Current status of esophageal cancer treatment

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Abstract

Esophageal cancer (EC) remains one of the most common and aggressive diseases worldwide. This review discusses some debates in the modern management of the disease. Endoscopic procedures for early cancer (T1a−b) are now embedded in routine care and the challenge will be to more accurately select patients for endoscopic resection with or without adjuvant therapy. Perioperative multimodal therapies are associated with improved survival compared to surgery alone for locally advanced esophageal cancer. However, there is no global consensus on the optimal regimen. Furthermore, histological subtype (adenocarcinoma *vs.* squamous cell cancer) plays a role in the choice for treatment. New studies are underway to resolve some issues. The extent of the lymphadenectomy during esophagectomy remains controversial especially after neoadjuvant chemoradiation. The ideal operation balances between limiting surgical trauma and optimizing survival. Minimally invasive esophagectomy and enhanced recovery pathways are associated with decreased morbidity and faster recovery albeit there is no consensus yet what approach should be used. Finally, immune checkpoint inhibitors present promising preliminary results in the novel treatment of advanced or metastatic EC but their widespread application in clinical practice is still awaited.

Keywords: Esophageal cancer; endoscopic resection; minimally invasive esophagectomy; multimodal treatment; fast-track protocols

Introduction

Esophageal cancer (EC) is the eighth most common type of malignancy worldwide. It is one of the deadliest types of cancer and represents 5.3% of all cancer-related deaths (1). Despite advances in diagnostic tools, surgical techniques and perioperative care, 5-year survival after surgical resection is only 40%−50%. This is explained by advanced stage of the disease when symptoms occur and diagnosis is made. After surgery, locoregional or distant recurrence occurs in up to 60% of patients (2,3). The classification of EC into two histologically subtypes, esophageal adenocarcinoma (AC) and squamous cell carcinoma (SCC), is important as optimal treatment for each type may differ (4).

According to the Worldwide Esophageal Cancer Collaboration Investigators, both understaging and overstaging during the initial assessment of the disease remain problematic due to the limitations of the endoscopic and imaging techniques available (5). Computed tomography (CT), endoscopic ultrasound (EUS) and fluorodeoxyglucose positron emission tomography (FDG-PET) are complementary in the assessment of local extension of the tumor (cT-stage) and the assessment of lymph node involvement (cN-stage). Positron emission tomography combined with CT (PET-CT) is indicated for investigating the presence of distant metastases (M-stage) as suggested by the American Joint Committee on Cancer (AJCC) (6). Magnetic resonance imaging (MRI) is mainly indicated in patients with a suspicion of oligometastatic disease (7).

Esophagectomy is still the cornerstone in the treatment

of curable and resectable EC but nowadays, multimodal treatment is widely applied. In recent decades, minimally invasive surgical and endoscopic techniques in combination with enhanced recovery protocols have reduced the morbidity and mortality of treatments. There are several new developments in the management of EC and some are addressed in this review.

Endoscopic treatment for early EC

Endoscopic resection of early EC was initially applied as a diagnostic tool. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are equally effective techniques (8). The infiltration depth for mucosal carcinomas is classified as m1 (carcinoma *in situ*), m2 (infiltration of lamina propria) and m3 (infiltration of muscularis mucosae). Submucosal carcinomas are classified as sm1−3, respectively (9). The risk for lymph node metastases increases with the depth of infiltration which can be assessed by the pathologist after *en-bloc* endoscopic resection. Secondly, assessment of lymphovascular and perineural invasion and grade of differentiation of the tumor also play a role in the risk for lymph node metastases.

The prevalence of involved lymph nodes in T1a (confined in the mucosa) tumors is estimated to be less than 2%, but for T1b (confined in the submucosa) tumors it may be as high as 30% (10,11). A recent review concluded that T1a AC has a 0−15% risk of lymph node disease, while the risk is 4%−50% for T1b AC. In patients with T1a SCC 0−13% was diagnosed with tumor positive nodes, while the rate was estimated 5%−51% for patients with a T1b tumor (12). Complete endoscopic resection is currently the recommended treatment for cT1a EC in the absence of high-risk histologic features. Lee *et al*. concluded that tumor size and lymphovascular invasion were the strongest independent predictors of lymph node metastases (13). Dickinson *et al*. found that tumor size, depth of invasion, resection margin and grade of differentiation were all associated with the risk of lymph node metastases (14). Another study confirmed that lymphovascular involvement, poor differentiation grade and tumor size >30 mm are independent risk factors for lymph metastases (15). A systematic review found that lymphovascular infiltration was the most important predictor for lymph node metastases in AC and sm3 invasion with microvascular invasion was the strongest predictors in SCC (16).

