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Stage-directed individualized therapy in esophageal cancer

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Esophageal cancer is the eighth most common cancer worldwide, and the incidence of esophageal carcinoma is rapidly increasing. With the advent of new staging and treatment techniques, esophageal cancer can now be managed through various strategies. A good understanding of the advances and limitations of new staging techniques and how these can guide in individualizing treatment is important to improve outcomes for esophageal cancer patients. This paper outlines the recent progress in staging and treatment of esophageal cancer, with particularly attention to endoscopic techniques for early-stage esophageal cancer, multimodality treatment for locally advanced esophageal cancer, assessment of response to neoadjuvant treatment, and the role of cervical lymph node dissection. Furthermore, advances in robot-assisted surgical techniques and postoperative recovery protocols that may further improve outcomes after esophagectomy are discussed.

Keywords: esophageal cancer; tumor staging; esophageal surgery; robot-assisted; neoadjuvant chemoradiation; anastomotic leakage

Introduction

Esophageal cancer is the eighth most prevalent cancer worldwide, and the incidence of esophageal carcinoma has increased rapidly over the past decades.[1,2] Historically, esophagectomy with *en bloc* lymphadenectomy has been the cornerstone of treatment with curative intent.[3] With advances in staging and treatment techniques, patients with esophageal cancer can now be cured using various treatment strategies. Currently, cancer stage and histologic subtype are increasingly being used to guide treatment in patients with esophageal cancer. The aim of this review is to summarize the most recent advances in esophageal cancer staging and treatment. First, the different methods for staging of esophageal tumors, regional lymph nodes, and distant metastases are discussed. Second, different stage-specific treatment strategies are outlined, such as the clinical introduction of novel endoscopic techniques for the treatment of early-stage esophageal cancer, as well as multimodality treatment for locally advanced esophageal cancer, and whether cervical lymph node dissection should be performed. Finally, the advances of robot-assisted surgical techniques and postoperative management after esophagectomy are discussed.

Clinical staging of esophageal carcinoma

One of the key concerns in the treatment of esophageal cancer is accurate staging of the extent of disease. This allows for prediction of prognosis and stage-directed individualized treatment to achieve the best possible outcomes. Staging of esophageal tumors consists of upper gastrointestinal endoscopy with biopsy to verify diagnosis, endoscopic ultrasonography (EUS) to obtain information on depth of tumor invasion and locoregional nodal disease, and positron emission tomography with integrated

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computed tomography (PET/CT) to evaluate locoregional spread and distant metastases.[4,5] In general, tumor stages are classified according to the 7th edition of the International Union Against Cancer tumor–node–metastasis classification.[6]

Tumor staging

In cases where esophageal cancer is clinically suspected, diagnosis should be confirmed by pathological examination. It is recommended that at least six biopsies be obtained from the tumor site for pathological examination.[7] EUS is the preferred diagnostic modality to assess depth of tumor invasion, as has been shown by a meta-analysis that reported pooled sensitivities and specificities for distinguishing different T stages of 81–92% and 85–99%, respectively.[8] However, it has been found that the diagnostic ability of EUS to distinguish T1 and T2 lesions is not as good as it is for more advanced lesions.[9] One study that specifically assessed T2N0 tumors found that 55% of patients with T2 disease were overstaged while 32% were understaged.[10] This may partially be explained by the significant learning curve that has been associated with EUS staging of esophageal cancer.[11] Therefore, it is recommended that EUS is performed by an experienced endoscopic ultrasonographer.[12] These are important considerations to take into account when tumor stage is used to guide therapy.

The ability to distinguish the different histologic layers of the esophageal wall by CT is limited, owing to poor contrast resolution.[13,14] However, CT is valuable for the exclusion of T4b tumors, which is indicated by the preservation of fat planes.[11,15] The addition of PET/CT scanning to the staging process of esophageal tumors has improved the ability to detect distant hematogenous metastases and is now recommended in most clinical practice guidelines worldwide.[16] A recent meta-analysis showed a pooled primary esophageal tumor detection rate of 93% with PET.[17] However, PET/CT currently has no role in T staging of esophageal tumors owing to the limited spatial resolution of PET, which especially limits identification of tumor infiltration depth and early-stage carcinomas with small volumes.[15,18]

Magnetic resonance imaging (MRI) is an imaging technology that has the potential to overcome the important limitations of conventional staging methods in the management of patients with esophageal cancer. However, the use of conventional MRI for the assessment of different stages is comparable to CT and therefore yields no additional information.[19,20] In this regard, another subject of note is the continuous technologic progress of PET/CT and MR image generation, and PET with integrated MRI has now been clinically introduced for esophageal cancer staging.[21,22] These developments may prove to play further important roles in preoperative esophageal cancer staging.

