Surgical treatment of esophageal cancer in the era of multimodality management

Alicia S. Borggreve,1,3,∗ B. Feike Kingma,1,∗ Serg A. Domrachev,2 Mikhail A. Koshkin,3 Jelle P. Ruurda,1 Richard van Hillegersberg,1 Flavio R. Takeda,4 and Lucas Goense1

1Department of Surgery, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands. 2Moscow State University of Medicine and Dentistry, Moscow, Russia. 3Moscow Clinical Scientific Center, Moscow, Russia. 4Sao Paulo Institute of Cancer, University of Sao Paulo School of Medicine, Sao Paulo, Brazil

Address for correspondence: Lucas Goense, Department of Surgery, University Medical Center Utrecht, Utrecht University, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands. L.Goense-2@umcutrecht.nl

Over the last decades, the treatment of resectable esophageal cancer has evolved into a multidisciplinary process in which all players are essential for treatment to be successful. Medical oncologists and radiation oncologists have been increasingly involved since the implementation of neoadjuvant therapy, which has been shown to improve survival. Although esophagectomy is still considered the cornerstone of curative treatment for locally advanced esophageal cancer, it remains associated with considerable postoperative morbidity, despite promising results of minimally invasive techniques. In this light, both physical status and response to neoadjuvant therapy may be important factors for selecting patients who will benefit from surgery. Furthermore, it is important to optimize the entire perioperative trajectory: from the initial outpatient clinic visit to postoperative discharge. Enhanced recovery after surgery is increasingly recognized for esophagectomy and emphasizes perioperative aspects, such as nutrition, physiotherapy, and pain management. To date, several facets of esophageal cancer treatment remain topics of debate, such as the preferred neoadjuvant treatment, anastomotic technique, extent of lymphadenectomy, organization of postoperative care, and the role of surgery beyond locally advanced disease. Here, we describe the current and future perspectives in the surgical treatment of patients with esophageal cancer in the context of the available literature.

Keywords: esophageal cancer; esophageal surgery; patient selection; perioperative treatment; enhanced recovery

Introduction

The management of esophageal cancer is complex and highly variable between countries and centers. Multimodality treatment, which implies neoadjuvant chemoradiotherapy or perioperative chemotherapy in combination with esophageal resection, is increasingly applied worldwide, since it has shown a survival benefit over surgery alone.1–4 Treatment teams today do not involve a surgeon alone but are truly multidisciplinary, with the participation of medical oncologists, radiation oncologists, gastroenterologists, dieticians, and physiotherapists. Although the role of perioperative treatment has significantly evolved with the introduction of neoadjuvant and adjuvant treatment strategies, there is general international consensus that surgery remains a fundamental part of the curative treatment of locally advanced esophageal cancer.1

Here, we summarize the advances in surgical treatment in the era of multimodality management of esophageal cancer. In the first section, we provide an overview of patient selection for surgery and perioperative therapy. In the second section, we address commonly used surgical techniques for esophageal cancer, with a particular focus on minimally invasive surgery, anastomotic techniques, the extent of lymphadenectomy, and the role of surgery in advanced disease. Finally, we discuss the introduction of enhanced recovery protocols after esophagectomy.
Patient selection for surgery

Esophagectomy is a highly complex surgical procedure that is associated with relatively high morbidity, mortality, and recurrence rates.1 The eligibility of a patient for surgical resection strongly depends on the extent of the disease, as well as on the general condition of the patient. Decisions on the initial treatment approach of esophageal cancer are based on clinical staging, which should be carried out with the utmost accuracy.2 Adequate staging at least includes a complete clinical examination and a computed tomography (CT) scan of the neck, chest, and abdomen.1,5 Furthermore, to determine whether lymphatic or distant metastatic disease is present in patients with more advanced tumors that are candidates for surgical resection, endoscopic ultrasound (EUS) and 18F fluorodeoxyglucose positron emission tomography–CT (PET-CT) should be performed.1,2,6,7 A multidisciplinary team is then necessary for choosing the appropriate treatment for each patient individually, not only on the basis of on the previously mentioned tumor stage, but also depending on tumor location, histological subtype, comorbidities, and age. In general, patients with locally advanced disease (cT1N+ and cT2-4aN0-3) are potential candidates for neoadjuvant treatment followed by surgical resection.

In patients with early esophageal cancer (high-grade dysplasia (Tis), mucosal (T1a), and submucosal cancer (T1b)), endoscopic therapy (endoscopic mucosal resection, as well as endoscopic submucosal dissection) is highly successful and is the preferred therapeutic approach.2,8,9 Depending on several histopathological parameters of the resected specimen, such as irradicality, the presence of lymphovascular invasion, deeper submucosal tumor invasion, and poor differentiation, subsequent surgical resection is indicated.1,10,11 In patients not eligible for surgery, endoscopic therapy followed by chemotherapy or chemoradiotherapy might be considered as an alternative treatment.

In addition to tumor stage, the location of the esophageal tumor influences a patients’ eligibility for surgical resection. Patients with proximal esophageal tumors are usually poor candidates for surgery because of limitations in surgical techniques (e.g., confined working space and poor overview).12 Furthermore, due to its anatomical proximity to the hypopharynx, surgery includes a combined pharyngo-laryngo-esophagectomy in some cases, resulting in permanent tracheostomy and affecting the quality of life of these patients enormously.13 Thus, these patients frequently depend on definitive chemoradiotherapy with encouraging 3-year outcomes and acceptable toxicity.13

Comorbidity

Accurate patient selection for surgery does not only depend on tumor characteristics, but also on assessment of comorbidities, patient nutritional status, and cardiopulmonary function.