Endoscopic resection can be curative when the tumor is completely removed and the risk for lymph node metastases is very low. This risk should be lower than the risk of death due to esophagectomy (<2%−5%). Whenever the calculated risk of lymph node metastases is higher, additional treatment may be indicated. In fact, the limitations of the accuracy of the diagnostic tools available either single or in combination should be strongly taken under consideration. A recent study showed that 27% of patients diagnosed as clinical N0 had tumor-positive lymph nodes in the specimen after esophagectomy (17). Herein, extended criteria for the non-surgical approach of high-risk T1a tumors and those staged as T1b are currently under investigation in selected patients. Moreover, decreased quality of life after esophagectomy and the benefit of preserving esophagus together with patients' preferences and age/frailty of the patient all play a role in decision making.

When pathological examination shows that the tumor is beyond the criteria for endoscopic treatment alone, additional treatment is indicated. Until recently, most clinicians would advocate radical esophagectomy as the treatment of choice. An alternative treatment, especially for patients unfit for surgery, is chemoradiation (CRT). In a prospective study, patients diagnosed with T1 SCC of the thoracic esophagus were divided in three therapeutic arms; Arm A consisted of patients with resected T1a without lymphovascular involvement and a negative resection margin who received no adjuvant therapy; Arm B included patients with resected T1b tumors with a negative resection margin or T1a tumors with lymphovascular invasion who received prophylactic CRT; Arm C patients were those with a positive vertical resection margin who received definite CRT (18). The 3-year overall survival (OS) was 90.7% in group B and 92.6% in all patients. The authors concluded that CRT as an adjunct to high risk AC seems valid. More support for the efficacy and safety of endoscopic resection and adjuvant CRT comes from a recent review (19). Local recurrence was reported in 14% of the patients and could still be identified and successfully treated with salvage resection (20). Overall, distant metastases were seen in up to 27.2% of the patients. Interestingly, this proportion had undergone non-radical resections already known since the time of primary excision (21). The 3-year OS ranged from 87% to 100%. However, radiotherapy techniques and dosages as well as chemotherapy regimens varied among the studies.

Table 1 summarizes recent guidelines on the treatment of early EC. In Japan, the absolute indication for endoscopic

Table 1 International guidelines on endoscopic and surgical treatment of early esophageal cancer

Tumor stage	Japan (9)	USA (8,22,23)	Europe (7,24)
T1a–m1/2	ER[†]	AC: ER[‡]; SCC: ER[‡]	AC: ER[§]; SCC: ER[§]
T1a–m3	ER/surgery[††]/ER+CRT[†††]	AC: ER[‡]; SCC: ER[‡‡]	AC: ER[§]; SCC: ER[§§]
T1b–sm1	Surgery[††]/CRT	AC: ER[‡‡]; SCC: ER[‡‡]	AC: ER[§§]; SCC: ER[§§]
T1b–sm2/3 SCC/AC	Surgery[††]/CRT	Surgery[††]/CRT	Surgery[††]/CRT[§§§]

m, mucosa; m1, limited to the epithelium; m2, invasion of the lamina propria mucosae; m3, invasion of the muscularis mucosae; sm, submucosa; SCC, squamous cell carcinoma; AC, adenocarcinoma; ER, endoscopic resection; CRT, chemoradiotherapy; [†], if ≥3/4th to complete encircling of the circumference: additional chemo(radio)therapy; [††], evaluate patient's surgical tolerability; [†††], when vascular invasion presents; [‡], absolute indication when well differentiated (G1/2), no evidence of lymph (L0) or vascular invasion (V0); [‡‡], relative indication, only in selected cases (high risk of lymph node metastases); [§], absolute indication when L0–V0; [§§], relative indication when G1/2, depth of invasion ≤200 µm (SCC) or 500 µm (AC), L0, V0, no ulceration (multidisciplinary discussion); [§§§], further treatment after endoscopic resection when: ≥sm2/>200 µm/poorly differentiated/lymphatic invasion (L+)/vascular invasion (V+)/positive vertical margins.