Lymph node staging

Locoregional lymph nodes include those that are involved in the sites of lymphatic drainage of the esophagus and are generally resected *en bloc* with the primary tumor during esophagectomy. In order to direct treatment decision making, preoperative lymph node staging is crucial, but the diagnostic accuracy has been poor so far. Inaccuracy has been indirectly demonstrated by the fact that pathological rather than clinical nodal stage is an independent prognostic factor for overall survival.[23]

Diagnostic modalities to determine the presence of lymph node metastases include EUS, CT, PET/CT, and ultrasonography of the neck. Unfortunately, all techniques have their limitations. CT scanning has limited diagnostic performance due to its inability to detect metastases in normal-sized lymph nodes, and lymph node enlargement due to inflammation may result in false-positive diagnosis.[24,25] According to a recent meta-analysis, the role of PET/CT is relatively limited owing to a low sensitivity of 55% (range 34–74%) for the detection of locoregional lymph node metastases.[26] However, PET has a high reported specificity of 96% (range 93–98%) in a per-lesion analysis.[26] However, reported specificities were not that high in two other meta-analyses.[16,24] EUS is more sensitive (80%, range 75–84%) compared with PET/CT in the assessment of locoregional nodal metastases and is therefore the preferred modality for lymph node staging.[24] Moreover, EUS has the added benefit over PET/CT of allowing fine-needle aspiration of suspicious lymph nodes during the diagnostic procedure. However, EUS cannot visualize lymph nodes that are distant from the surrounding of the esophagus, and it is not feasible in the case of tumor stenosis.[27] Therefore, clinical N stage should not be determined on the basis of abnormal-appearing regional lymph nodes on EUS only. The higher specificity of PET/CT can support the role of EUS in this regard, although the diagnostic accuracy of both modalities combined remains unsatisfactory.[24]

For staging of esophageal cancer, the use of external ultrasonography of the neck is still recommended, since this is an accurate method to detect cervical metastases.[28] However, since the introduction of PET/CT, the additional role of external ultrasonography to detect cervical lymph node metastases in esophageal cancer staging may be limited. This is suggested by two large series that found no additional value of external ultrasonography over PET/CT with regard to the detection of cervical lymph node metastases.[29,30] Only one study has shown an additional value of 4% (3/74) of external ultrasonography over CT and PET imaging.[31] However, in the latter study, the CT and PET scans were performed separately, which may yield lower diagnostic accuracy compared with integrated PET/CT scanning.[31] This implies that external ultrasonography may be omitted in the standard workup of patients with esophageal cancer. However, histopathologic confirmation in PET/CT-suspected lesions remains required because of potential false-positive lesions.[32]

M staging

Distant metastases are frequently present at initial staging in esophageal cancer patients. Recently, many studies have shown that PET/CT allows for detection of metastases beyond those covered with conventional staging.[19] In a meta-analysis, the reported sensitivity and specificity for distant metastases identified with PET were 67% (95% confidence interval (CI): 58–76) and 97% (95% CI: 90–100), respectively.[16] In this regard, adding PET to the conventional staging process (including CT) leads to changes in patient management in 3–20% of patients.[33–36] Therefore, a diagnostic PET/CT is clinically valuable and most likely cost effective, as it can prevent a noncurative surgical procedure by detecting distant metastases.[37]

Since neoadjuvant chemoradiotherapy (nCRT) followed by surgery is increasingly applied as treatment with curative intent for patients with resectable esophageal cancer, restaging after neoadjuvant treatment is increasingly important. Distant metastases may manifest during neoadjuvant treatment, which implies that curative treatment is no longer possible.[38] Several studies have assessed the utility of PET/CT for detecting interval metastases, which occurred in 8–17% of patients.[39–41] Therefore, most of these studies recommend a restaging PET/CT in patients eligible for surgery.