Results of a large population-based study showed that substantial percentages of patients diagnosed with esophageal cancer have histories of hypertension (56%), congestive heart failure (21%), smoking (71%), and diabetes mellitus (18%).14 This is reflected in the majority of patients having an American Society of Anesthesiologists (ASA) score of 3 (65%).14 From a cohort of 1057 patients who underwent transthoracic esophagectomy, only 31.6% (n = 334) fulfilled the criteria of a low comorbidity status (ASA score ≤2, WHO/ECOG score ≤1, age ≤ 65 years, body mass index (BMI) 19–29 kg/m²).15

The previously mentioned comorbidities are well-known risk factors for several postoperative complications. For example, anastomotic leakage is associated with pre-existent cardiovascular disease, such as heart failure, coronary artery disease, peripheral vascular disease, and hypertension.14 In the context of risk factor evaluation, a patients’ vascular status can be objectively evaluated by arterial calcification on a CT scan. Patients with arterial calcifications have a higher risk of developing anastomotic leakage and esophageal conduit necrosis after esophagectomy compared with patients without calcifications.16–19 Preoperative identification of these high-risk patients could aid in selecting patients who would potentially benefit from ischemic conditioning of the gastric conduit to reduce anastomotic leakage rates.20,21

Some studies suggest that diabetes mellitus is associated with impaired anastomotic healing and thus increases the risk of anastomotic leakage after esophagectomy. However, this relationship has not been consistently described in the literature. A recent review and meta-analysis including 16 observational studies concluded that diabetes mellitus was significantly associated with an increased risk of anastomotic leakage after esophagectomy (OR:
1.63; 95% CI: 1.25–2.12; P < 0.001). Interestingly, in subgroup analyses, this association was mainly found in surgical populations from Europe and America (OR: 1.42; 95% CI: 1.22–1.65; P < 0.001) but not in Asian populations (OR: 2.27; 95% CI: 0.86–6.05; P = 0.1). The authors hypothesized that the limited number of included studies—with only 1540 Asian patients—was more likely to result in a weakened persuasive power of their pooled estimates.

Preoperative pulmonary function (reflected in the forced expiratory volume in 1 second expressed as a percentage of the forced vital capacity and peak expiratory flow) is also associated with major complications after esophagectomy. Pulmonary complications can be reduced by minimally invasive surgery, thoracic epidural analgesia, and early enteral nutrition. Other strategies to improve preoperative condition of the patient include physical therapy to increase cardiorespiratory function. A systematic review including 12 studies evaluating the effects of preoperative exercise therapy on postoperative complication rate and length of hospital stay concluded that preoperative exercise therapy can be effective for reducing postoperative complication rates and length of hospital stay after cardiac or abdominal surgery. The effect of preoperative inspiratory muscle training on the incidence of postoperative pneumonia in patients undergoing esophagectomy was studied in a multicenter randomized controlled trial (the PREPARE study), of which the results will be published in the near future.

As far as patients who are not surgical candidates are concerned, definitive chemoradiotherapy functions as a suitable alternative to surgical resection.

Age
Age has historically been a selection criterion for treatment and management in cancer patients. The association of age with severity of complications after esophagectomy is demonstrated by an adjusted OR of 1.02 per year increase in age (95% CI: 1.00–1.04, P = 0.014). However, age itself might not influence postoperative outcomes as much as assumed. Age ≥80 years is currently related to a decreased likelihood of esophagectomy compared with definitive chemotherapy (OR: 0.79, 95% CI: 0.65–0.96, P < 0.015), as well as a decreased likelihood of palliative therapy versus no treatment (OR: 0.73, 95% CI: 0.65–0.81, P < 0.001) and a decreased likelihood of trimodality therapy compared with definitive chemoradiation (OR: 0.15, 95% CI: 0.12–0.18, P < 0.001), taking persons between 70 and 79 years of age as a reference category. In this same series, all therapies were associated with improved survival in older age. Thus, old age should not be the only reason to exclude patients from surgical treatment that might improve survival. Treatment decisions should be made individually and with appropriate caution in older patients. A preoperative geriatric assessment is advisable to obtain a holistic view of the patient, which can give insight in the risk of postoperative complications, such as delirium.

Perioperative treatment for locally advanced esophageal cancer
For locally advanced disease (cT1N+ and cT2-4aN0-3), treatment practices vary around the globe. However, there is a worldwide consensus that surgery alone should no longer be the standard of care for treatment of these tumors. Over the last decades, numerous strategies have been evaluated to improve the treatment results by adding perioperative or neoadjuvant chemo(radio)therapy to surgical resection. The MAGIC study and the French FNCLCC/FFCD 9703 study were the first to show an overall survival benefit for perioperative chemotherapy in patients with lower esophageal, gastroesophageal junction (GEJ), and gastric adenocarcinoma. After these results, the CROSS study combined carboplatin/paclitaxel with 41.4 Gy radiation and demonstrated a 14% increase in 5-year overall survival for patients with esophageal cancer (both squamous cell carcinoma and adenocarcinoma) treated with neoadjuvant chemoradiotherapy followed by surgery compared with surgery alone. However, the recently presented phase III FLOT 4 trial has shown that the FLOT regimen (docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil (5-FU)) improves the outcome of patients with esophageal adenocarcinoma and locoregional disease as compared with the ECF/ECX triplet (epirubicin, cisplatin, and 5-FU or capecitabine). Currently, several randomized trials comparing perioperative chemotherapy and neoadjuvant chemoradiotherapy are being undertaken. The NeoAegis