treatment of early EC is stage cT1a (9). Patients diagnosed as cT1a–m3 or more advanced stages should be offered esophagectomy. If the patient's tolerability is questionable, there is a relative indication for endoscopic resection only. Adjuvant CRT may be indicated in some patients after endoscopic resection. In Western countries, T1a–m1/2 tumors can be treated endoscopically, while AC patients classified as T1a–m3 or T1b–sm1 may undergo endoscopic resection only if the lesion is well differentiated, less than 20 mm in diameter, without evidence of lymphovascular disease or presence of ulceration (22-24). T1a–m3 or T1b–sm1 SCC should be treated with surgery and endoscopic treatment is only reserved for selected patients who are not strong surgical candidates (7,10-13,22-24).

Definitive CRT could be an alternative treatment option for patients diagnosed with early SCC who are not eligible for endoscopic resection. Some observational studies, however, report that local control rate was not higher than 70% (25-27). Combined endoscopic resection and adjuvant CRT were superior to definite CRT (28). To date, endoscopic resection plus adjuvant therapies has not been directly compared to esophagectomy in a randomized clinical trial (RCT) (29). Given the limited number of patients that would qualify for such an RCT, this may not be feasible. Furthermore, randomizing patients between a surgical and non-surgical treatment is most likely difficult in terms of patient recruitment due to patient's preferences (18).

The outcome of endoscopic resection has been compared to esophagectomy in a few retrospective cohort studies of moderate to poor quality. A recent study reported equivalent survival for both groups (30). Not surprisingly, endoscopic resection was associated with shorter hospital stay, lower 90-day mortality and lower 30-

day readmission rate. Another study showed that esophagectomy was also associated with more complications. The recurrence rate in the endoscopic group was 13% (31). Therapy-related hospital expenditure was also lower after endoscopic treatment compared to esophagectomy, according to a multicenter study (32). A population-based study from China evaluated the oncologic results of 2,661 patients after endoscopic or surgical treatment of early EC and found no differences in survival (33).

Given the complexity of the disease and the changing treatments, guidelines and opinions, the treatment of early EC should be discussed in a multidisciplinary team. Patient's performance status, preference, age and comorbidities all play a role in the decision making. While endoscopic techniques further evolve, learning curves become shorter and criteria for endoscopic treatment stretches, surgery has undergone an enormous technical evolution with minimally invasive techniques now becoming the procedure of choice. Surgery has become much safer and individualized to the needs of the patient and disease stage with the aim to reduce the impact on patient's quality of life.

Perioperative treatment for locally advanced EC

Perioperative therapies are now incorporated in the radical treatment of locally advanced EC. It is still unclear which neoadjuvant and adjuvant treatment regimen is best and if multimodal treatment should be given to all patients, including cT2N0M0 cancers. Lack of uniformity in the different treatment strategies between East and West and variation in the response to different therapies between AC

and SCC have led to significant limitations in the interpretation of the evidence.

In 2006 the MAGIC trial showed that patients who received three preoperative and three postoperative cycles of epirubicin, cisplatin and fluorouracil (FU) had a better OS compared to the surgery alone group. However, the vast majority of patients had gastric cancer. The MAGIC regimen was adapted in the treatment of gastric and junctional cancer in a large part of the Western world (34). Another multicenter RCT showed improved survival for patients with esophageal AC or SCC who underwent neoadjuvant chemotherapy followed by surgery compared to surgery alone (35). The impact of neoadjuvant therapy on survival for locally advanced resectable EC (T1N1M0 or T2−3N0−1M0) was further investigated by the multicenter CROSS trial (36). The 5-year OS of patients who underwent neoadjuvant chemoradiotherapy plus surgery was significantly higher (37). The CROSS regimen was effective for patients with SCC but of a lower magnitude for AC (38).

For early-stage EC the role of neoadjuvant therapy is questionable. Mariette et al. showed that upfront surgery was non-inferior compared to neoadjuvant CRT for EC stage I/II regardless of the histologic type (39). Another European retrospective study compared patients with cT2N0 disease after surgery alone to patients after neoadjuvant therapy plus surgery (40). The study concluded that neoadjuvant therapy had no effect upon survival or recurrence rates. Focusing on SCC stage II, data from retrospective analyses also support surgery alone (41). A recent review showed no survival benefit when neoadjuvant therapy was administered for cT2N0 EC (42).

