Review article

Optimal surgical approach for esophageal cancer in the era of minimally invasive esophagectomy and neoadjuvant therapy

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SUMMARY. The optimal surgical technique for the potentially curative treatment of patients with esophageal cancer is still under debate. The transhiatal esophagectomy (THE) with limited lymphadenectomy mainly focuses on a decrease of postoperative morbidity and mortality by preventing a formal thoracotomy. The transthoracic esophagectomy (TTE) with extended two-field lymphadenectomy attempts to improve the radicality of the resection and thus to increase locoregional tumor control, but is associated with increased postoperative morbidity. The recent introduction of different minimally invasive techniques probably decreases postoperative morbidity following TTE, with reduction of especially pulmonary complications, but high-quality evidence is still limited. It is widely agreed that extended lymphadenectomy as performed during TTE provides the benefit of more accurate staging, but its effect on improvement of survival is still debated. The literature on this topic is contradictory and the choice of surgical approach is primarily driven by personal opinions and institutional preferences. Moreover, the available evidence is mainly based on patients who underwent surgery alone without neoadjuvant therapy. Results of recent studies suggest that neoadjuvant chemoradiotherapy abolishes any possibly positive effect of extended lymphadenectomy as performed during TTE on survival, but this effect should be confirmed in future research. This review gives an overview and reflects the authors’ personal view on the role of TTE and THE in the treatment of potentially curative treatment of patients with locally advanced esophageal cancer in the era of minimally invasive esophagectomy and neoadjuvant treatment and outlines future research perspectives.

KEY WORDS: esophageal cancer, minimally invasive esophagectomy, neoadjuvant therapy, transhiatal esophagectomy, transthoracic esophagectomy.

INTRODUCTION

For several decades it has been debated what is the optimal surgical technique for the potentially curative primary treatment of patients with locally advanced esophageal cancer. Over the years, two main different surgical strategies have evolved. On the one hand, the limited transhiatal approach (transhiatal esophagectomy [THE]) was developed, which mainly focused on a decrease of postoperative morbidity and mortality by preventing a formal thoracotomy. On the other hand, the extended transthoracic approach (transthoracic esophagectomy [TTE]) was introduced with two-field lymphadenectomy (posterior mediastinum and upper abdomen) in an attempt to improve the radicality of the resection and thus to increase locoregional tumor control. It is widely agreed that extensive lymphadenectomy provides the benefit of more accurate staging, but its effect on improvement of survival is still under debate.

In esophageal cancer, lymphatic dissemination occurs early and is unpredictable. It has been shown that 20–40% of all early submucosal (T1b) esophageal tumors have already disseminated to regional lymph nodes. Therefore, endoscopic treatment is generally reserved for patients with mucosal (T1a) disease. Moreover, the pattern of lymphatic dissemination is unpredictable with skip metastases at more distant sites while lymph nodes in the direct vicinity of the primary tumor are negative. This is one of the reasons why the sentinel node concept is still...
ROLE OF LYMPHADENECTOMY

In a large retrospective study on 2303 patients (60% AC, 40% SCC) that underwent R0 resections from nine high-volume centers around the world, it was shown using multivariable analysis that a high total number of resected nodes is an independent prognosticator of (favorable) survival after primary surgical resection of esophageal or junctional cancer. The optimal threshold for this survival benefit was removal of at least 23 nodes, and the operation most likely to achieve this threshold was found to be an en bloc resection. These findings are arguments in favor of maximizing the extent of lymphadenectomy and therefore in favor of TTE over THE.

In contrast, a recent nonrandomized study from two British centers showed a similar long-term oncological outcome after THE and TTE for patients with AC (88%) or SCC (12%), while hospital stay was shorter after THE. This advantage of THE over TTE in short-term recovery without substantially jeopardizing long-term oncological outcome was also confirmed in a recent meta-analysis that included 52 studies with 3389 TTE patients and 2516 THE patients (52% AC, 48% SCC). In addition to shorter hospital stay (on average 4 days less in patients who underwent THE, 95% confidence interval [CI] 1–7, \( P < 0.01 \)), THE was associated with shorter operative time (THE procedures took a mean of 85 minutes shorter, 95% CI 40–129, \( P < 0.001 \)), less pulmonary complications (17.3% vs. 21.4%, odds ratio [OR] 1.37, 95% CI 1.05–1.79, \( P = 0.02 \)) and lower postoperative mortality (7.2% vs. 10.6%, OR 1.48, 95% CI 1.20–1.83, \( P < 0.001 \)). On the other hand, patients who underwent THE experienced more anastomotic leaks and more recurrent nerve palsies. Furthermore, lymph node retrieval was significantly higher after TTE, with a mean difference of eight nodes (95% CI 1–14, \( P = 0.02 \)). These results must be interpreted with caution, because this analysis included both randomized and non-randomized studies which probably led to a selection bias in favor of the THE group, because more advanced tumors might have been treated preferentially with TTE. Finally, it should be noted that the enhanced short-term recovery after THE was questioned in a large volume, multicenter observational study in more than 17,000 patients who underwent THE or TTE; no differences were found in overall morbidity and mortality. However, a preference for THE in patients with poor performance status probably led to selection bias in favor of the TTE group.