194 Ann. N.Y. Acad. Sci. 1434 (2018) 192–209 © 2018 The Authors. Annals of the New York Academy of Sciences published by Wiley Periodicals, Inc. on behalf of The New York Academy of Sciences.
study\textsuperscript{37} compares CROSS versus MAGIC and the German ESOPEC study compares FLOT versus CROSS in patients with esophageal adenocarcinoma.\textsuperscript{38} The Chinese CMISG1701 study compares overall survival between neoadjuvant chemotherapy (cisplatin/paclitaxel) with neoadjuvant chemoradiotherapy (cisplatin/paclitaxel with 40 Gy radiation), both followed by esophagectomy for locally advanced resectable esophageal squamous cell carcinoma.\textsuperscript{39} The NEO SCOPE study investigates whether induction chemotherapy followed by either oxaliplatin/capecitabine or paclitaxel/carboplatin, both combined with 45 Gy radiation, is superior as neoadjuvant regimen in pathological complete response of resectable esophageal adenocarcinoma.\textsuperscript{40} Finally, the PROTECT-1402 study compares three cycles of FOLFOX combined with concurrent radiotherapy (41.4 Gy) or carboplatin and paclitaxel with the same radiation regimen for esophageal and junctional cancer.\textsuperscript{41} An overview of these studies (including ClinicalTrials.gov identifiers) is presented in Table 1.

Besides chemotherapy and radiation treatment, targeted therapies are emerging. Patients with esophageal adenocarcinoma should be tested for overexpression of the human epidermal growth factor receptor 2 (HER2) protein on tumor biopsy.\textsuperscript{1} If a high level of HER2 expression is identified, HER2 antibodies, such as trastuzumab and pertuzumab, could be added to perioperative or neoadjuvant therapy (RTOG 1010 phase III study, NCT01196390; PETRARCA phase II/III study, NCT02581462; INNOVATION phase II study, NCT02205047; TRAP phase I b study, NCT02120911).\textsuperscript{34} Another targeted therapy includes the addition of the vascular endothelial growth factor receptor-2 antibody ramucirumab, which interacts with the angiogenic pathway in tumorigenesis.\textsuperscript{34} Its value is currently being assessed in patients with HER2-negative GEJ and gastric adenocarcinoma (RAMSES phase II/III study NCT02661971). Moreover, the addition of immunotherapeutic strategies to neoadjuvant chemoradiation or perioperative chemotherapy is being evaluated, such as programmed death ligand 1–targeted therapy with atezolizumab or pembrolizumab (PERFECT phase II study, NCT03087864; KEYNOTE-590 phase III study, NCT03189719).

From the adjuvant perspective, chemotherapy and radiotherapy have not been integral parts of the treatment of resectable esophageal cancer. A recent network meta-analysis demonstrated that, in contrast to surgery combined with neoadjuvant therapy, surgery combined with adjuvant therapies appeared less effective and showed no survival advantage when compared with surgery alone (HR: 0.87, 95% CI: 0.67–1.14, \(P = 0.321\)).\textsuperscript{42} Furthermore, adjuvant chemotherapy after neoadjuvant chemoradiotherapy followed by surgery did not provide additional benefit for esophageal cancer patients without residual disease (ypT0N0, HR: 0.82, 95% CI: 0.50–1.35) or without nonnodal residual disease (ypT+N0, HR: 0.93, 95% CI: 0.74–1.17).\textsuperscript{43} Yet, in patients with residual nodal disease (ypTanyN+), adjuvant chemotherapy may provide a survival benefit (HR: 0.70, 95% CI: 0.57–0.85).\textsuperscript{43} However, since this has not been investigated in a formal randomized controlled trial, further research is needed before routine application in clinical practice.

**Complete responders to neoadjuvant therapy**

As a pathologic complete response to neoadjuvant therapy is observed in a substantial fraction of patients (up to 23% of patients with an adenocarcinoma and 49% of patients with a squamous cell carcinoma following neoadjuvant chemoradiotherapy\textsuperscript{3}), it is argued that these patients may not benefit from subsequent surgery.\textsuperscript{44} Patients with a pathologic complete response have a favorable prognosis with a lower risk of developing a local regional recurrence and an increased survival compared with other subgroups.\textsuperscript{37,45–48} Several studies have been initiated to preoperatively identify these patients for an organ-preserving approach, avoiding unnecessary surgery-related morbidity, followed by active surveillance. In this light, various diagnostic strategies, such as endoscopic biopsies and/or EUS,\textsuperscript{49} 18F-FDG PET(-CT),\textsuperscript{50,51} diffusion-weighted,\textsuperscript{52–55} and dynamic contrast–enhanced\textsuperscript{56} magnetic resonance imaging (MRI), are being researched to predict response and ultimately avoid surgery in selected patients. The MUNICON-1 and MUNICON-2 trials have shown that PET-based therapy individualization could be a feasible approach for GEJ adenocarcinomas.\textsuperscript{176,177} Furthermore, at least four...
Table 1. Overview of neoadjuvant and perioperative treatment studies for esophageal cancer

