adequately and deemed fit enough by the medical team, it should be emphasized that surgery is the only curative option. Especially because of improvements in surgical quality with decreasing morbidity rates[4], and because it is increasingly possible to offer a tailored treatment including different types of systemic therapy with the aim to increase survival[23–25].

Minimally invasive surgery

With the introduction of minimally invasive gastrectomy, it was assumed that patients' recovery would be accelerated compared to open procedures, as there is less surgical trauma[26]. Minimally invasive gastrectomy is increasingly performed for gastric cancer. A recently conducted Dutch randomized controlled trial shows no evident differences in length of hospitalization, postoperative complication rates and oncological safety between open and minimally invasive gastrectomy[27]. This thesis, discussing several nationwide retrospective studies in which an open procedure was compared with minimally invasive surgery, contributes to the accumulating evidence for the safety and benefits of minimally invasive surgery. Advantages such as fewer postoperative complications and shorter hospital stay were confirmed in several studies, with the note that caution is advised with minimally invasive total gastrectomy.

Centralization of gastric cancer care has been taking place since 2012. This means that a hospital must perform at least 20 gastric resections annually in order to be allowed to continue performing the procedure. Research has shown that this reduces the risk of complications and thus improves care[28–30]. This thesis shows that several aspects of the surgical treatment of gastric tumors are closely related to experience and the frequent performance of the surgical procedure. For example, it appears that patients with diffuse type tumors at the gastroesophageal junction might be better treated in a hospital that performs at least 20 resections per year. Consideration should also be given to increasing the number of procedures annually required for performing a minimally invasive total gastrectomy, as the learning curve may be longer for this procedure due to its greater complexity. For minimally invasive total gastrectomy, completion of the learning curve was previously reported to involve performing approximately 100 procedures[31]. It may also be suggested that centralizing the surgical treatment of gastrointestinal stromal

tumors is justified, as it has been shown that laparoscopic resection of large gastrointestinal stromal tumors can be performed safely in a center of expertise.

Other advantages of minimally invasive surgery are the use of cameras during laparoscopy and robot-assisted surgery with which indocyanine green can be used. With this, lymph nodes become fluorescent and – with the proper scopes and cameras – light up and can be detected during the procedure. This could potentially lead to a more precise lymphadenectomy and higher lymph node yield, which in turn is associated with a better survival[32–35]. Also, indocyanine green can be used to visualize the vascularization of the tissue with which the gastroesophageal anastomosis is created, which can prevent the anastomosis being made with tissue that has poor vascularization. Although this technique has shown benefits in esophageal cancer, the use of indocyanine green in the case of gastric cancer is still being investigated. One last benefit of minimally invasive surgery, whereby recorded videos can be analyzed later, is that it creates an opportunity for the application of artificial intelligence. By applying machine learning on large video databases for intstance, it is possible to learn a machine to recognize patterns and identify anatomical variations. This allows studies to be set up that may determine predictive factors, for example for the occurrence of anastomotic leakage.

Morbidity

It is important to continuously look for ways to reduce postoperative complications, both in the interest of the patient and in the public interest. In particular, decreasing complications rates are likely to reduce costs. In this thesis, a relatively new parameter for evaluating postoperative complications was presented for the first time in relation to gastric cancer. This population-attributable fraction confirmed anastomotic leakage and pulmonary complications as having the greatest impact on postoperative outcomes. Nevertheless, it is important to once again draw attention to the prevention of both the obvious and most frequently occurring complications, as well as the complications that might be estimated as less serious, such as wound infections, which can have a great impact on some outcomes. Surgical improvement programs should focus on preventing and managing the complications that have most impact. Furthermore, in the occurrence of postoperative morbidity, type, extent and method of the procedure are important contributors, but also the patient's physical condition and compliance to the enhanced recovery programs[36,37].

The high risk of complications may also be a factor that contributes to a patient's wish to refrain from surgery, and in the decision whether or not to perform non-curative gastric resection in patients with metastatic disease.

Treatment of metastatic disease

Due to improving staging possibilities, (limited) metastatic disease may become apparent more often, for example, oligometastases, positive cytology or limited peritoneal metastases. It is known that patients with metastatic disease have a poor prognosis, but some of these patients may benefit from surgical resection in terms of survival[38,39]. Also, it has been reported that quality of life is improved after non-curative resection with relieve of obstructive or other symptoms[40–43]. Research in this thesis showed that fit patients with metastatic disease who undergo non-curative resection have the same complication risks as patients undergoing resection with curative intent. Although guidelines do not yet provide advice on how to treat patients with positive peritoneal cytology and/or limited peritoneal disease, there are numerous studies that show possible survival gains for these patients if they are treated with, for example, HIPEC[44–47]. Randomized controlled trials to confirm this are ongoing[48]. Future research will show whether non-curative surgery in gastric cancer patients with oligometastases or (limited) peritoneal metastases may offer benefits in some selected cases[49,50], but there is also strong data that refutes this[51].