Stage-directed individualized therapy

Treatment for early-stage tumors

Early-stage esophageal cancer comprises high-grade dysplasia (Tis) and mucosal (T1a) and submucosal cancer (T1b).[6] Endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) have become attractive procedures as both diagnostic and therapeutic modalities for the management of early-stage adenocarcinoma or squamous cell carcinoma of the esophagus.[42] Both techniques are able to achieve margin-negative resection of tumors while avoiding an invasive esophagectomy and allowing preservation of the esophagus, without compromising survival, in a selected group of patients.[43–45] After endoscopic resection, reclassification of tumor stage occurs in between 39% and 53% of the cases. [46] This is probably caused by biopsy sampling failure, limited quality of the biopsy sample, and misinterpretation of the muscular anatomy by the pathologist.[46]

Although early-stage tumors carry a relatively low risk of lymph node involvement, this risk cannot be excluded, owing to lymphatic involvement in the muscularis mucosa.[47] According to previous reports, the proportion of lymph node metastases in T1 esophageal tumors is different between cases with mucosal and submucosal cancer.[48–50] Incidence rates of nodal metastases for patients with mucosal T1a tumors range between 3% and 7%,[51] while in patients with submucosal involvement the incidence of metastases can reach 30%.[48,52,53] Moreover, the depths of submucosal tumor invasion and lymphovascular invasion have been reported as strong independent predictors for lymph node metastases.[46,51,54]

Given the poor prognosis of patients with lymph node metastases, it is essential to recognize patients with early-stage esophageal cancer who are at high risk of lymph node involvement. In this regard, for patients in whom the risk of lymph node metastases is high after EMR or ESD (deep submucosal tumor invasion and lymphovascular invasion), treatment with esophagectomy and adequate lymphadenectomy is recommended.[51]

According to a recent meta-analysis, there is little difference between EMR and ESD with regard to procedural complications, number of patients requiring surgery, positive resection margins, lymph node recurrence, and local recurrences. However, an advantage of ESD is its ability to achieve *en bloc* resection, thereby avoiding piecemeal resections.[46,55] However, it has been suggested that this comes at the cost of an increased risk of perforation, bleeding, and a longer procedure time.[44]

Treatment for T2N0 tumors

Although a multimodality treatment approach is increasingly recommended for patients with locally advanced esophageal cancer, clinical T2N0 esophageal cancer represents a unique challenge with regard to appropriate treatment selection. T2N0 esophageal cancer is an early-stage disease with tumor infiltration beyond the submucosa, and therefore it carries a high risk of nodal disease.[56] One of the concerns of treating patients with T2N0 esophageal cancer is that clinical staging is often inaccurate and the presence of occult nodal disease is missed. Despite advances in staging techniques, understaging rates between 25% and 68% have been reported for patients with cT2N0 esophageal cancer undergoing surgery only.[10,56–61]

Owing to the risk of nodal disease and concerns regarding the reliability of current clinical staging techniques, a multimodality treatment approach is recommended by some studies in cT2N0 esophageal cancer patients.[59,62] However, so far most studies have failed to prove a survival benefit for a multimodality treatment approach compared with a surgery-alone approach for early-stage esophageal tumors.[59,62] This was confirmed by a recently conducted randomized controlled trial (RCT) and a large retrospective propensity score–matched study.[60,61] The latter study showed that, despite understaging of lymph nodes (50%), patients in the surgery-alone group achieved an overall survival and recurrence rate comparable to a multimodality treatment approach.[60] A disadvantage of neoadjuvant therapies is the associated toxicity, which may negatively affect quality of life and can contribute to an increase in postoperative morbidity and mortality.[61,63–65] Therefore, it has been suggested that a multimodality approach for patients with T2N0 disease on the basis of clinical understaging is not the appropriate strategy for these patients.[60]

On the other hand, several studies have provided evidence that the benefit of nCRT may be most advantageous in small tumors with regard to achievement of a pathologic complete response (pCR).[66,67] Currently, different diagnostic modalities are being assessed to determine the accuracy by which a pCR can be detected, with the goal of eventually studying the feasibility and outcome of a tailored treatment algorithm in which complete responders could be offered close clinical follow-up instead of esophagectomy.[68,69] Routine use of a surgery-alone approach could deprive patients of the opportunity for organ-preservation strategies.

Treatment of locally advanced esophageal cancer

The most favorable therapy for locally advanced esophageal and gastroesophageal junction (GEJ) cancer (i.e., cT1b-N1, cT2-3Nx) remains a subject of active debate. Resection of the esophagus with *en bloc* lymphadenectomy remains the cornerstone of curative treatment for these patients.[3]

A multimodality treatment approach is increasingly applied since both perioperative chemotherapy (pCT) and nCRT have demonstrated a survival advantage over surgery alone.[70–74] However, according to a meta-analysis, the beneficial effect of pCT for patients with squamous cell carcinoma (hazard ratio (HR): 0.92 (95% CI: 0.81–1.04); $P = 0.18$) appears limited.[70] In the same meta-analysis, nCRT proved beneficial for squamous cell carcinoma (HR: 0.80 (95% CI: 0.68–0.93); $P = 0.004$).[70] This result was confirmed by the CROSS trial, in which nCRT followed by surgery was compared with surgery alone in 360 EUS-staged patients with esophageal squamous cell carcinoma and adenocarcinoma.[75] This trial reported significantly improved R0 resection rates and improved overall survival and achieved a higher rate of pCR, favoring the multimodality group. The results were found to be clinically relevant for both squamous cell carcinoma (HR overall survival: 0.48 (95% CI: 0.28–0.83); $P = 0.008$) and adenocarcinoma (HR overall survival: 0.73 (95% CI: 0.55–0.98); $P = 0.038$).[71] Therefore, nCRT followed by radical surgery can be considered the preferred treatment for patients with locally advanced squamous cell carcinoma of the esophagus.