However, the potential benefit of radiotherapy in the neoadjuvant setting remains debatable. The NeoRes RCT showed no difference in survival between neoadjuvant chemotherapy and neoadjuvant CRT for patients with EC after transthoracic esophagectomy (43). Given the potential extra toxicity of radiotherapy, this finding may be an argument in support of better selection of patients who may need addition of radiotherapy (44). On the other hand, it has also been reported that CRT for advanced Siewert type I and II AC resulted in better pathological response of the primary tumor and the involved lymph nodes (45). Burmeister et al. reported a lack of benefit of additional radiotherapy in the neoadjuvant setting (46). Finally, the German POET trial, that failed to meet 3-year OS due to poor accrual, showed that preoperative CRT was associated with a trend towards improved 5-year OS compared to

preoperative chemotherapy alone (47). There are many differences between the studies including the extent of the lymph node dissection, the chemotherapy regimens, dosages and designs of radiotherapy plans, the compliance of patients and the different location and histologic type of their tumors. This makes it difficult to draw firm conclusion as to the benefit of radiation to neoadjuvant chemotherapy. But neoadjuvant treatment with at least some chemotherapy regimen is now standard treatment worldwide for AC and SCC.

In Japan, the effect of perioperative therapy for SCC, which is the predominant histologic type in Asia, has been extensively evaluated. The JCOG9907 trial validated the superiority of neoadjuvant over adjuvant chemotherapy for SCC (48). Based on that study, cisplatin plus 5-FU is currently applied for stage II/III EC followed by radical surgery in Japan. JCOG1109 is an ongoing trial aiming to compare three therapeutic strategies for SCC: cisplatin/5-FU vs. docetaxel vs. cisplatin/5-FU plus radiotherapy (49). This may answer the question if radiation together with chemotherapy is of benefit. A recent study from China on neoadjuvant CRT plus surgery vs. surgery alone showed a survival benefit for multimodal treatment (50). The optimal treatment for locally advanced AC in the Asian population is less clear due to the limited number of cases. However, extrapolation of the European studies on neoadjuvant CRT to the Asian population may be valid.

Given the benefit of neoadjuvant treatment, more recent studies aimed to compare different chemotherapy regimens to define the most potent regimen without increasing toxicity. A phase III multicenter RCT (OEO5) showed that four cycles chemotherapy (epirubicin, cisplatin, capecitabine) was not associated with a survival benefit compared to two cycles of cisplatin plus FU (51). The phase III FLOT4 trial showed higher 5-year OS and R0 resection rate for patients after FLOT (FLO/FLOT: 5-FU, leucovorin, oxaliplatin, ± docetaxel) compared to the ECF/ECX regimen. However, only one third of the patients had a junctional or distal esophageal AC (52). FLOT chemotherapy did not increase toxicity. This regimen now is favored by many for AC of the esophagus and stomach (53-55).

There is no evidence to support the routine application of adjuvant treatment in patients that underwent surgery. Before the implementation of neoadjuvant therapy for EC, an RCT showed improved 5-year disease-free survival for patients with SCC who received adjuvant chemotherapy compared to surgery alone, while a meta-analysis

concluded that postoperative therapy was not associated with a survival advantage compared to surgery alone (56,57). Another meta-analysis evaluated the impact of postoperative therapy for SCC only (58). Overall, only adjuvant CRT showed a small survival benefit but at the costs of increased morbidity. Given the high morbidity rates after esophagectomy and the impaired physical status of the patients after major surgery, adjuvant therapies may only be selectively applied in patients at high risk for recurrence.

One question is still open for debate: does adjuvant therapy improve survival in patients that already received neoadjuvant treatment plus surgery? Studies investigating this question are mostly of retrospective design and refer to SCC patients. An observational study showed that adjuvant therapy was associated with survival advantage in completely resected, pN0, distal esophageal AC, irrespective of high-risk histopathologic characteristics (59). However, in this retrospective study, not all patients had previously received neoadjuvant therapy. Another RCT reported a survival benefit for SCC after neoadjuvant therapy plus adjuvant therapy compared to patients without adjuvant therapy (60). The results of an RCT from China investigating the effect of adjuvant CRT on SCC are eagerly awaited (61).