Nevertheless, surgical treatment of fit patients with metastatic gastric cancer should certainly be considered. Much effort has been and is being made to optimize the staging options. The possibly associated higher detection rate of metastatic disease is a good motivation for setting up future research and to investigate whether treatment in the case of metastatic gastric cancer can be improved, in terms of quality of life and survival gain. For both optimization of staging and surgical treatment, future research should focus on offering the most tailored staging and treatment.

CONCLUSIONS

Part 1. Staging

- The prospective observational cohort study evaluates the addition of FDG-PET/CT and staging laparoscopy to initial staging by CT and gastroscopy in patients with locally advanced gastric cancer, hypothesizing a treatment change in 27% of patients and a cost reduction (PLASTIC-study, chapter 2).
- In guiding clinical decision making during neoadjuvant chemotherapy in gastric cancer, aiming to avoid unnecessary surgical procedures or chemotherapy cycles, the additive value of restaging-CT is limited (chapter 3).
- After revision of the guidelines, FDG-PET/CT and SL have increasingly been implemented in the Netherlands, at the expense of prolonged waiting times from diagnosis to start of treatment, without being associated with the proportion of non-curative procedures (chapter 4).
- FDG-PET/CT has a limited role in detecting distant metastases, but frequently detects incidental findings, warranting additional diagnostic investigations. SL plays an important role in clinical decision making by detecting metastatic or non-resectable disease, thereby changing the treatment strategy (chapter 5).

Part 2. Surgical treatment

- Worldwide, surgeons favor a minimally invasive surgical approach over an open approach, especially for early cancers. In addition, D2 lymphadenectomy and perioperative therapy are increasingly adopted (chapter 6).
- For gastric and GEJ diffuse type cancer, including signet ring cell carcinomas, the use of perioperative chemotherapy plus surgery is associated with better outcomes and lower overall mortality compared to surgery alone. Combined therapy is preferably performed in high-volume gastric surgery centers (chapter 7).
- Of patients with gastric cancer who start neoadjuvant chemotherapy, 1 out of 10 does not proceed to surgical resection, for which the main reason is progression of disease (chapter 8).
- Of patients with potentially curable gastric cancer, 33% does not undergo a resection, mostly due to patient refusal, worse performance status or comorbidity (chapter 9).

- Benefits of minimally invasive gastrectomy during its early introduction were demonstrated for distal gastrectomy but not for total gastrectomy. Minimally invasive total gastrectomy was associated with anastomotic leakage more frequently when compared to open total gastrectomy (chapter 10).
- Minimally invasive gastric surgery for large GIST is safe, feasible, and oncologically sound, allowing for a controlled resection and reduced patient morbidity (chapter 11).
- Anastomotic leakage and pulmonary complications are the major attributors to deteriorated clinical outcomes after gastrectomy. Therefore, surgical improvement programs should focus on reducing these complications (chapter 12).
- Non-curative gastrectomy does not lead to additional postoperative risks compared to curative gastrectomy in patients with similar characteristics and may be considered in fit patients with advanced gastric cancer (chapter 13).