| Study                                      | Comparison                                                                 | Experimental treatment                                      |
|--------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------|
| **Perioperative chemotherapy**             |                                                                           |                                                             |
| MAGIC                                      | Perioperative chemotherapy versus surgery                                 | ECF                                                         |
| FNCLCC/FFCD 9703                           | Perioperative chemotherapy versus surgery                                 | Cisplatin/fluorouracil                                      |
| FLOT4 trial (NCT01216644)                 | Comparison of two perioperative chemotherapy regimens                     | FLOT/ECF                                                   |
| **Neoadjuvant chemoradiotherapy**          |                                                                           |                                                             |
| CROSS                                      | Neoadjuvant chemoradiotherapy versus surgery                              | Carboplatin/paclitaxan and 41.4 Gy                         |
| NeoAegis (NCT01726452)                    | Neoadjuvant chemoradiotherapy versus perioperative chemotherapy           | Carboptatin/paclitaxan and 41.4 Gy                         |
| ESOPEC (NCT02509286)                      | Neoadjuvant chemoradiotherapy versus perioperative chemotherapy           | Carboptatin/paclitaxan and 41.4 Gy                         |
| CMISG1701 (NCT03001596)                   | Neoadjuvant chemoradiotherapy versus perioperative chemotherapy           | Carboptatin/paclitaxan and 40 Gy                          |
| PROTECT-1402 (NCT02359968)                | Comparison of two chemotherapy regimens, both with concurrent radiotherapy | Carboptatin/paclitaxan with 41.4 Gy                        |
| NEOSCOPE (NCT01843829)                    | Induction chemotherapy (oxaliplatin/capecitabine) followed by a comparison of two preoperative chemoradiotherapy regimens | Carboptatin/paclitaxan and 45 Gy; Oxaliplatin/capecitabine and 45 Gy |
| **Immunotherapies**                        |                                                                           |                                                             |
| RTOG 1010 (NCT01196390)                   | HER2 antibodies in addition to neoadjuvant chemoradiotherapy with carboplatin/paclitaxel (radiation dose not specified) | Trastuzumab                                               |
| PETRARCA (NCT02581462)                    | HER2 antibodies in addition to perioperative chemotherapy with FLOT      | Trastuzumab and pertuzumab                                 |
| INNOVATION (NCT02205047)                  | HER2 antibodies in addition to perioperative chemotherapy with cisplatin/capecitabine or cisplatin/5-fluorouracil | Trastuzumab                                               |
| TRAP (NCT02120911)                        | HER2 antibodies in addition to neoadjuvant chemoradiotherapy with carboplatin/paclitaxel and 41.4 Gy | Trastuzumab and pertuzumab                                 |
| RAMSES (NCT02661971)                      | VEGFR2 antibody treatment in addition to perioperative chemotherapy with FLOT | Ramucirumab                                               |
| PERFECT (NCT03087864)                     | PD-L1–targeted therapy in addition to neoadjuvant chemoradiotherapy with carboplatin/paclitaxel and 41.4 Gy | Atezolizumab                                              |
| KEYNOTE-590 (NCT03189719)                | PD-L1–targeted therapy in addition to perioperative chemotherapy with cisplatin/5-fluorouracil | Pembrolizumab                                             |

Note. All studies with ClinicalTrials.gov identifiers are currently enrolling patients or awaiting results. ECF, epirubicin, cisplatin, and fluorouracil; ECX, epirubicin, cisplatin, and capecitabine; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; FOLFOX, fluorouracil, oxaliplatin, folonic acid; Gy, gray; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death ligand 1; VEGFR2, vascular endothelial growth factor receptor-2.

large trials (recruiting ≥200 patients) are currently studying the accuracy of various diagnostic modalities for pathologic complete response assessment and/or the safety of active surveillance after a complete clinical response (the French ESOSTRATE trial, NCT02551458; the Korean ESO-PRESSO trial, NCT01740375; the Dutch PRIDE study; and the Dutch SANO trial, Netherlands Trial Register ID NTR6803).

Enhanced recovery after esophagectomy in the preoperative setting

The principles of enhanced recovery after surgery (ERAS) were developed in 2001 by a group of...
surgeons who later established the ERAS Society.\textsuperscript{57} Since then, the ERAS Society has published various evidence-based multidisciplinary guidelines that aim to minimize the surgical stress response (minimally invasive techniques, carbohydrate loading), facilitate early postoperative mobilization (minimum number of drains, regional analgesia), and stimulate early postoperative resumption of oral intake. Although ERAS guidelines were published for several gastrointestinal surgical procedures, including colonic surgery, pancreatoduodenectomy, rectal surgery, bariatric surgery, and gastrectomy, consensus is lacking regarding the optimal approach to patients undergoing esophagectomy.\textsuperscript{58–63} While the composition of the optimal perioperative care pathway remains a subject of debate for esophagectomy, several enhanced recovery protocols have been suggested, with some reporting a median length of hospital stay of 8 days.\textsuperscript{64,65} Key elements of an ERAS program for esophagectomy can be found in Table 2.