The optimal perioperative therapy for locally advanced esophageal or GEJ adenocarcinoma has not yet been established.[61,70,76] Two meta-analyses have suggested a greater survival benefit of nCRT over pCT.[70,73] However, in both meta-analyses, indirect treatment comparisons were applied, and the difference between the two groups did not reach statistical significance. Three studies have made an attempt to directly compare nCRT with pCT for patients with esophageal or GEJ adenocarcinoma in RCTs.[77–79] In these trials, CRT achieved significantly higher rates of pCR (13–28% in the nCRT groups versus 0–9% in the pCT groups).[77–79] Results with regard to R0 resection rates were inconsistent, and none of the trials reported a difference in survival and recurrent disease between the two multimodality treatment arms.[77–79] It is essential to point out that these RCTs were insufficiently powered to identify possible subtle survival differences between the two perioperative treatment arms. Currently, different randomized trials comparing pCT and nCRT regimens are being carried out and should resolve limitations in the current literature (CROSS versus MAGIC (NCT01726452), Neoscope-trial (NCT01843829), TOPGEAR-trial (NCT01924819)).[80,81]

Response prediction

The degree of pathologic response to nCRT is an important new determinant of prognosis and is key to more individualized multimodality treatment for patients with locally advanced esophageal cancer.[82,83] Poorly responding patients may benefit from treatment intensification/modification or primary surgery without nCRT. On the other hand, in patients with a pCR, a wait-and-see policy, including omission of surgery and close clinical follow-up, may be preferable in some cases. Patients with a good but incomplete response to nCRT (i.e., microscopic residual disease) most likely represent the group that truly benefits from both nCRT and surgery. Therefore, seeking powerful tools for predicting response to nCRT for esophageal cancer is an important focus of modern research, with the ultimate aim of tailoring treatment to the individual patient.

A recent meta-analysis including 12 studies reported that endoscopic biopsy results after nCRT appear negative in 91% (95% CI: 86–95) of patients with a true pCR, but also in 65% (95% CI: 56–74) of patients with residual cancer.[84] A meta-analysis including 20 studies reported that ^{18}F-FDG PET before and (during or) after nCRT clinically predicts a poor response in 68% (95% CI: 64–73) of pathologic poor responders, but also in 33% (95% CI: 28–38) of pathologic good responders.[85] Therefore, although posttreatment endoscopic biopsy and sequential ^{18}F-FDG PET scanning are moderately predictive for pathologic response, these modalities are not reliable enough to guide tailored-treatment decision making.[66]

Various opportunities for improvement in treatment response prediction are currently under investigation. In order to improve the sensitivity of endoscopic biopsy after nCRT, extensive sampling protocols and deeper bite-on-bite submucosal biopsies have recently been suggested.[86] Response evaluation with ^{18}F-FDG PET might be improved by extending the time period from the end of nCRT, because, after 12 or more weeks, the artifacts attributable to radiation-induced inflammation are expected to have largely dissolved.[68] In addition, diffusion-weighted MRI may prove useful for response prediction, as recent pilot studies have shown promising results.[69,87] Future efforts should include large, high-quality studies focusing on multimodality (rather than single-modality) approaches and standardization of techniques to ultimately provide sufficient and generalizable predictive ability to safely guide tailored-treatment decision making.

Treatment of T4b tumors

Esophageal tumors invading structures, such as the aorta and trachea (T4b), have historically been considered as unresectable, and guidelines recommend definitive chemoradiotherapy (dCRT) as the treatment of choice.[28,88,89] The oncologic results of dCRT have been acceptable, with reported 5-year survival rates of approximately 20–25%.[90,91] However, locoregional recurrence at the site of the primary tumor occurs in 41% of patients after dCRT for unresectable esophageal cancer.[92] Furthermore, esophageal stenosis and perforations occur in approximately 25% of patients after dCRT and are often associated with a fatal outcome.[92]