REFERENCES

1. Integraal Kankercentrum Nederland. Diagnostiek, behandeling en follow-up van het maagcarcinoom 2016. Published 2016. http://www.oncoline.nl/uploaded/docs/Maagcarcinoom/Richtlijn maagcarcinoom.pdf
2. Smyth E, Schöder H, Strong VE, et al. A prospective evaluation of the utility of 2-deoxy-2-[^{18} F]fluoro- <scp>D</scp> -glucose positron emission tomography and computed tomography in staging locally advanced gastric cancer. *Cancer*. 2012;118(22):5481-5488. doi:10.1002/cncr.27550
3. Smyth EC, Shah MA. Role of (18F) 2-fluoro-2-deoxyglucose positron emission tomography in upper gastrointestinal malignancies. *World J Gastroenterol*. 2011;17(46):5059-5074.
4. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, et al. Early outcomes from the Dutch Upper Gastrointestinal Cancer Audit. *Br J Surg*. 2016;103(13):1855-1863.
5. International Union Against Cancer. *TNM: Classification of Malignant Tumors 7th Edition*.; 2009.
6. International Union Against Cancer. TNM: Classification of Malignant Tumors 8th edition. 2016;(December):1-16.
7. Kaneko Y, Murray WK, Link E, Hicks RJ, Duong C. Improving Patient Selection for 18F-FDG PET Scanning in the Staging of Gastric Cancer. *J Nucl Med*. 2015;56(4):523-529.
8. Kuten J, Levine C, Shamni O, et al. Head - to - head comparison of - [68 Ga] Ga - FAPI - 04 and - [18 F]- FDG PET / CT in evaluating the extent of disease in gastric adenocarcinoma. *Eur J Nucl Med Mol Imaging*. 2021;(0123456789).
9. Jiang D, Chen X, You Z, et al. Comparison of - [68 Ga] Ga - FAPI - 04 and - [18 F]- FDG for the detection of primary and metastatic lesions in patients with gastric cancer : a bicentric retrospective study. 2021;(0123456789).
10. Kitajima K, Nakajo M, Kaida H, et al. Present and future roles of FDG-PET/CT imaging in the management of gastrointestinal cancer: An update. *Nagoya J Med Sci*. 2017;79(4):527-543.
11. Cunningham D, Allum WH, Stenning SP, et al. Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. *N Engl J Med*. Published online 2007:11-20.
12. Dassen AE, Dikken JL, Bosscha K, et al. Gastric cancer: Decreasing incidence but stable survival in the Netherlands. *Acta Oncol (Madr)*. 2014;53(1):138-142.
13. Kwee RM, Kwee TC. Modern imaging techniques for preoperative detection of distant metastases in gastric cancer. *World J Gastroenterol*. 2015;21(37):10502-10509.
14. Topal B, Demey K, Topal H, et al. Cytoreductive surgery and Hyperthermic intra-operative peritoneal chemotherapy with Cisplatin for gastric peritoneal Carcinomatosis Monocentric phase-2 nonrandomized prospective clinical trial. Published online 2017:1-7.
15. Borggreve AS, Goense L, Brenkman HJF, et al. Imaging strategies in the management of gastric cancer: Current role and future potential of MRI. *Br J Radiol*. 2019;92(1097).
16. Jamel S, Markar SR, Malietzis G, Acharya A, Athanasiou T, Hanna GB. Prognostic significance of peritoneal lavage cytology in staging gastric cancer: systematic review and meta-analysis. *Gastric Cancer*. 2017;21(1):10-18.
17. Badgwell B, Cormier JN, Krishnan S, et al. Does neoadjuvant treatment for gastric cancer patients with positive peritoneal cytology at staging laparoscopy improve survival? *Ann Surg Oncol*. 2008;15(10):2684-2691.
18. Yamamoto M, Kawano H, Yamaguchi S, et al. Comparison of Neoadjuvant Chemotherapy to Surgery Followed by Adjuvant Chemotherapy in Japanese Patients with Peritoneal Lavage Cytology Positive for Gastric Carcinoma. *Anticancer Res*. 2015;35(9):4859-4863.
19. Ishigami H, Yamaguchi H, Yamashita H. Surgery after intraperitoneal and systemic chemotherapy for gastric cancer with peritoneal metastasis or positive peritoneal cytology findings. *Gastric Cancer*. 2017;20(s1):128-134.
20. Badgwell B, Blum M, Das P, et al. Phase II Trial of Laparoscopic Hyperthermic Intraperitoneal Chemoperfusion for Peritoneal Carcinomatosis or Positive Peritoneal Cytology in Patients with Gastric Adenocarcinoma. *Ann Surg Oncol*. 2017;24(11):3338-3344.
21. Cabana MD, Rand CS, Powe NR, et al. Why Don ' t Physicians Follow A Framework for Improvement.