**Outpatient clinic**

In the preadmission phase, structured counseling by a multidisciplinary team is considered key to preparing patients for surgery. First, this increases information retention and offers the possibility of correcting potential misconceptions about disease and treatment, which can reduce patient anxiety.\textsuperscript{66,67} Second, the time between diagnosis and surgery can be used to evaluate and monitor the nutritional state, which is at risk of deteriorating in esophageal cancer patients. At time of diagnosis, most esophageal cancer patients are malnourished owing to local tumor effects causing dysphagia, anorexia, and cancer-related cachexia.\textsuperscript{68} Weight loss and nutritional deficiencies are further increased by toxicities related to neoadjuvant therapy. Since malnutrition is in turn associated with an increased risk of postoperative infectious complications, nutritional screening is advised in all patients before esophagectomy.\textsuperscript{64,69–74}

According to the latest guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN), nutritional intervention is indicated for patients who are at severe nutritional risk (i.e., >10–15% weight loss within 6 months, BMI <18.5 kg/m\textsuperscript{2}, Subjective Global Assessment Grade C, or serum albumin <30 g/L without evidence of hepatic or renal dysfunction).\textsuperscript{75,76} Nutritional intervention should involve nutrition support with sip feeds, enteral tube feeding, or parenteral feeding, in that order of preference.\textsuperscript{75,76}

Various methods for nutritional intervention during neoadjuvant therapy before esophagectomy are summarized in a recently published review.\textsuperscript{68} All studies showed that esophageal stents can be successful to palliate dysphagia in esophageal cancer patients, although the overall stent migration rate was 30%.\textsuperscript{68} Instead of stenting to allow oral intake, enteral feeding can be initiated through a nasoduodenal, nasojejunal, or jejunostomy tube. Since long periods of nasoduodenal or nasojejunal tube feeding can be discomforting for patients, some surgeons advocate laparoscopic placement of a feeding jejunostomy at an early stage before esophagectomy.\textsuperscript{77} Studies on nutrition support by initiation of jejunostomy tube feeding prior to esophagectomy were all retrospective in nature and demonstrated an increase in weight ranging from 0.4 to 11.8 kg.\textsuperscript{68} Only one comparative study was included in the previously mentioned review that compared esophageal stenting to jejunostomy feeding, which reported no significant difference between the two groups with respect to complication rates (22% for esophageal stenting versus 14% for jejunostomy, $P = 0.11$) or weight gain (4.4 kg for esophageal stenting versus 4.2 kg for jejunostomy, $P = 0.59$).\textsuperscript{68}

---

**Table 2. Essential elements of enhanced recovery after esophagectomy (ERAS)**

| At the outpatient clinic | Structured multidisciplinary counseling |
|-------------------------|----------------------------------------|
|                         | Evaluation and optimization of the nutritional state |
|                         | Stimulation of smoking and alcohol cessation |
|                         | Possibly inspiratory muscle training |
| Shortly before surgery  | Avoidance of prolonged fasting |
|                         | Carbohydrate loading |
| During surgery          | Minimally invasive surgical techniques |
| After surgery           | Stimulation of early postoperative mobilization |
|                         | Adequate pain management |
|                         | Limitation of drains, lines, and catheters |
|                         | Possibly early resumption of oral intake |
The optimal nutritional approach for patients with resectable esophageal cancer undergoing neoadjuvant treatment before esophagectomy has yet to be determined.

Finally, if applicable, patients should be encouraged and supported to cease alcohol abuse and smoking during the preadmission phase, which reduces the risk of postoperative complications.

**Before surgery**

Shortly before esophagectomy, ERAS aims to minimize the surgical stress response and thereby decrease insulin resistance, which may reduce postoperative morbidity and length of hospital stay.\(^{80–82}\) In this context, ingestion of an oral carbohydrate solution a few hours before esophagectomy is advised, as it is believed to cause an initial increase in baseline insulin sensitivity and in that way dampens surgery-induced insulin resistance.\(^{82}\) Although randomized controlled trials were inconsistent, a recent meta-analysis of studies including a variety of surgical procedures indicated that carbohydrate loading may be associated with a reduced length of hospital stay compared with placebo or fasting.\(^{83,84}\) While the reported carbohydrate doses are varying, an amount of 400 mL of 12.5% carbohydrate solution may be advised.\(^{76}\) It must be noted that prolonged preoperative fasting should be avoided to reduce patient discomfort and prevent the body from entering a catabolic state that aggravates the surgical stress response.\(^{85,86}\) The traditional practice of fasting from midnight before surgery was based on the doctrine that this would reduce the risk of aspiration during the induction anesthesia, which was based on outdated and sparse literature.\(^{80,87,88}\) Convincing evidence has emerged that ingestion of solid foods until 6 h and clear liquids until 2 h before elective surgery is safe, which led to adaptation of the ASA guidelines.\(^{89,90}\) These eased limitations can most likely also be applied to esophagectomy, although caution is warranted in patients with dysphagia, as they may have an increased risk of aspiration.\(^{64,76}\)