For patients with recurrent or persistent esophageal cancer after completed dCRT, salvage surgery has been proposed as a rescue procedure. A recent meta-analysis demonstrated a survival benefit of salvage surgery over second-line CRT.[93] However, salvage surgery is often accompanied by increased morbidity and treatment-related mortality.[93] The poor results of dCRT in unresectable cT4 tumors and the morbidity of salvage surgery following dCRT have led to the hypothesis that planned surgery after induction CRT may be a reasonable alternative. In this regard, recent studies have shown that it is feasible to perform a radical resection, while preserving vital organs (trachea and aorta), in patients with tumor response to induction treatment.[94,95] However, radical esophagectomy after induction therapy in these patients has been associated with a higher risk of in-hospital mortality.[94] Nonetheless, reported R0 resection rates range between 61% and 88%.[94,95] As this is a rather new strategy, identifying prognostic indicators for R0 resections could contribute to a better selection of appropriate candidates for esophagectomy after induction therapy in patients with initially unresectable cT4 tumors, although secondary radical esophagectomy after induction therapy has been associated with a higher risk of in-hospital mortality.[94]

Cervical lymph node metastases

Historically, there has been much debate regarding the optimal type of lymphadenectomy for resectable esophageal cancer, particularly with regard to whether an extended lymphadenectomy improves survival at the cost of a possible increased morbidity.[96] In Asian countries, esophagectomy is commonly combined with a three-field lymphadenectomy, as evidence supports that 20–40% of the patients with squamous cell carcinoma have unforeseen lymph node metastases in the cervical region.[97–99] However, most surgeons in North America and Europe have been reluctant to adopt this strategy, as most cancers occur in the distal esophagus and GEJ, in which less cervical lymph node metastases occur, and because of fear for increased postoperative morbidity.[100] Moreover, for patients without proven cervical metastases, it has been suggested that two-field lymphadenectomy is sufficient, since it can dissect recurrent nerve chain lymph nodes in the upper mediastinum up to the cervical region, achieve the same oncologic outcomes, and result in easier perioperative management.[101,102]

Recently, two meta-analyses were conducted that compared three-field versus two-field lymphadenectomy strategies including patients with or without cervical lymph node metastases.[103,104] Both studies concluded that a three-field approach significantly improves overall survival (HR: 0.64; 95% CI: 0.56–0.73; $P < 0.001$ and relative risk (RR): 1.37; 95% CI: 1.18–1.59; $P < 0.01$), at the cost of a higher prevalence of anastomotic leakage (HR: 1.46; 95% CI: 1.19–1.79; $P < 0.001$) and recurrent nerve paresis (RR: 1.43; 95% CI: 1.28–1.60; $P = 0.02$).[103,104] However, both meta-analyses included a heterogeneous group of retrospective case series with a paucity of large-sample prospective studies.[103,104] As the quality of a meta-analysis reflects that of the constituent studies, the current evidence suffers from the inherent drawbacks of combining data from nonrandomized case series. In this regard, there are currently different randomized trials underway comparing a two-field versus a three-field approach, which should resolve the limitations in the current literature (NCT00193817 ($n = 700$) and NCT01807936 ($n = 400$)).

Some physicians argue that the presence of cervical lymph node metastases equals systemic disease and that survival will not increase despite removal of these lymph nodes. For others, the presence of lymph node involvement—even at a distance from the primary tumor—–justifies an aggressive approach with radical esophagectomy combined with a three-field lymphadenectomy.[97] So far, several studies have presented the results of esophagectomy with three-field lymphadenectomy in patients positive for cervical lymph node metastases. In these studies, the 5-year overall survival rates after esophagectomy ranged from 13% to 42%.[105–107] These results suggest that a resection with three-field lymphadenectomy with curative intent may be feasible for patients with positive cervical lymph node metastases.[108] Caveats include heterogeneity among studies with regard to tumor type, (neo)adjuvant treatment strategies, and study design. Other studies have suggested beneficial effects of CRT with regard to survival of cervical lymph node metastases from esophageal squamous cell carcinoma.[109,110] In North American and European countries, different palliative treatment strategies are widely applied for patients with cervical lymph node metastases. The lack of prospective randomized studies to determine the optimal treatment strategy for patients with positive cervical lymph nodes at initial staging makes it difficult to issue treatment recommendations.

Sentinel node concept

As noted earlier in this review, staging modalities have limited diagnostic accuracy with regard to lymphatic involvement in esophageal cancer patients.