Jama. 1999;Vol 282:1458-1465.
22. Davis DA, Taylor-Vaisey A. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. *CAN MED ASSOC J*. 1997;157(4):408-416.
23. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ra. *Lancet*. 2019;393(10184):1948-1957.
24. Earle CC, Maroun J, Zuraw L, et al. Neoadjuvant or adjuvant therapy for resectable gastric cancer? A practice guideline. *Can J Surg*. 2002;45(6):438-446.
25. Wang X, Tang S, Cui X, et al. Cytokine-induced killer cell/dendritic cell–cytokine-induced killer cell immunotherapy for the postoperative treatment of gastric cancer: A systematic review and meta-analysis. *Med (United States)*. 2018;97(36):1-9.
26. Kitano S, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. *Surg Laparosc Endosc*. 1994;4(2):146-148.
27. van der Veen A, Brenkman HJF, Seesing MFJ, et al. Laparoscopic Versus Open Gastrectomy for Gastric Cancer (LOGICA): A Multicenter Randomized Clinical Trial. *J Clin Oncol*. 0(0):JCO.20.01540.
28. van Putten M, Nelen SD, Lemmens VEPP, et al. Overall survival before and after centralization of gastric cancer surgery in the Netherlands. *Br J Surg*. 2018;105(13):1807-1815.
29. Jensen LS, Nielsen H, Mortensen PB, Pilegaard HK, Johnsen SP. Enforcing centralization for gastric cancer in Denmark. *Eur J Surg Oncol*. 2010;36(SUPPL. 1):S50-S54.
30. Nelen SD, Heuthorst L, Verhoeven RHA, et al. Impact of Centralizing Gastric Cancer Surgery on Treatment, Morbidity, and Mortality. *J Gastrointest Surg*. 2017;21(12):2000-2008.
31. Jung DH, Son S-Y, Park YS, et al. The learning curve associated with laparoscopic total gastrectomy. *Gastric Cancer*. 2016;19(1):264-272.
32. Songun I, Putter H, Kranenbarg EMK, Sasako M, van de Velde CJH. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol*. 2010;11(5):439-449.
33. Wu CW, Hsiung CA, Lo SS, et al. Nodal dissection for patients with gastric cancer: A randomised controlled trial. *Lancet Oncol*. 2006;7(4):309-315.
34. Tummers QRJG, Boogerd LSF, De Steur WO, et al. Near-infrared fluorescence sentinel lymph node detection in gastric cancer: A pilot study Clinical Trials Study. *World J Gastroenterol*. 2016;22(13):3644-3651.
35. Brenkman HJF, Goense L, Brosens LA, et al. A High Lymph Node Yield is Associated with Prolonged Survival in Elderly Patients Undergoing Curative Gastrectomy for Cancer: A Dutch Population-Based Cohort Study. *Ann Surg Oncol*. 2017;24(8):2213-2223.
36. Mortensen K, Nilsson M, Slim K, et al. Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery after Surgery (ERAS) Society recommendations. *Br J Surg*. 2014;101(10):1209-1229.
37. Gustafsson UO, Scott MJ, Schwenk W, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced recovery after surgery (ERAS®) society recommendations. *World J Surg*. 2013;37(2):259-284.
38. Hartgrink HH, Putter H, Klein Kranenbarg E, Bonenkamp JJ, van de Velde CJH. Value of palliative resection in gastric cancer. *Br J Surg*. 2002;89(11):1438-1443.
39. Sun J, Song Y, Wang Z, et al. Clinical significance of palliative gastrectomy on the survival of patients with incurable advanced gastric cancer: A systematic review and meta-analysis. *BMC Cancer*. 2013;13.
40. Samarasam I, Chandran BS, Sitaram V, Perakath B, Nair A, Mathew G. Palliative gastrectomy in advanced gastric cancer: Is it worthwhile? *ANZ J Surg*. 2006;76(1-2):60-63.
41. Izuishi K, Mori H. Recent strategies for treating stage IV gastric cancer: Roles of palliative gastrectomy, chemotherapy, and radiotherapy. *J Gastrointest Liver Dis*. 2016;25(1):87-94.
42. Lasithiotakis K, Antoniou SA, Antoniou GA, Kaklamanos I, Zoras O. Gastrectomy for stage IV gastric

cancer. A systematic review and meta-Analysis. *Anticancer Res*. 2014;34(5):2079-2086.
43. Collins A, Hatzaras I, Schmidt C, et al. Gastrectomy in Advanced Gastric Cancer Effectively Palliates Symptoms and May Improve Survival in Select Patients. *J Gastrointest Surg*. 2014;18(3):491-496.
44. Coccolini F, Cotte E, Glehen O, et al. Intraperitoneal chemotherapy in advanced gastric cancer . Meta-analysis of randomized trials. *Eur J Surg Oncol*. 2014;40(1):12-26.
45. Matharu G, Tucker O, Alderson D. Systematic review of intraperitoneal chemotherapy for gastric cancer. *Br J Surg*. 2011;98(9):1225-1235.
46. Badgwell BD, Ikoma N, Blum Murphy MA, et al. A phase II trial of cytoreduction, gastrectomy, and hyperthermic intraperitoneal perfusion with chemotherapy for patients with gastric cancer and stage IV peritoneal disease. *J Clin Oncol*. 2020;38(4_suppl):361-361.
47. Glehen O, Gilly FN, Arvieux C, et al. Peritoneal carcinomatosis from gastric cancer: A multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. *Ann Surg Oncol*. 2010;17(9):2370-2377.
48. Koemans WJ, Van Der Kaaij RT, Boot H, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy versus palliative systemic chemotherapy in stomach cancer patients with peritoneal dissemination, the study protocol of a multicentre randomised controlled trial (PERISCOPE II). *BMC Cancer*. 2019;19(1):1-8.
49. Al-Batran SE, Goetze TO, Mueller DW, et al. The RENAISSANCE (AIO-FLOT5) trial: Effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III tri. *BMC Cancer*. 2017;17(1):1-7.
50. Kroese TE, van Hillegersberg R, Schoppmann S, et al. Definitions and treatment of oligometastatic oesophagogastric cancer according to multidisciplinary tumour boards in Europe. *Eur J Cancer*. 2022;164:18-29.
51. Fujitani K, Yang HK, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): A phase 3, randomised controlled trial. *Lancet Oncol*. 2016;17(3):309-318.