**Minimally invasive surgery**

Traditional open esophagectomy (OE) is a highly invasive procedure that is associated with considerable morbidity.\(^{91–93}\) Over the last decades, minimally invasive techniques have been increasingly adopted for esophageal surgery.\(^{94}\) An important aim of minimally invasive surgery is to reduce the physiological stress response to trauma, which can in turn diminish postoperative immunosuppression and susceptibility to infections.\(^{95,96}\) Additionally, laparoscopic and thoracoscopic procedures are generally associated with less pain when compared with their open alternatives, which promotes recovery.\(^{97–99}\) In this context, minimally invasive esophagectomy (MIE) was introduced in the 1990s and found to be a safe alternative to OE in various studies.\(^{100,101}\) The term MIE is used to describe an esophagectomy procedure that avoids the invasiveness of thoracotomy and laparotomy by performing thoracoscopy and laparoscopy, respectively. Although the worldwide implementation of MIE is at an advanced stage, only one randomized controlled trial has been conducted to compare MIE to OE (i.e., the TIME trial).\(^{94,102}\) Patients were included from five high-volume centers (>30 esophagectomies per year), and MIE was significantly associated with fewer postoperative pulmonary infections during hospitalization (12% versus 34%) and within 2 weeks after surgery (9% versus 29%), less blood loss (median 200 versus 475 mL), shorter hospitalization (median 11 versus 14 days), lower pain scores during the first 10 postoperative days (median Visual Analogue Scale 2 versus 3), and better short-term quality of life scores when compared with OE.\(^{102}\) As no differences were found regarding 3-year overall and disease-free survival, the results from this study suggest that MIE provides short-term advantages while maintaining oncological standards.\(^{102,103}\)

Despite promising results for MIE, recent population-based studies did not unequivocally support its superiority over OE.\(^{104–107}\) While the length of hospitalization was repeatedly shown to be shorter for MIE, pulmonary complications and overall morbidity were generally equal.\(^{104–107}\) Moreover, a higher reoperation rate was consistently reported for MIE in these studies.\(^{104–107}\) The authors postulated that this might be attributable to a learning effect, as MIE is a relatively novel and technically complex procedure that is still in its implementation phase.\(^{105}\) A recent retrospective multicenter study investigated the learning curve for MIE and found that a plateau is reached after 119 cases, based on the evaluation of anastomotic leakage rates when making a transition from a cervical to an intrathoracic anastomosis.\(^{108}\) As the mean anastomotic leakage rate decreased from 18.8% (first time quintile) to
4.5% (fifth time quintile) during this time period, it appears that patients are exposed to additional risks during the learning phase.\textsuperscript{108}

The thoracoscopic part of MIE is particularly difficult to master, especially when performing an intrathoracic anastomosis. A hybrid procedure that avoids the need for a technically challenging thoracoscopic phase has been proposed and investigated in a multicenter trial (i.e., the MIRO trial).\textsuperscript{109} Patients were randomly allocated to receive either hybrid (laparotomy and thoracotomy) or open (laparoscopy and thoracotomy) esophagectomy with an intrathoracic anastomosis.\textsuperscript{109} Although the full results have not been made available, major pulmonary complications were reported to be significantly less frequent in the hybrid group (30.1% versus 17.7%) in a recently published abstract by the American Society of Clinical Oncology.\textsuperscript{110} In combination with several case-matched studies, these findings suggest that morbidity may already be reduced by only performing the abdominal phase minimally invasively.\textsuperscript{111,112} In this light, hybrid esophagectomy might be an option for surgeons in low-volume centers who would face challenges in completing their thoracoscopic learning phase owing to insufficient caseload. However, the additional value of avoiding an open thoracic phase has not yet properly been investigated, and therefore comparative studies for full versus hybrid MIE are warranted. A pilot trial was conducted to investigate the feasibility of a randomized three-armed study that compares open versus hybrid versus full MIE.\textsuperscript{113} As patient recruitment was achieved rapidly, this trial is currently being continued into a definitive randomized controlled trial.

In an attempt to overcome the technical challenges of MIE, robot-assisted MIE (RAMIE) was introduced in 2003.\textsuperscript{114} Robotic assistance allows for more natural hand movements and provides an enhanced three-dimensional vision of the surgical field.\textsuperscript{115} These adjustments increase accuracy and enable surgeons to perform more complex dissections, such as a meticulous mediastinal lymphadenectomy or a hand-sewn intrathoracic anastomosis in the context of esophagectomy. Since its introduction, RAMIE has been shown to be a safe and oncologically adequate alternative to OE and conventional MIE.\textsuperscript{114–116} Furthermore, with its technical advantages, RAMIE may be an option for patients who were traditionally deemed inoperable due to a tumor or lymph node metastasis in the upper mediastinum. In a recent prospective study, 31 patients with an upper mediastinal tumor (cranial border at 18–24 cm from the incisors) or lymph node metastasis (level 2 and/or 4) underwent RAMIE, and the authors concluded that the technique is feasible for this patient group, although it was associated with relatively high mortality (i.e., 10%).\textsuperscript{117} More research is needed regarding the clinical merits and possibly extended operability criteria of RAMIE. The ROBOT trial, which compared RAMIE to OE in terms of short-term surgical and oncological outcomes, will be published soon.\textsuperscript{118}

### Anastomotic techniques

After esophagectomy for cancer, gastrointestinal continuity is most commonly restored by gastric tube reconstruction with an esophagogastroscopic anastomosis. Several anastomotic techniques are available to construct an esophagogastrostomy. In this section, we describe postoperative morbidity and mortality, functional results, and oncologic outcomes of various commonly used anastomotic techniques.