Therefore, during transthoracic esophagectomy, an extensive mediastinal and upper abdominal lymph node dissection is performed to clear all possible metastatic disease. However, the extent of lymphadenectomy during esophagectomy in patients with esophageal cancer has been associated with increased postoperative morbidity.[111] For patients without tumor-positive lymph nodes in the resected specimen, the extensive lymphadenectomy may be regarded as redundant. In these patients, morbidity could be limited by tailoring the extent of lymph node dissection. It was hypothesized that this could be accomplished by the application of sentinel node identification and mapping in order to guide the extent of lymphadenectomy.[112]

In esophageal cancer, sentinel node identification by radioactive tracer was first reported by Kitagawa *et al.* in 2000.[113] In the following years, several other clinical studies on this subject were performed, mainly in Japanese institutes.[114–117] In a recent meta-analysis, different methods for esophageal sentinel node identification were assessed (i.e., radionuclide, blue dye, and CT lymphography). The pooled accuracies using technetium-99, blue-dye, and CT lymphoscintigraphy were 90% (95% CI: 74–97), 79% (95% CI: 68–87), and 90% (95% CI: 74–97), respectively.[118] The calculated sensitivities of all techniques in this systematic review were below 90%, which represents the main limitation for clinical implementation of this concept in esophageal surgery.[118]

The relatively high false-negative rate in sentinel node mapping for esophageal cancer is partially caused by the complex lymphatic drainage of the esophagus, with widespread lymph-capillary networks.[119] Other limitations include the lack of universally approved radioactive tracers for clinical use, the need for an invasive procedure to inject the tracer, and the inability to distinguish positive nodes close to the primary tumor owing to the strong radioactive signal from the primary tumor.[120] Based on the current evidence, the sentinel node concept in esophageal cancer is technically feasible in early-stage disease. However, owing to the relatively high false-negative rate, there is currently insufficient evidence to support a wide introduction of sentinel node mapping into clinical practice. Therefore, further studies should focus on improving the value of sentinel node mapping before this concept could prove useful in the treatment of esophageal cancer patients.

Surgical techniques

Robotic surgery

Minimally invasive esophagectomy (MIE) has been shown to reduce surgical trauma compared with an open (transthoracic) approach, resulting in decreased morbidity and mortality.[121] Short-term oncologic results for MIE are comparable to those of open esophagectomy.[121] However, a minimally invasive approach for esophageal surgery is technically demanding.[122] Despite the advantages of a minimally invasive procedure, multiple MIE programs were stopped owing to safety issues and concern of the high technical complexity. Therefore, MIE is currently not routinely applied as standard procedure for patients with resectable esophageal cancer.[123]

Recently, robot-assisted minimally invasive esophagectomy (RAMIE) was introduced with the aim of reducing associated morbidity in patients after esophagectomy while enabling a safe and radical oncologic resection.[124–126] The potential benefit of robotic surgery lies with the easy manipulation and high-quality visualization compared with an MIE approach. A recent review reported on the growing experience with and interest in RAMIE.[127] Most included studies in this review emphasized the benefits of a stable and three-dimensional image. This allows for a "zoomed-in" focus on the operative field and enables a fine dissection of the esophagus and lymph nodes in a precise and accurate way, which is helpful when operating on moving structures in the mediastinum. During dissection of the esophagus in the chest, instruments have to reach deep into the thorax, and the fulcrum effect at the ribs might hamper smooth manipulation during conventional thoracoscopy.[125] Especially at the level of the thoracic inlet and toward the diaphragm, instruments tend to approach the operative field in a parallel manner, therefore compromising maneuverability. The advantages of robotic surgery eliminate these problems in manipulation and enable a dissection along the border of the superior vena cava and along the recurrent nerves.[127] Moreover, robotic surgery allows real-time fluorescence guidance, which may help to identify anatomic landmarks and judge vascularization of the gastric conduit.[128] This might further enhance oncologic results and reduce anastomotic leak rates.[129]

The first experiences with RAMIE demonstrated feasibility and safety with satisfying short-term oncologic results.[130] Long-term overall survival data have not yet been reported. The preliminary results of the RAMIE procedures reflect early adaptation, and therefore the complementary ability of robotic assistance to MIE has not yet been translated to solid end points.[127] Currently, the benefits of RAMIE do not yet outweigh the increased costs that are associated with this procedure. Therefore, RAMIE should for the moment be considered as an innovative surgery that offers potential benefits, but that needs to be established in clinical trials to justify the additional healthcare costs. Currently, an RCT comparing open esophagectomy with RAMIE is being executed.[131]