HIVEX TRIAL

The limited THE and the extended TTE have been compared in a randomized trial (HIVEX trial), which was performed in two high-volume Dutch centers. This trial included 220 patients with AC of the mid-to-distal esophagus or AC of the gastric cardia substantially involving the distal esophagus. By preventing a formal thoracotomy, postoperative pulmonary complications occurred less frequently (27% after THE vs. 57% after TTE, \( P < 0.001 \)) and artificial ventilation time (1 day after THE vs. 2 days after TTE, \( P < 0.001 \)) and hospital stay (15 days after THE vs. 19 days after TTE, \( P < 0.001 \)) were shorter after THE. However, in-hospital mortality was comparable between the two groups (2% after THE vs. 4% after TTE, \( P = 0.45 \)). Interestingly, the more extended TTE did not lead to a higher percentage of tumor-free resection margins (72% in the THE group vs. 71% in the TTE group), but the median number of removed lymph nodes was two times as high after TTE compared to THE (median 31 vs. 16, \( P < 0.001 \)). This improved lymph node retrieval did not translate into a significantly better overall 5-year survival; 34% after THE and 36% after TTE (\( P = 0.71 \)). However, in a subgroup analysis of patients with a truly esophageal (type 1) cancer a better long-term survival was achieved, more specifically in those patients with a limited number of positive nodes (23% after THE vs. 64% TTE, \( P = 0.02 \)). It should be noted that stage migration might have played a role in the improved survival in this TTE group, because the total number of resected lymph nodes was higher after TTE. Furthermore, relevance and level of evidence of these results are questionable for SCC, because only patients with AC were included. The final conclusion of that randomized trial was that in advanced type 1 esophageal cancer patients TTE was the preferred technique, especially in case of a limited number of positive nodes, while THE should be preferred in patients with a type 2 tumor which is located at the EGJ and in patients with a poor general condition without clinically suspected lymph nodes at or above the carina.
ROLE OF MINIMALLY INVASIVE ESOPHAGECTOMY

Over the last decade, minimally invasive techniques (laparoscopy, thoracoscopy) have been developed and are increasingly applied in esophageal cancer surgery. The potential advantage of minimally invasive esophagectomy (MIE) might be the limitation of surgical trauma while potentially preserving the radicality of the resection and the extent of lymph node dissection. Several surgical approaches and combinations of techniques have been described, varying from hybrid procedures (thoracoscopy in combination with laparotomy or thoracotomy with laparoscopy) to even completely minimally invasive approaches (thoracoscopy with laparoscopy). So far, only one randomized trial has been published as a full paper, comparing open with minimally invasive TTE.24 This trial included 115 patients with resectable cancer of the esophagus or EGJ. MIE was shown to have a lower postoperative pulmonary infection rate (relative risk 0.35, 95% confidence interval 0.16–0.78, \( P = 0.005 \)).24 However, this trial was criticized, mainly because of the subjectivity of the primary endpoint, the limited number of included patients, the short length of follow-up, and the high recurrent nerve palsy rate with a (secondary?) high pneumonia rate in the open esophagectomy group.25–27 It was concluded that larger trials with longer follow-up are needed to establish more definite conclusions concerning the exact role of minimally invasive techniques.26 Recently, the results of the French MIRO trial have been presented and published in abstract form. This trial randomly assigned 207 patients between open TTE and hybrid MIE (laparoscopic gastric mobilization and open thoracotomy). Both postoperative morbidity (OR 0.31, 95% CI 0.18–0.55, \( P = 0.0001 \)) and pulmonary complications (30.1% vs. 17.7%, \( P = 0.037 \)) were lower in the hybrid arm.28 These preliminary results suggest that a hybrid TTE approach using laparoscopy and thoracotomy reduces postoperative complications as compared to open TTE using both laparotomy and thoracotomy. In order to determine whether the complication rate after hybrid TTE can be decreased even more, a trial is needed in which patients are randomized between hybrid MIE and fully minimally invasive MIE.