#### Cervical versus intrathoracic anastomosis

During esophagectomy for cancer, either the lowest part of the thoracic esophagus is resected, followed by an intrathoracic esophagogastrointestinal anastomosis high in the chest, or the whole thoracic esophagus is resected and combined with a part of the cervical esophagus, followed by a cervical esophagogastrointestinal anastomosis. Both intrathoracic and cervical anastomoses are commonly performed worldwide, although the first is increasingly applied.\textsuperscript{94}

So far, four randomized trials have assessed clinical outcomes after either an intrathoracic or cervical anastomosis.\textsuperscript{119,120,122} In one of these clinical trials, the intrathoracic anastomosis was significantly associated with a lower anastomotic leakage rate when compared with the cervical anastomosis.\textsuperscript{119} Although the other three clinical trials did not report a statistically significant difference in leakage rates between the two methods,\textsuperscript{120,121,123} two of these suggested a nonsignificant difference in leakage rates in favor of an intrathoracic anastomosis.\textsuperscript{120,122} This difference was confirmed by two meta-analyses—including all four clinical trials—that concluded that an intrathoracic anastomosis could be associated with lower anastomotic leakage rates.
(pooled leakage risk: 13.6% versus 2.9%\textsuperscript{123,124} for the cervical versus intrathoracic anastomosis, respectively). However, the evidence of the currently available clinical trials is limited, because they all included a limited number of patients (32–92 patients per study) with few events (2–13 events per study), leading to uncertain estimates.\textsuperscript{119,120,122} In this regard, three large population-based studies—including 2086,\textsuperscript{125} 2944,\textsuperscript{126} and 2969\textsuperscript{12} patients—confirmed that an intrathoracic anastomosis is associated with lower leakage rates and shorter hospital stay. Reported factors that may explain the lower leakage rate associated with an intrathoracic anastomosis include less tissue ischemia due to the shorter distance the blood supply must travel and less risk of tension on the anastomosis.\textsuperscript{14,124}

Although leakage rates from the intrathoracic anastomosis may be lower, some surgeons prefer a cervical anastomosis, because the sequelae of cervical anastomotic leakage are claimed to be less severe.\textsuperscript{127} It is hypothesized that cervical anastomotic leakage can be easily diverted by opening the neck wound, thus preventing mediastinal contamination. However, the studies that support this hypothesis are rare and included a limited number of patients.\textsuperscript{128,129} Furthermore, it should not be underestimated that cervical anastomotic leakage can also lead to severe intrathoracic complications (pleural empyema and mediastinal abscess) in up to 62% of patients.\textsuperscript{130,131} In this regard, a previously mentioned meta-analysis and two large population-based studies found no difference in inhospital mortality between cervical and intrathoracic anastomoses.\textsuperscript{124,125,132} However, one of these studies indicated that length of intensive care stay and length of hospital stay were longer in patients after an intrathoracic anastomotic leakage.\textsuperscript{125} This suggests that the clinical course of anastomotic leakage is indeed more severe for intrathoracic anastomoses, but that this does not increase the risk of postoperative mortality.

Prevention of adverse events (i.e., recurrent laryngeal nerve palsy and stricture formation) leading to subsequent functional complaints (i.e., impaired swallowing and dysphagia) after esophagectomy is important, because it can impair quality of life. In this context, a meta-analysis of clinical trials and a large population-based study assessed recurrent laryngeal nerve palsy rates after esophagectomy and found that an intrathoracic anastomosis is associated with a statistically significant lower incidence of recurrent nerve trauma.\textsuperscript{124} This is likely explained by the close anatomical relation of the recurrent laryngeal nerve with the esophagus in the cervical region. Regarding benign strictures requiring dilatation, none of the four conducted clinical trials and the two subsequent meta-analyses reported a difference in the incidence between the cervical and intrathoracic anastomotic approaches.\textsuperscript{119,121–124} It should be noted, however, that fair comparison of trials is restricted, due to the lack of consensus regarding definition, diagnostic criteria, and threshold of treatment for anastomotic strictures.

Oncologic outcomes after esophageal surgery may also be influenced by the choice of anatomic location of the anastomosis, as a cervical anastomosis allows for a higher proximal resection margin. In this regard, one trial reported a statistically significant higher irradical resection rate in patients after an intrathoracic anastomosis compared with those receiving a cervical anastomosis (33% versus 10%, respectively; \textit{P} < 0.05).\textsuperscript{122} Two other trials and a large population-based study that also reported on this finding did not find a difference in radical resection rates.\textsuperscript{119,121,125} Patient selection remains important in this context, as patients with supracarinal tumors are likely not eligible for an intrathoracic anastomosis. However, owing to neoadjuvant chemoradiotherapy, an intrathoracic anastomosis is likely safe in patients with infracarinal tumors.\textsuperscript{126}

In summary, on the basis of the current available evidence, an intrathoracic anastomosis is associated with reduced anastomotic leakage rates and recurrent nerve paresis rates compared with a cervical anastomosis. However, the currently available clinical studies are limited by their moderate quality and relatively small sample size. Currently, a randomized controlled trial is underway in order to demonstrate whether a minimally invasive cervical or intrathoracic anastomosis should be preferred for patients with infracarinal esophageal tumors (the ICAN trial\textsuperscript{133}).