Cervical versus intrathoracic anastomosis

Following esophagectomy for cancer, restoration of the gastrointestinal tract is performed by gastric tube reconstruction with a cervical or intrathoracic esophagogastric anastomosis. Currently, both intrathoracic and cervical anastomoses are used worldwide, although there is an ongoing trend toward an increased use of intrathoracic anastomoses.[132] Performing a cervical anastomosis in general, and specifically for patients with multiple risk factors, has been associated with higher leakage rates when compared with an intrathoracic anastomosis in two recent meta-analyses (odds ratio (OR): 4.7; 95% CI: 1.6–13.9; $P = 0.005$ and OR: 3.43; 95% CI: 1.1–10.8; $P = 0.03$).[133,134] Possible explanations for this include less tissue ischemia with intrathoracic anastomosis due to the shorter length the blood supply must travel, a shorter gastric tube, or less traction on the anastomotic site of the intrathoracic anastomosis.[133–135] Furthermore, a recent meta-analysis showed that an intrathoracic anastomosis is associated with a reduced risk of recurrent laryngeal nerve trauma after esophagectomy.[133]

Many physicians accept the increased risk of leakage and recurrent nerve trauma that is associated with a cervical anastomosis because of wider oncologic resection margins and less dangerous complications in case of anastomotic leakage.[136] Cervical anastomotic leakages are associated with potentially life-threatening intrathoracic complications, including pleural empyema and mediastinal abscess.[137] Incidence rates of 44–62% have been reported for intrathoracic manifestation after cervical anastomotic leakage.[137–139] A recent meta-analysis showed that cervical and intrathoracic anastomoses are equally safe with regard to perioperative mortality and pulmonary complications.[133] Currently, there is no evidence to indicate that the additional esophageal resection in the neck reduces tumor recurrence or improves survival.[133,136] For late complications, such as anastomotic strictures, the location of the anastomosis per se does not seem to influence stricture rates, but rather the preferred anastomotic technique appears more significant (i.e., fewer for hand-sewn and linear stapled versus circular stapled).[140]

In general, studies comparing intrathoracic and cervical anastomosis after esophageal surgery have relatively small sample sizes and considerable variation with regard to surgical approach and technique. These limitations increase the need for further studies to more accurately determine possible differences between intrathoracic and cervical anastomoses.

Anastomotic leakage

Risk factors

Anastomotic leakage is a commonly encountered complication following esophageal resection and is associated with increased postoperative morbidity, length of hospital stay, and mortality.[75,141–143] Moreover, anastomotic leakage has been associated with reduced long-term cancer-specific survival following esophagectomy.[144] Despite improvements in surgical technique and perioperative care, the incidence of anastomotic leakage after esophagectomy remains relatively high (up to 30%).[75,141] Multiple factors, such as nCRT, anatomic site of anastomosis, diabetes mellitus, body mass index, age, coronary artery disease, hypertension, renal insufficiency, peripheral vascular disease, and smoking, have been reported to contribute to the risk of anastomotic leakage after esophagectomy.[135,145]

Identification of risk factors for anastomotic leakage after esophageal resection could assist in early diagnosis and subsequently confine the impact of this complication. Currently, accurate prediction of anastomotic leakage based on standard patient or treatment-related characteristics remains difficult. However, recently a retrospective cohort study identified atherosclerotic calcification of the thoracic aorta as determined by routine diagnostic

CT scans as a significant predictor for anastomotic leakage after esophagectomy.[146] Atherosclerotic calcification has also been associated with multiple cardiovascular risk factors that are also related to anastomotic leakage, such as age, diabetes, peripheral vascular disease, and renal dysfunction.[135] Therefore, scoring of calcification on a preoperative CT scan may aid in the recognition of high-risk patients for anastomotic leakage who have not yet been diagnosed with these typical risk factors and may have less obvious clinical manifestations.[147]

Identification of patients with an increased risk of anastomotic leakage may have considerable implications. When confronted with this knowledge preoperatively, the physical status of the patient to endure an anastomotic leak requires special attention. Furthermore, after surgery, these patients should be monitored intensively for signs of clinical deterioration. Also, these patients may benefit from drain amylase measurement and early assessment of the anastomosis with endoscopy before mediastinal manifestation or ischemia-associated sepsis becomes clinically apparent.[148] Endoscopy to detect anastomotic leakage following esophageal resection has been shown to be an accurate method to provide information on the condition of the gastric tube.[149,150] Therefore, adequate prediction of anastomotic leakage may aid in the selection of patients for whom endoscopy is deemed clinically relevant and could prevent an unnecessary and invasive endoscopy for a substantial number of patients.