In summary, preoperative CRT has become a standard treatment for cT2−T4, N1−3 EC for both histologic subtypes in many Western centers. However, the benefit of adding radiotherapy before esophagectomy for AC is still questioned by some. In the East, evidence on the optimal approach for SCC has shown a benefit of neoadjuvant chemotherapy followed by radical esophagectomy, but data on AC are still lacking mainly due to the low incidence compared to SCC. *Table 2* presents landmark studies comparing the different perioperative strategies. Meanwhile, ongoing RCTs aim to further clarify the optimal regimen. The ESOPEC trial aims to compare the efficacy of FLOT to the CROSS regimen and the Neo-AEGIS trial will compare survival between the MAGIC/FLOT and the CROSS regimen (62,63). The PROTECT-1402 trial will compare neoadjuvant CRT with paclitaxel-carboplatin *vs.* neoadjuvant CRT with FU-oxaliplatin-folinic acid (FOLFOX) for AC or SCC Siewert type I or II stage II or III. All patients will be treated with Ivor-Lewis esophagectomy (64). The results of these trials may further define the role of perioperative therapies in the multimodal treatment of AC.

Targeted therapy and immunotherapy in advanced EC

Based on studies in other human cancers, targeted agents (trastuzumab for advanced gastric cancer in HER-positive patients), the vascular endothelial growth factor receptor-2 (VEGFR-2) monoclonal antibody (ramucirumab for metastatic gastric or junctional cancer) and the anti-programmed death 1 (PD-1) antibodies have been introduced in the management of EC with various results (65-67).

The KEYNOTE-028, the KEYNOTE-059 and the KEYNOTE-180 trials have presented acceptable toxicity rates and duration of antitumor activity of pembrolizumab in patients with advanced esophageal cancer that tested positive for the programmed death ligand-1 (PD-L1) (68-70). On the other hand, the phase III KEYNOTE-061 RCT analyzed the effect of pembrolizumab *vs.* paclitaxel in patients with gastric or gastroesophageal cancer with progression over treatment and failed to show a difference in OS (71). Although the introduction to immunotherapy is quite novel and existing evidence is still modest, the need for therapies that improve outcomes for patients with advanced esophageal malignancy resulted in the presentation of international recommendations. The National Comprehensive Cancer Network guidelines recommend the VEGFR-2 antibody ramucirumab combined to paclitaxel or docetaxel or irinotecan as second-line treatment of unresectable or metastatic disease (72).

Interestingly, the KEYNOTE-590 will investigate the potential benefit of additional administration of pembrolizumab to 5-FU plus cisplatin among cases diagnosed with unresectable or metastatic EC (73). Despite advances in the management of advanced esophageal malignancy, evidence in the literature is still scarce. Currently composing an evolving field, the role of immune checkpoint blockade in clinical practice remains to be further investigated.

Optimal extent of lymph node dissection in era of perioperative therapy

The decision on the extent of lymph node dissection for EC is based on location of the tumor and distribution of involved lymph nodes. Also, patient's fitness may limit the surgical trauma and extent of nodal dissection. In the East, two and three-field lymph node dissections for SCC are

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Table 2 List of landmark randomized controlled trials (RCTs) on perioperative strategies in multimodal treatment of esophageal cancer