Appendices

Summary in Dutch
(Nederlandse samenvatting)

Authors and affiliations

Review committee

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List of publications

Curriculum Vitae

SUMMARY IN DUTCH (NEDERLANDSE SAMENVATTING)

Maagkanker is de vijfde meest gediagnosticeerde kanker en de derde belangrijkste oorzaak van kankergerelateerde sterfte wereldwijd. In 2020 werden meer dan een miljoen nieuwe gevallen en ongeveer 768.000 sterfgevallen geregistreerd. De wereldwijde prevalentie van maagkanker varieert, met een hoge prevalentie in Aziatische landen en een lage prevalentie in westerse landen. Vanwege de hoge prevalentie in Aziatische landen, wordt de bevolking gescreend op maagkanker. Als gevolg daarvan wordt maagkanker bij Aziatische patiënten vaak in een vroeg stadium vastgesteld, terwijl gevorderde tumoren in westerse landen vaker voorkomen. Gevorderde tumoren kunnen zich door de maagwand uitbreiden en vaak zijn lymfeklieren betrokken. Het is bekend dat deze kenmerken een verhoogd risico geven op peritoneale en afstandsmetastasen. Van de 1200 nieuw gediagnosticeerde patiënten per jaar in Nederland ondergaan slechts ongeveer 500 patiënten een curatieve behandeling. De meeste patiënten komen niet in aanmerking voor curatieve behandeling vanwege een gevorderd tumorstadium, gemetastaseerde of niet-resectabele ziekte, of vanwege patiëntgerelateerde factoren, zoals comorbiditeiten. Voor degenen die een curatieve behandeling ondergaan, blijft de algehele 5-jaarsoverleving in westerse populaties slecht, ongeveer 40%, vanwege het gevorderde tumorstadium bij diagnose, wat geassocieerd is met een hoog risico op terugkeer van de tumor.

Ondanks dat er veel onderzoek wordt gedaan op het gebied van maagkanker, blijven er enkele lacunes in de kennis bestaan. Het blijft bijvoorbeeld een uitdaging om de beste stadiëringsopties en perioperatieve therapie te identificeren, om de meest gunstige chirurgische benadering te bepalen om het aantal complicaties te verminderen, en om de behandeling te bepalen in het geval van gemetastaseerde ziekte.

Deel 1. Stadiëring

Hoofdstuk 2. PLASTIC-studie: protocol

Het initiële stadiëringsproces van maagkanker bestaat uit gastroscopie en CT, terwijl andere modaliteiten zoals FDG-PET/CT en stadiëringslaparoscopie bijkomende metastasen of niet-resectabele ziekte kunnen detecteren. Dit hoofdstuk beschrijft het protocol van de PLASTIC-studie, een multicenter prospectieve observationele studie die de toevoeging van FDG-PET/CT en stadiëringslaparoscopie aan het stadiëringsproces evalueert. De hypothese was dat het

toevoegen van beide modaliteiten zou resulteren in een meer op maat gemaakte behandeling, gepaard gaand met een betere kwaliteit van leven en een verlaging van de zorgkosten.

Hoofdstuk 3. Restadiërings-CT tijdens neoadjuvante chemotherapie

De toegevoegde waarde van restadiërings-CT werd geëvalueerd na 2 van de 3 neoadjuvante chemotherapiecycli (MAGIC-regime). Een multicenter beoordeling van behandelingswijzigingen op basis van restadiërings-CT toonde aan dat metastasen en tumorprogressie werden gevonden bij respectievelijk slechts 1% en 7% van de patiënten, resulterend in een behandelingswijzigingen, zoals annulering van chirurgische resectie of een aanpassing van het chemotherapieregime. Bij 3% van de patiënten werden metastasen op afstand niet geïdentificeerd door de restadiërings-CT, resulterend in een futiele laparotomie. Deze bevindingen geven aan dat een restadiërings-CT een beperkte impact heeft op de klinische besluitvorming.

Hoofdstuk 4. Implementatie van FDG-PET/CT en stadiëringslaparoscopie

Na opname in de Nederlandse richtlijnen, werd de implementatie van FDG-PET/CT en stadiëringslaparoscopie en hun associatie met logistiek en het aantal niet-curatieve procedures bestudeerd. Deze landelijke vergelijking toonde aan dat het gebruik van FDG-PET/CT en stadiëringslaparoscopie van ongeveer 20% naar 60% steeg na introductie in de richtlijnen. Beide modaliteiten waren geassocieerd met extra wachttijd tot de start van de behandeling, maar hadden geen invloed op het aantal niet-curatieve procedures. Deze resultaten laten zien dat de implementatie van het gebruik van beide modaliteiten tijdens de onderzoeksperiode succesvol is gestart, maar dat er nog ruimte is voor verbetering wat betreft wachttijden.