Stent placement for anastomotic leakage

Anastomotic leakage following esophagectomy remains a complicated clinical situation. It has been suggested that 73% of the diagnosed anastomotic leaks result in adaptations of planned postoperative clinical management.[151] Historically, treatment for anastomotic leakage included aggressive surgical re-exploration with primary anastomotic repair or conservative treatment with drainage and intravenous broad-spectrum antibiotics, at the cost of high morbidity rates with subsequent prolonged hospital stay. The introduction of endoscopically placed self-expandable metallic or plastic stents has provided an alternative avenue for the treatment of this condition. [152]

In the hands of an experienced gastroenterologist or surgeon, placement of self-expandable stents is technically feasible, with most studies reporting 100% technical success rates.[152,153] Successful placement of a stent covering the anastomotic leak and preventing mediastinal spillage should eventually result in complete healing of the anastomotic dehiscence. A recent systematic review reported complete healing rates of 81%, with no significant difference in the healing rates between plastic and metallic stents.[152] Stents can be placed for a 4- to 8-week period of time, which will give sufficient time for healing of most anastomotic leaks, and should then be removed.[154]

However, a few caveats should be acknowledged. First, for an esophagogastric anastomosis (gastric pull-through) the gastric conduit must be nonangulated and viable.[155] Second, placement of a stent is technically difficult for high anastomoses (within 2 cm of the cricopharyngeus muscle) and will result in an intolerable foreign body sensation.[155] Moreover, stent migration has been reported in 20–40% of cases, and stent removal may cause disruption of the healed mucosa, resulting in recurrence of the anastomotic leak.[151,152] In general, endoscopic management of esophageal anastomotic leakage with the use of stents has been shown to be technically feasible and effective. Therefore, esophageal stenting may be considered as a therapeutic option in patients with anastomotic leakage with limited mediastinal spillage.[151,152]

Enhanced recovery after esophagectomy

Enhanced recovery after surgery (ERAS) is a multimodal treatment strategy that is effective in various types of gastrointestinal surgery.[156] Important aspects of ERAS include minimally invasive surgery, early start of oral intake, and early postoperative mobilization. Although many ERAS elements have been introduced in esophageal surgery, early start of oral intake remains a matter of debate.[157,158] Fear of increased pulmonary complications due to aspiration and aggravation of anastomotic leakage are the primary arguments for delaying oral intake following esophagectomy.[159] Several (enteral) routes have been developed, such as a surgically placed jejunostomy or nasojejunal tube, to overcome the nil-by-mouth period following esophagectomy and to ensure adequate nutritional support.[158] It is still unclear whether the amount of (tube) feeding during the first postoperative days influences outcome.[159] Often, less than half of the mean nutritional requirement has been met on the eighth postoperative day, and patients have significant weight loss (8 kg) at 6 months postoperatively, despite jejunostomy tube feeding.[160,161] Weight loss even persists up to 3 years postoperatively and mainly occurs when tube feeding is stopped.[162]

Only three studies investigating early oral intake have included patients undergoing esophagectomy. Lassen *et al.*[163] showed that early oral intake following upper gastrointestinal surgery reduced the duration of hospital admission without an increase in postoperative morbidity. However, only a few patients who underwent an esophagectomy were included (2%).[163] A recent randomized trial by Mahmoodzadeh *et al.*[164] showed that early oral intake was safe and accelerated recovery. However, a substantial number of these patients underwent gastric surgery (34%), and the results were subjected to selection bias.[164] Another study only included patients undergoing esophagectomy and showed faster postoperative gastric emptying.[165]

In contrast, some retrospective cohort studies suggest that prolonged delay of oral intake (even up to 4 weeks) reduces anastomotic leakage rates and improves recovery.[166,167] However, these studies included small numbers of patients and have a retrospective character in which other factors in the postoperative protocol were changed as well. Therefore, more research is needed to assess the feasibility and safety of immediate oral intake following esophagectomy.[168]

Conclusions and future directions

It is now generally accepted that adequate staging is important for the guidance of treatment decisions in patients with esophageal cancer. A good understanding of the limitations and advances in these staging techniques and how they can guide treatment is important for improving outcomes for esophageal cancer patients. A high proportion of esophageal cancer patients may benefit from an individualized treatment approach, for which scientifically proven treatment algorithms are needed. New surgical techniques in combination with enhanced recovery strategies have shown potential to reduce the incidence of postoperative complications. In case of these complications, early recognition and minimally invasive treatments are of particular interest, as they limit associated morbidity. Without question, one of the most important factors associated with improved outcomes is the clinical expertise of multidisciplinary teams with regard to the advances in diagnostic and therapeutic interventions in patients with esophageal cancer.

Conflicts of interest

Both Prof. Dr. van Hillegersberg and Dr. Ruurda are proctoring surgeons for Intuitive Surgical, Inc. and train other surgeons in robot-assisted minimally invasive esophagectomy. The other authors report no conflicts of interest.

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