RCTs	Publication of design/results	Country	Status	Type	Therapeutic arms
JCOG9204 (56)	2003	Japan	Completed	SCC	Adjuvant chemotherapy *vs.* Surgery alone
MAGIC (34)	2006	UK	Completed	Gastric AC	Perioperative 3 cycles epirubicin, cisplatin, 5-FU *vs.* Surgery alone
OEO2 (35)	2009	UK	Completed	AC+SCC	Neoadjuvant 2 cycles cisplatin, 5-FU *vs.* Surgery alone
FNCLCC/FFCD (53)	2011	Germany	Completed	Esophageal + Gastric AC	Neoadjuvant 2–3 cycles of cisplatin, 5-FU *vs.* Surgery alone
Burmeister *et al.* (46)	2011	Australia	Completed	AC	Neoadjuvant cisplatin, 5-FU *vs.* Neoadjuvant cisplatin, 5-FU, RT
JCOG9907 (48)	2012	Japan	Completed	SCC	Neoadjuvant cisplatin, 5-FU *vs.* Adjuvant cisplatin, 5-FU
JCOG1109 (49)	2013	Japan	Ongoing	SCC	Neoadjuvant cisplatin, 5-FU *vs.* Neoadjuvant docetaxel *vs.* Neoadjuvant cisplatin, 5-FU, RT
FFCD9901 (39)	2014	Germany	Completed	AC+SCC	Neoadjuvant 2 cycles FU, cisplatin, RT *vs.* Surgery alone
CROSS (37)	2015	the Netherlands	Completed	AC+SCC	Neoadjuvant 5 cycles carboplatin, paclitaxel, RT *vs.* Surgery alone
Zhao *et al.* (60)	2015	China	Completed	SCC	Neoadjuvant 2 cycles paclitaxel, cisplatin, 5-FU (PCF) plus adjuvant 2 cycles PCF *vs.* Neoadjuvant 2 cycles PCF
ESOPEC (62)	2016	Germany	Ongoing	AC	FLOT *vs.* CROSS
PROTECT-1402 (64)	2016	Germany	Ongoing	AC+SCC	Neoadjuvant paclitaxel, carboplatin, RT *vs.* Neoadjuvant FU, oxaliplatin, folinic acid (FOLFOX)
POET (47)	2017	Germany	Closed Early	AC	Neoadjuvant FU, cisplatin *vs.* Neoadjuvant FU, cisplatin, RT
OEO5 (51)	2017	UK	Completed	AC	Neoadjuvant 4 cycles epirubicin, cisplatin, capecitabine *vs.* Neoadjuvant 2 cycles cisplatin, FU
Neo-AEGIS (63)	2017	ICORG	Results awaited	AC	MAGIC *vs.* CROSS
NEOCRTEC5010 (50)	2018	China	Completed	SCC	Neoadjuvant 2 cycles vinorelbine, cisplatin, RT *vs.* Surgery alone
Guo *et al.* (61)	2018	China	Ongoing	SCC	Adjuvant 3 cycles paclitaxel, cisplatin *vs.* Adjuvant RT *vs.* Surgery alone
FLOT4 (52)	2019	Germany	Completed	Esophageal + Gastric AC	Neoadjuvant plus adjuvant FLO/FLOT: 5-FU, leucovorin, oxaliplatin ± docetaxel *vs.* Neoadjuvant plus adjuvant ECF/ECX
NeoRes (43)	2019	Scandinavia	Completed	AC+SCC	Neoadjuvant cisplatin, 5-FU *vs.* cisplatin, 5-FU, RT

SCC, squamous cell carcinoma; AC, adenocarcinoma; UK, United Kingdom; FU, fluorouracil; RT, radiotherapy; ICORG, Irish Clinical Research Group; ECF/ECX, epirubicin, cisplatin, 5-FU/capecitabine.

standardized, while in the Western countries the optimal lymphadenectomy mainly for AC is still under debate. Before administration of perioperative therapy, a transthoracic two-field lymphadenectomy was thought to have a better oncologic outcome in some, but not all patients compared to transhiatal esophagectomy (38). Several studies looked at the optimal and minimum number of lymph nodes that need to be obtained to achieve accurate staging and survival (74,75). Most studies found that at least 15 up to 23 lymph nodes is an adequate number (76,77).

Neoadjuvant therapy has the potential to decrease the size of the primary tumor and eliminate the number of the lymph nodes involved. The observation of pathologic

complete response (pCR) after neoadjuvant CRT in a relevant proportion of patients (30%) fueled the discussion on the survival benefit of extended lymphadenectomy after neoadjuvant treatment (37,78). In support of a limited nodal dissection is minimizing surgical morbidity (79). The French FFCD9901 trial compared neoadjuvant CRT plus surgery *vs.* surgery alone in stage I and II EC. This study showed that neoadjuvant CRT reduced the total number of lymph nodes retrieved as well as the total number of positive lymph nodes (39). This was in accordance with a *post-hoc* analysis of the CROSS trial (37). Survival was not associated with the number of dissected nodes after preoperative therapy. However, these are observations that need validation ideally from a RCT to show if a limited lymphadenectomy does not compromise survival after neoadjuvant treatment. This study likely will not be performed as most surgeons have still a widespread believe in maximizing lymph node dissection for EC. Maximal lymphadenectomy should probably remain the standard approach (80). The answer may come from getting more insight in the biology and genetics of EC at the time of diagnosis that determines patient's prognosis, response to neoadjuvant treatment and possibly individualized surgical resection in the near future.