Thoracoscopic TTE clearly diminishes the surgical trauma to the chest wall in comparison with a conventional thoracotomy, potentially leading to a decreased postoperative pulmonary complication rate.24 In comparison with a limited transhiatal resection (which completely abolishes the necessity of a thoracotomy/thoracoscopic), however, thoracoscopic TTE still requires a limited trauma to the chest wall (four port sites) and a prolonged (partial) collapse of the right lung throughout the thoracic phase of the operation. It is well established that a lung collapse leads to an increased risk of pulmonary complications.22 Taking into account the relatively low complication rate after open THE, the impact of this prolonged partial lung collapse in combination with the limited trauma to the chest wall during thoracoscopic TTE needs to be evaluated in a randomized trial, comparing the minimally invasive TTE with a conventional or minimally invasive THE.29,30

THORACIC VERSUS CERVICAL ANASTOMOSIS

Using the transhiatal technique, an anastomosis between the proximal esophagus and the replacement conduit is required at the cervical level. In contrast, a transthoracic technique allows for a choice between a cervical and a thoracic anastomosis. After TTE, some surgeons favor a cervical anastomosis despite the increased rate of leakage,31 possible stricture formation, and recurrent laryngeal nerve damage, because of a longer proximal tumor-free margin and a potentially reduced morbidity in case of an anastomotic leak.32 The latter is based on the assumption that an anastomotic leakage will likely be confined to the neck, instead of leaking into the mediastinum and pleural cavity. However, a recent meta-analysis on this topic did not find significant differences in pulmonary complications (OR 0.86, 95% CI 0.13–5.59, \( P = 0.87 \)) or tumor recurrence (OR 2.01, 95% CI 0.68–5.91, \( P = 0.21 \)).33 This study included only three small randomized trials with a total of 175 patients, but suggests that performing a cervical anastomosis after TTE does not decrease the risk of intrathoracic complications as compared to a thoracic anastomosis after TTE. Indeed, in two large retrospective cohort studies, the risk of developing intrathoracic manifestations due to leakage of a cervical anastomosis was shown to be significantly less in patients who underwent THE as compared to patients who underwent TTE. This was explained by the difference in pleural dissection. It was hypothesized, that after THE, a bilaterally intact parietal pleura may confine infections and prevent extension into the mediastinum and pleural cavity.34,35

These studies have been performed before the introduction of neoadjuvant therapy, and studies comparing cervical with thoracic anastomoses after neoadjuvant therapy are lacking. In the randomized CROSS trial comparing neoadjuvant chemoradiotherapy, followed by surgery to surgery alone, almost all anastomoses were performed at the level of the neck, and no significant difference was identified in anastomotic leakage rate.36 However, the effect of radiotherapy on anastomotic healing in the chest might be of significant importance and should be further explored. In case of a thoracic anastomosis, the required length of the gastric tube can be...
shorter with potentially improved oxygenation of the tip and enhanced anastomotic healing. On the other hand, the intrathoracic esophageal remnant might show more radiation damage, which might hamper intrathoracic anastomotic healing.