Hoofdstuk 5. PLASTIC-studie: resultaten

Dit hoofdstuk beschrijft de resultaten van de PLASTIC-studie, waarvan het protocol is gepresenteerd in hoofdstuk 2. Het percentage patiënten bij wie de intentie van de behandeling veranderde op basis van de toevoeging van FDG-PET/CT en stadiëringslaparoscopie aan het stadiëringsproces werd onderzocht. Deze multicenter prospectieve observationele studie wees uit dat FDG-PET/CT een beperkte toegevoegde waarde heeft, waarbij metastasen op afstand slechts bij 3% van de patiënten worden gedetecteerd, maar secundaire bevindingen bij 20% van de patiënten. Aan de andere kant draagt stadiëringslaparoscopie aanzienlijk bij aan nauwkeurige

stadiëring, door gemetastaseerde of niet-resectabele ziekte te detecteren bij 19% van de patiënten, waardoor een significante bijdrage wordt geleverd aan het veranderen van de intentie van de behandeling. Op basis van de resultaten van de PLASTIC-studie zouden richtlijnen voor de stadiëring van gevorderde maagkanker stadiëringslaparoscopie moeten omvatten, terwijl het routinematige gebruik van FDG-PET/CT niet wordt ondersteund.

Deel 2. Chirurgische behandeling

Hoofdstuk 6. Maagkankerchirurgie wereldwijd

Dit internationale onderzoek onder chirurgen analyseerde de wereldwijde status van de chirurgische behandeling van maagkanker in 2019 en bracht veranderingen aan het licht ten opzichte van een eerder onderzoek in 2014. In tegenstelling tot het vorige onderzoek gaf de meerderheid van de chirurgen de voorkeur aan een minimaal invasieve benadering voor vroege maagkanker en aan een open benadering bij vergevorderde kanker. In vergelijking met het onderzoek van 2014 hadden perioperatieve chemotherapie en een D2-lymfadenectomie vaker de voorkeur. Deze resultaten weerspiegelen wereldwijde trends in de behandeling van maagkanker.

Hoofdstuk 7. Behandeling van diffuus type maagkanker

In dit hoofdstuk werd overleving vergeleken tussen patiënten met diffuus type maagkanker of kanker ter plaatse van de gastro-oesofageale overgang die primaire chirurgie of neoadjuvante chemo(radio)therapie plus chirurgie ondergingen. Deze landelijke cohortstudie wees uit dat neoadjuvante chemotherapie plus chirurgie voor zowel maag- als gastro-oesofageale overgangskanker geassocieerd was met een betere overleving in vergelijking met alleen chirurgie. Bovendien was de behandeling van gastro-oesofageale overgangskanker in ziekenhuizen met een hoog volume geassocieerd met betere resultaten. Deze bevindingen geven aan dat neoadjuvante chemotherapie moet worden aanbevolen en dat verdere centralisatie van de behandeling van deze tumoren wordt aanbevolen.

Hoofdstuk 8. Ongepland uitblijven van resectie na neoadjuvante chemotherapie

Neoadjuvante chemotherapie is niet zonder risico op complicaties. De resultaten in dit hoofdstuk laten zien dat bij 11% van de patiënten die zijn gestart met neoadjuvante chemotherapie chirurgische resectie niet doorging. Ziekteprogressie en mortaliteit tijdens of

binnen 30 dagen na beëindiging van chemotherapie waren de meest voorkomende redenen voor het uitblijven van de maagresectie. Deze studie benadrukt het belang van zorgvuldige patiëntselectie voor neoadjuvante chemotherapie.

Hoofdstuk 9. Afzien van resectie bij potentieel curabele maagkanker

In dit hoofdstuk worden redenen om af te zien van maagresectie bij potentieel curabele maagkanker onderzocht. Uit deze studie bleek dat 33% van de patiënten met potentieel curabele maagkanker geen maagresectie onderging. De meest voorkomende geregistreerde redenen waren weigering door de patiënt, klinische conditie, comorbiditeit en uitgebreidheid van de ziekte. Bovendien werden hogere leeftijd, lagere sociaaleconomische status en slechte tumorkenmerken geïdentificeerd als geassocieerde factoren. Deze resultaten kunnen een weerspiegeling zijn van gedeelde besluitvorming, patiëntselectie en praktijkvariatie tussen ziekenhuizen.

Hoofdstuk 10. Minimaal invasieve chirurgie: totale versus distale maagresectie

De introductie van minimaal invasieve totale en distale maagresectie, twee chirurgische procedures met verschillende complexiteit, werden geëvalueerd. In deze studie met landelijke data toonden propensity score matched analyses aan dat de voordelen van minimaal invasieve chirurgie werden aangetoond voor distale maagresectie, maar niet voor totale maagresectie. De resultaten van deze studie suggereren dat verdere centralisatie van maagkankerchirurgie moet worden overwogen, aangezien mogelijk langere leercurven voor minimaal invasieve totale maagresectie waarschijnlijk lijken.