Furthermore, the "active surveillance" approach is currently under investigation (SANO trial). This study tries to identify patients that may not need surgery at all after neoadjuvant CRT. It involves regular clinical response evaluations after neoadjuvant therapy in clinically complete responders to detect residual/recurrent disease (81-83). As long as the effect of complete response is confirmed, esophagectomy is withheld. A similar study from France is also enrolling patients (84).

Minimally invasive esophagectomy (MIE)

Since the first publication on MIE in the 1990s, a plethora of papers on techniques and outcomes after this approach have been published. One of the most often cited papers on MIE reported a median hospital stay of 8 days, mortality rate of 0.9% and 3-year survival of 58.4% after McKeown and Ivor Lewis MIE (85). Most retrospective studies claim that MIE is associated with lower morbidity and comparable oncological outcomes (86-88). A meta-analysis by Dantoc *et al.* showed that MIE resulted in a higher number of resected lymph nodes (89). Robotic-assisted MIE (RAMIE) is another evolving approach (90).

In order to define the contemporary outcomes after MIE, the EsoBenchmark Collaborative was initiated. Some 13 expert international centers collected data on patients that underwent MIE (91). The study reported that anastomotic leak rate was approximately 16%. However, a multicenter analysis by the same group identified many techniques for reconstruction after esophagectomy and found an association between anastomotic leakage and impaired long-term survival in EC patients (92,93). The oncologic outcome does not seem to be compromised following MIE, however, postoperative complications after open or MIE may partially be responsible for impaired survival. Another nation-wide retrospective study found that MIE was superior to open esophagectomy with lower postoperative morbidity rates and surgery-related mortality, while another study showed no advantages for MIE (94,95). MIE was associated with a higher anastomotic leak rate. Probably this reflects the technical challenges of MIE and introduction of this technique should be carefully performed and audited.

A few RCTs compared the short-term outcome between open esophagectomy and MIE. The French MIRO trial compared open esophagectomy to hybrid esophagectomy (laparoscopic abdominal phase and right thoracotomy) (96). The hybrid procedure was associated with a lower intraoperative and postoperative complication rate, lower major pulmonary complications and a trend towards a better 3-year survival rate (97). Reducing the incidence of postoperative atelectasis by minimizing the incision may be the explanation of the observed differences. The Dutch TIME trial also showed that totally MIE was associated with a lower rate of pulmonary infections, shorter hospital stay and improved quality of life (98). There was no difference in radicality of the resection. Quality of life assessment showed that impaired role and social functioning were less suppressed after MIE, while within 2 years after surgery patients' quality of life after MIE returned to baseline (99).

Two Austrian centers published another RCT comparing morbidity, 30-day mortality, ICU stay, hospital stay, operative time and survival between MIE and open esophagectomy (100). The study was closed after recruitment of 26 patients due to the alarming occurrence of anastomotic leakages. The ROMIO trial is an ongoing study that randomizes patients to hybrid or open esophagectomy (101). Finally, the Dutch ROBOT-trial compared open esophagectomy to robot-assisted MIE and

revealed lower overall postoperative complications after the robot-assisted approach compared to the open technique (102). The MIE resulted in less blood loss, lower cardiopulmonary complications and better control of postoperative pain. Additionally, functional recovery and quality of life were better in the MIE arm.

A large series from Korea found that patients after totally robotic esophagectomy and patients after combined laparotomy and robot-assisted thoracoscopy had equal 90-day mortality rate, and overall abdominal and respiratory complications, contrary to the previous study by Mariette *et al* (97,103). A study from China concluded that RAMIE also had comparable outcomes to thoraco-laparoscopic MIE in 215 patients with SCC (104). The results of two ongoing RCTs from China evaluating RAMIE *vs.* thoracoscopic esophagectomy are awaited (105,106).