**IMPACT OF NEOADJUVANT CHEMORADIOThERAPy ON SURGICAL STRATEGY**

It should be underlined that all above trials comparing different surgical techniques mainly included patients who underwent primary surgical resection without neoadjuvant therapy. But even after careful selection of patients for potentially curative primary surgical resection, 5-year survival rarely exceeds 40%, and the majority of patients still die of recurrent disease. For this reason, many studies have been performed worldwide to test the potential value of adding preoperative neoadjuvant therapy to primary surgical resection. The most recent meta-analysis has shown that both neoadjuvant chemotherapy (nCT) and neoadjuvant chemoradiotherapy (nCRT) are able to improve long-term treatment outcome. This meta-analysis showed a trend in favor of nCRT over nCT by comparing treatment arms of different trials (hazard ratio [HR] for all-cause mortality for nCRT vs. nCT 0.88, 95% CI 0.76–1.01, \(P = 0.07\)), but direct comparisons are limited. Especially for patients with AC, explaining why the Neo-AEGIS trial, that compared nCRT with nCT by comparing treatment arms of different trials (hazard ratio [HR] for all-cause mortality for nCRT vs. nCT 0.88, 95% CI 0.76–1.01, \(P = 0.07\)), but direct comparisons are limited. Especially for patients with AC, explaining why the Neo-AEGIS trial, that compared nCRT with nCT in patients with AC, is ongoing. Ever since, a Dutch multicenter randomized controlled study (CROSS trial) was completed, comparing nCRT followed by surgery with surgery alone in patients with SCC or AC of the esophagus (type 1) or EGI (type 2). The applied regimen of five cycles of carboplatin and paclitaxel with 23 fractions of 1.8 Gy concurrent confocal radiotherapy was shown to have low toxicity with \(>90\)% of patients tolerating the complete planned regimen. In-hospital mortality after subsequent surgical resection was not influenced (4% in both treatment arms), and also in-hospital morbidity was comparable between the two groups. Interestingly, median survival doubled from 24% in the surgery alone arm to 49% in the combined treatment arm (\(P = 0.003\)), and 5-year survival improved from 34% to 47%. The difference in overall survival in the CROSS trial was not due to poor survival in the surgery alone group, but can be attributed to improved survival in the chemoradiotherapy followed by surgery group. This is supported by the superior overall survival in the surgery alone group in the CROSS trial as compared to that reported in earlier randomized trials. Based on these results, nCRT according to CROSS followed by surgery is now considered standard of care in many countries. It should be noted that the survival benefit of nCRT found in the CROSS trial was not supported by a recently published French randomized trial (Fédération Francophone de Cancérologie Digestive 9901 trial) comparing nCRT followed by surgery with surgery alone in patients with stage I and II esophageal cancer. Neoadjuvant therapy consisted of cisplatin and fluorouracil with 45 Gy concurrent radiotherapy. Neither the 3-year overall survival rate nor the microscopically radical resection rate was improved in the nCRT followed by surgery group. Based on these results, the benefit of nCRT for patients with early-stage tumors is debatable. Possibly, treatment with surgery alone is already effective in these patients, which is supported by the high radical resection rate (92%) in the surgery alone group of the French trial. However, the generalizability of the results of the French trial has been questioned due to its low case volume in many of the participating centers, its toxic nCRT regimen with less sophisticated radiation techniques in comparison with the CROSS trial and its remarkably high postoperative mortality rate. Therefore, we caution to conclude that nCRT is not beneficial in early-stage cancer, and we believe that, as long as high-quality evidence on the effect of nCRT on early-stage tumors is lacking, the results from the CROSS trial (which included stage II cancers) should be considered leading, especially for stage II cancers.

Neoadjuvant treatment according to CROSS has a significant downstaging effect both on the primary tumor and on the regional lymph nodes. In the CROSS trial, the percentage of patients with (residual) positive lymph nodes in the resection specimen decreased from 76% in the surgery alone group to 32% in the combined treatment group. Moreover, a substantial number of patients (29%) did not have any vital tumor cells left in the resection specimen after nCRT. This high pathologically complete response rate led to the imperative to reconsider the necessity of standard esophagectomy in all patients. Therefore, we hope to propose in the near future a ‘Surgery As Needed approach in Oesophageal cancer patients (SANO approach).’ In this approach, patients will undergo active surveillance after completion of nCRT. Esophagectomy will be offered only to patients in whom a locoregional recurrence is highly suspected or proven. This organ-preserving strategy would be preferred, but only if long-term survival would be comparable to that of the present standard surgery approach. As a first step toward an organ-preserving strategy, we are currently performing the multicenter phase II feasibility pre-SANO trial to determine the accuracy by which residual disease after nCRT can be detected. Furthermore, in France, a phase II/III randomized trial comparing standard surgery with surgery on demand in case of recurrence in clinically complete responders after nCRT is currently being initiated (ESOSTRATE trial).
As underlined above, the randomized HIVEX trial comparing THE and TTE for subcarinal tumors was performed in patients who did not undergo neoadjuvant therapy. In that trial, TTE did not lead to a higher rate of tumor-free margins (71% after TTE vs. 72% after THE) but roughly doubled the number of removed nodes (median ± standard deviation = 31 ± 14 after TTE vs. 16 ± 9 after THE, \( P < 0.001 \)). The randomized CROSS trial has shown, however, that in patients after nCRT, the total number of resected nodes is significantly lower than in patients after primary surgery.45 Interestingly, this positive correlation between the total number of resected nodes and the number of resected positive nodes remained unchanged. Furthermore, after primary surgery, the total number of resected nodes had a positive correlation with survival (HR per 10 additionally resected nodes, 0.76; \( P = 0.007 \)), which is in line with an earlier retrospective international study, as discussed above.15,43 The randomized CROSS trial has shown, however, that in patients after nCRT, the total number of resected nodes was associated with improved survival, while in a comparable group of patients who were randomly allocated to undergo nCRT plus surgery, this association was lost. The randomization procedure within the CROSS trial renders asymmetry between treatment arms unlikely as a possible explanation for the (disappearance of the) observed association in this secondary analysis. These data question the necessity of maximization of surgical lymph node retrieval after nCRT, both for diagnostic purposes and for therapeutic reasons.