Hoofdstuk 11. Minimaal invasieve chirurgie: gastrointestinale stromale tumoren

De veiligheid en haalbaarheid van minimaal invasieve resectie van grote (>5 cm) gastro-intestinale stromale tumoren van de maag in het Universitair Medisch Centrum Utrecht werden beoordeeld. Intra- en postoperatieve complicaties waren acceptabel en bij 96% werd een R0-resectie bereikt. Deze resultaten geven aan dat minimaal invasieve chirurgie zorgt voor gecontroleerde en oncologisch volledige resectie van grote gastro-intestinale stromale tumoren van de maag.

Hoofdstuk 12. Minimaal invasieve chirurgie: klinisch meest relevante postoperatieve complicaties

Het doel van dit nationale onderzoek was om de klinisch meest relevante complicaties na maagresectie te identificeren. Door gebruik te maken van de populatie-attributieve fractie (PAF), bleken naadlekkage en pulmonale complicaties de grootste algehele impact te hebben op de meeste vooraf gedefinieerde uitkomsten, zoals sterfte. Ook intra-abdominale abcessen en wondinfecties hadden een grote impact op de uitkomsten. Deze resultaten geven richting aan waar chirurgische kwaliteitsverbeteringsprogramma's zich op zouden moeten richten.

Hoofdstuk 13. Non-curatieve maagresectie

Postoperatieve morbiditeit en mortaliteit bij patiënten die een niet-curatieve maagresectie ondergingen, werden vergeleken met een beoogde curatieve maagresectie. Na het creëren van twee vergelijkbare groepen met propensity score matching, verschilden postoperatieve mortaliteit, morbiditeit, re-interventies en heropnamepercentages niet significant tussen beide groepen. Deze bevindingen suggereren dat, na kritische evaluatie, niet-curatieve maagresectie vaker kan worden overwogen bij fitte patiënten.

Conclusie

In dit proefschrift werden verschillende aspecten van preoperatieve stadiëring en van chirurgische behandeling van maagkanker onderzocht. Hierbij lag de nadruk op FDG-PET/CT en stadiëringslaparoscopie en minimaal invasieve chirurgie. Er werd aangetoond dat er weinig toegevoegde waarde is van FDG-PET/CT aan het stadiëringsproces, maar dat laparoscopie een significante bijdrage levert door detectie van metastasen en daarmee het voorkomen van onnodige chirurgie. Bij sommige patiënten met maagkanker wordt afgezien van chirurgie vanwege de wens van de patiënt of de klinische conditie, maar ook ziekteprogressie en mortaliteit tijdens neoadjuvante behandeling zijn belangrijke factoren. Patiënten die wel een operatie ondergaan, hebben baat bij minimaal invasieve chirurgie, waarbij postoperatief optredende naadlekkage en pulmonale complicaties de grootste impact op bepaalde uitkomsten hebben. Het onderzoek in dit proefschrift draagt bij aan een meer op maat gemaakte behandeling voor patiënten met maagkanker.