In summary, RCTs showed that totally MIE and hybrid esophagectomy may reduce pulmonary complications compared to open esophagectomy. It is important to stress that there is a learning curve for MIE and surgeons should be well trained and proctored before they introduce these techniques in their practice. Some studies show more anastomotic complications and this should be carefully monitored. Most importantly, survival needs to be awaited. The question whether total MIE esophagectomy is superior to hybrid MIE remains unanswered. Recent meta-analyses mainly including cohort studies show no superiority of one approach over the other (107). Advances may potentially further decrease surgical trauma, reduce hospital stay and accelerate recovery while improving quality of life of patients. Perioperative enhanced management is another important factor that may result in better outcomes. An overview of studies on MIE is summarized in *Table 3*.

Enhanced recovery and standardized pathways

Enhanced recovery after surgery (ERAS) protocols have been incorporated in EC surgery with the intention to reduce hospital stay, increase patient's well-being and decrease postoperative morbidity and mortality. Initially adapted in the perioperative management of colorectal cancer, fast-track recovery has been adopted for various operations (108-110). Since Cerfolio's first introduction of enhanced recovery pathways in EC patients, several studies

Table 3 List of landmark randomized controlled trials (RCTs) on minimally invasive esophagectomy

Trial	Country	Recruitment period	Surgical procedures compared		Number of patients		Primary endpoint
			Group A	Group B	Group A	Group B	
MIRO (96,99)	France	2009−2012	Hybrid; laparoscopic abdominal phase and right thoracotomy	Open	103	104	Major postoperative 30-day morbidity
TIME (98)	the Netherlands, Italy, Spain	2009−2011	Thoracoscopic and laparoscopic	Open	59	56	Postoperative pulmonary infection
MIOMIE (100)	Austria	2010−2011	Hybrid; laparoscopic abdominal phase and right thoracotomy	Open	14	12	Morbidity and 30-day mortality
ROMIO (101)	UK	2016− results awaited	Laparoscopically assisted/totally MIE	Open	203 (a.e.)	203 (a.e.)	Postoperative patient-reported physical function
RAMIE (105)	China	2017− ongoing	Robot-assisted MIE	Laparoscopy plus thoracoscopy	180 (a.e.)	180 (a.e.)	5-year OS
REVATE (106)	China	2018− ongoing	Robot-assisted esophagectomy	Hybrid thoracoscopy plus laparotomy or laparoscopy	95	95	LND quality assessment
ROBOT (102)	the Netherlands	2012−2016	Robot-assisted/thoracolaparoscopic	Open	54	55	Overall postoperative complications

MIE, minimally invasive esophagectomy; a.e., as expected; OS, overall survival; LND, lymph node dissection.

have evaluated this approach (111,112). The concept is that a multidisciplinary team approach and written pathways can minimize the postoperative hospital stay and improve quality of life (113).

ERAS protocols resulted in a reduction of incidence of anastomotic leak, decreased pulmonary complications and hospital stay according to a meta-analysis by Markar *et al*. (114). Meanwhile, Pisarska *et al*. found that pulmonary complications were less in the ERAS group compared to conventional perioperative management (115). Another review suggested that ERAS pathways decrease hospital stay and costs (116). Meta-analyses included prospective studies but mostly retrospective studies and the number of RCTs is limited. This underlines that reported between-studies heterogeneity and the discrepancy in definition of the measurements, selection of the parameters studied and interpretation of the results in each study (117). This analysis concluded that most of the endpoints of the RCTs favoured the ERAS approach.

To date, four RCTs have compared patients with ERAS *vs.* patients undergoing conventional postoperative management after esophagectomy (118-121). Preoperative nutritional assessment and prehabilitation, patient information, intraoperative anaesthetic management, perioperative feeding routes, tubes placement, postoperative mobilization, analgesia, admission to the ICU all differ among the fast-track protocols. Patients' compliance to the protocols or logistical hospital problems are also questionable. Moreover, variability of the surgical techniques may interfere with the final results causing a confounding and ameliorated effect on the groups that undergo minimally invasive procedures. In fact, only a few comparative studies thoroughly import details on the surgical techniques as part of their design (122,123).

The ERAS Society and Study Group recently proposed enhanced recovery guidelines for patients who undergo esophagectomy suggesting a common care pathway that could be widely used (124). A multidisciplinary infrastructure as presented in this consensus permits better adherence in daily clinical practice and may precisely format the great variety of the practices. Coordination between the different specialists and physicians and monitoring of adherence to the principles is strongly recommended. This rationale may eventually lead to a universal evaluation of the outcomes of ERAS perioperatively in EC patients.

Acknowledgements

Footnote

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