The same phenomenon was identified in a larger (albeit retrospective) analysis of 391 patients who underwent primary surgery and 626 patients who underwent nCRT according to CROSS followed by surgery.46 In the surgery alone group, TTE was associated with a significantly more favorable prognosis as compared to THE (HR for TTE vs. THE = 0.73, \( P = 0.023 \)), whereas in patients treated with nCRT followed by surgery, TTE was associated with a (nonsignificantly) less favorable prognosis (HR TTE vs. THE = 1.18, \( P = 0.246 \)). Again, these data suggest that maximization of surgical lymph node retrieval is probably relevant in patients who undergo surgery alone but question its necessity after nCRT.

In order to confirm these indirect arguments, a randomized trial is needed comparing TTE and THE in patients with (type 1) esophageal cancer who undergo nCRT according to CROSS. In our opinion, such trial should focus on patients with (type 1) esophageal cancer and not on patients with (type 2) junctional cancer, because the HIVEX trial has already shown sufficiently that in patients with type 2 junctional cancer, THE suffices. Even if they undergo primary surgical resection without preoperative neoadjuvant therapy THE is adequate, let alone in patients with type 2 junctional cancer who undergo nCRT followed by surgery. It should be noted that in the HIVEX trial, also type 1 malignancies were included, and conclusions regarding the absence of benefit of TTE for type 2 cancer are obtained from a subgroup analysis.

### CONCLUSION AND FUTURE DIRECTIONS

The optimal surgical strategy (transthoracic or transhiatal resection) for esophageal carcinoma remains unclear. A trend toward an improved 5-year survival after TTE was shown in a randomized trial, but this study was performed before implementation of nCRT and MIE.22 The extended lymphadenectomy in TTE might decrease the rate of locoregional recurrences and thus increase survival. However, the necessity of maximization of surgical lymph node retrieval after nCRT has recently been questioned.45,46 The recent introduction of MIE might decrease postoperative morbidity following TTE, with reduction of especially pulmonary complications, but high-quality evidence is still limited.

Therefore, some important questions remain to be addressed. First, several minimally invasive TTE approaches have been described, but the superiority of one technique over another in terms of postoperative complications and oncological outcome remains unknown. Randomization between the hybrid procedures, as performed in the recent MIRO trial23 versus a fully minimally invasive esophagectomy as described in the TIME trial,24 will reveal possible advantages of thoracoscopy over thoracotomy, both combined with laparoscopic gastric mobilization. A reduction in postoperative (pulmonary) complication rate after thoracoscopic TTE would only be acceptable if this is accompanied by a similar or improved oncological outcome. Furthermore, such trial design would allow for a second randomization procedure within each arm between a thoracic and a cervical anastomosis (four-arm study) to define the optimal location of the anastomosis.

Second, the oncological necessity of extended lymph node dissection in patients with type 1 esophageal AC or SCC (located below the carina) in the era of neoadjuvant therapy should be studied. If a randomized trial comparing TTE with THE shows that THE is adequate after nCRT, this will clearly have advantages in reducing especially pulmonary complications. Moreover, the discussion on thoracoscopy versus thoracotomy would then be futile.

Finally, direct comparison between minimally invasive THE and open THE will clarify whether the...
relatively low complication rate of an open THE can be decreased even more. Especially if THE would prove to be sufficient for patients who have been pretreated with nCRT or in the growing elderly population, minimization of surgical trauma and avoidance of postoperative complications is crucial.

References