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Beoordelingscommissie

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LIST OF PUBLICATIONS

1. AC van Riel, RH de Bruin-Bon, **EC Gertsen**, IM Blok, BJM Mulder, BJ Bouma. Simple stress echocardiography unmasks early pulmonary vascular disease in adult congenital heart disease. International Journal of Cardiology. 2015;197:312-314.
2. SG Ellesøe, CT Workman, P Bouvagnet, CA Loffredo, KL McBride, RB Hinton, K van Engelen, **EC Gertsen**, BJM Mulder, AV Postma, RH Anderson, VE Hjortdal, S Brunak and LA Larsen. Familial co-occurrence of congenital heart defectsfollows distinct patterns. Eur. Heart Journal. 2017;00:1–8.
3. HJF Brenkman, **EC Gertsen**, E Vegt, R van Hillegersberg (…), PD Siersema, JP Ruurda, on behalf of the PLASTIC study group. Evaluation of PET and Laparoscopy in STagIng advanced gastric Cancer: a multicenter prospective study (PLASTIC-study). BMC Cancer. 2018;18:450.
4. **EC Gertsen**, HJF Brenkman, E Vegt, R van Hillegersberg, PD Siersema, JP Ruurda. FDG-PET/CT en stadiëringslaparoscopie bij maagcarcinoom. Ned. Tijdsch Oncol 2018;15:155-8.
5. MJ van der Poel, PJ Tanis, HA Marsman, AM Rijken, **EC Gertsen**, S Ovaere, MF Gerhards, MG Besselink, M D'Hondt, PD Gobardhan. Laparoscopic combined resection of liver metastases and colorectal cancer: a multicenter, case-matched study using propensity scores. Surg Endosc. 2019;33:1124-1130.
6. **EC Gertsen**, HJF Brenkman, MFJ Seesing, L Goense, JP Ruurda, R van Hillegersberg, on behalf of the Dutch Upper Gastrointestinal Cancer Audit (DUCA) group. The introduction of minimally invasive surgery for distal and total gastrectomy: a propensity score matched analysis. Eur J Surg Oncol. 2019;45:403-409.
7. **EC Gertsen**, L Goense, HJF Brenkman, R van Hillegersberg, JP Ruurda, on behalf of the Dutch Upper Gastrointestinal Cancer Audit (DUCA) group. Identification of the clinically most relevant postoperative complications after gastrectomy: a population-based cohort study. Gastric Cancer. 2020 Mar;23(2):339-348.
8. **EC Gertsen**, C de Jongh, HJF Brenkman, AC Mertens, IAMJ Broeders, M Los, D Boerma, D ten Bokkel Huinink, L van Leeuwen, FJ Wessels, R van Hillegersberg, JP Ruurda. The added value of a restaging-CT during neoadjuvant chemotherapy for gastric cancer. Eur J Surg Oncol. 2020 Jul;46(7):1247-1253.
9. **EC Gertsen**, HJF Brenkman, L Goense, N Haj Mohammad, BLA Weusten, R van Hillegersberg, JP Ruurda, on behalf of the Dutch Upper Gastrointestinal Cancer Audit (DUCA) group. Non-curative gastrectomy for advanced gastric cancer does not result in additional risk of postoperative morbidity compared to curative gastrectomy. Surg Oncol. 2020 Dec;35:126-131.
10. **EC Gertsen**, G van Boxel, LAA Brosens, JP Ruurda, R van Hillegersberg. Minimally invasive surgery: also possible for large gastric gastrointestinal stromal tumors. Dig Surg. 2020;37(6):441-446.
11. **EC Gertsen**, AS Borggreve, HJF Brenkman, E Vegt, R Verhoeven, R van Hillegersberg, PD Siersema, JP Ruurda. Evaluation of the implementation of FDG-PET/CT and staging laparoscopy for gastric cancer. Ann Surg Oncol. 2020; 28(4):2384-2393.
12. **EC Gertsen**, HJF Brenkman, LAA Brosens, JCHBM Luijten, N Haj Mohammad, RHA Verhoeven, R van Hillegersberg, JP Ruurda. Refraining from resection in patients with potentially curable gastric carcinoma. Eur J Surg Oncol. 2020 Oct 22:S0748-7983(20)30862-3.
13. **EC Gertsen**, HJF Brenkman, L Haverkamp, M Read, JP Ruurda, R van Hillegersberg. Worldwide practice in gastric cancer surgery: a 6-year update. Digestive Surgery 2021; 38(4):266-274.
14. **EC Gertsen**, HJF Brenkman, R van Hillegersberg (…), E Vegt, PD Siersema, JP Ruurda. FDG-PET/CT and laparoscopy for staging of locally advanced gastric cancer: a multicenter prospective Dutch cohort study (PLASTIC). JAMA Surgery 2021 Dec 1;156(12):e215340.

CURRICULUM VITAE

Emma Claire Gertsen was born on the 25th of July 1989 in Rotterdam, The Netherlands. During her childhood she grew up at the beach in Noordwijk and graduated from the Rijnlands Lyceum in Oegstgeest (profile Culture and Society). Due to an incompatible high school profile, she had to reeducate to profile Nature and Health, which she completed in 2008 at the ROC in Leiden. For her Bachelor and Master studies Medicine starting in 2008 at the University of Amsterdam, she moved to Amsterdam in 2009 where she was an active member of several student organizations. During her studies she did an additional clerkship at the Department of Surgery in the Groote Schuur Hospital in Cape Town, South Africa. Emma's first employment was in 2016 at the Department of Surgery in Onze Lieve Vrouwe Gasthuis in Amsterdam as a resident not in training.

In 2017 Emma started as a PhD candidate at the Department of Surgery of the University Medical Center Utrecht under the supervision of Prof. Dr. J.P. Ruurda and Prof. Dr. R. van Hillegersberg. Her PhD program focused on the staging and surgical treatment of patients with gastric cancer. In this capacity, she collaborated with numerous physicians and hospitals throughout the Netherlands conducting a prospective multicenter study (PLASTIC study), of which the results were recently published. She also delivered multiple scientific lectures at several congresses reaching from London to Seoul. Shortly after starting her PhD, she established her own company EMMD, working as a medical doctor performing medical examinations and on-call shifts. From September 2020 to August 2021 she worked as a resident not in training at Sint Antonius Hospital in Nieuwegein after which she transferred back to her hometown Amsterdam where she continued her residency at the Amsterdam University Medical Center.