\textbf{Hand-sewn versus stapled anastomosis}

Hand-sewn anastomosis and stapled anastomosis with a mechanical device are the most commonly used methods to construct an esophagogastric anastomosis. At present, the choice of a hand-sewn or stapled anastomosis mostly depends on the
preference of the surgeon. So far, 10 clinical trials have been published that compared the hand sewing technique with the stapling technique for the esophagogastric anastomosis.\textsuperscript{120,122,134–141} In none of these clinical trials a statistically significant difference in the incidence of anastomotic leakage was reported.\textsuperscript{134–141} This finding was confirmed by two meta-analyses that did not find a difference in postoperative anastomotic leakage rates, other complications, or postoperative mortality between hand-sewn or stapled anastomosis.\textsuperscript{142,143} However, it was suggested in a subgroup analysis of 302 patients that the stapled approach may reduce anastomotic leakage rates compared with a single-layer hand-sewn esophagogastric anastomosis (RR: 0.37, 95% CI: 0.18–0.76, \(P < 0.01\)).\textsuperscript{142}

In two of the 10 clinical trials that compared the stapled and hand-sewn method, a statistically significant higher anastomotic stricture rate was found after stapled anastomotic construction.\textsuperscript{137,141} The other eight clinical trials did not report a difference in anastomotic strictures rates,\textsuperscript{134–136,138–140} although one study reported a nonsignificant difference toward more strictures in the stapled-group.\textsuperscript{138} A meta-analysis that included seven of the 10 clinical trials found that a stapled anastomosis was associated with a higher anastomotic stricture rate (OR: 1.76, 95% CI, 1.09–2.86; \(P = 0.02\)).\textsuperscript{143} A possible explanation for this higher stricture rate is that the compression of tissue in the stapling device results in tissue ischemia between the staples, leading to fibrosis.

In summary, the current evidence suggests that hand-sewn and stapled anastomoses are equally safe with regard to leakage rates, other complications, and postoperative mortality. However, stapled anastomoses are likely associated with more stricture formation when compared with hand-sewn anastomoses.

**Lymphadenectomy for esophageal cancer**

Lymph node status is an important prognostic factor in esophageal carcinoma and an independent predictor of survival.\textsuperscript{144,145} Therefore, lymph node dissection is considered to be an integral part of oncological surgery. For esophagectomy, a transthoracic approach is generally considered to be optimal in oncological terms, as it allows for two-field lymphadenectomy with upper mediastinal dissection.\textsuperscript{92,146} The alternative, transthiatal esophagectomy, was designed to reduce postoperative morbidity and mortality by avoiding thoracotomy and is therefore often reserved for patients with considerable comorbidity and high risk of complications following a potential thoracotomy.\textsuperscript{147} A prospective randomized study comparing a transthiatal resection with an extended transthoracic approach for middle and distal esophageal adenocarcinomas showed that median overall, disease-free, and quality-adjusted survival did not differ statistically between the groups.\textsuperscript{91,148} However, there was a trend reported toward improved long-term survival at 5 years with the extended transthoracic approach (51% for transthoracic approach versus 37% for the transthiatal approach in type I esophageal adenocarcinoma).\textsuperscript{91,148} In particular, patients with one to eight positive lymph nodes in the resection specimen showed a 5-year locoregional disease-free survival advantage if operated via the transthoracic route compared with the transthiatal approach (23% versus 64%, \(P = 0.02\)).\textsuperscript{148}

A higher lymph node yield was associated with improved survival in an international cohort of 2303 esophageal cancer patients who underwent surgery alone.\textsuperscript{149} In contrast, two studies that performed post hoc analyses on lymph node yield in patients treated with chemoradiotherapy followed by esophagectomy suggested that lymph node yield was not associated with survival.\textsuperscript{150,151} It should be noted, however, that these findings have to be interpreted with caution, and the debate on the benefit of extensive lymphadenectomy has not yet been settled. It is well known that more lymph nodes are resected with a transthoracic approach compared with a transthiatal approach in patients who undergo surgery alone as well as neoadjuvant chemoradiation followed by surgery.\textsuperscript{152} In a recently published post hoc analysis of a randomized controlled trial, a more favorable prognosis for the transthoracic approach was found in patients who underwent surgery alone, especially in patients with a limited number of positive lymph nodes.\textsuperscript{152} This benefit was absent in patients who underwent neoadjuvant chemoradiotherapy;\textsuperscript{152} however, this might be due to a lack of power for this post hoc analysis. A recent population-based study from the Netherlands including 2698 esophageal cancer patients who underwent neoadjuvant chemoradiotherapy contradicted these results and found a significant association between lymph node
yield during esophagectomy and increased overall survival.\textsuperscript{153} In subgroup analyses of patients with squamous cell carcinoma and adenocarcinoma, cN0 and cN+, transthoracic and transhiatal approaches, and ypN0 and ypN+, a high lymph node yield remained significantly associated with increased overall survival.\textsuperscript{153}

Moreover, a more extensive lymphadenectomy reflected by a higher lymph node yield during esophagectomy does not seem to decrease patients’ short- and long-term health-related quality of life, as reported by a Swedish population-based study including a total of 616 patients.\textsuperscript{154}

Taken together, there is no evidence to date that justifies reduction in the quality or the extent of lymphadenectomy in esophageal cancer after neoadjuvant therapy. A transthoracic lymphadenectomy allows for optimal staging and locoregional disease control, and an inadequate lymphadenectomy may lead to positive lymph nodes being missed.\textsuperscript{155} Data regarding the lymph node status of individual lymph node stations would be of great importance before deciding to modify the extent of lymphadenectomy. The distribution of lymph node metastases is currently researched in a multinational observational cohort study with 58 participating centers (i.e., the TIGER study, NCT03222895).

**The role of surgery beyond locally advanced disease**

Since multimodality treatment for esophageal cancer is increasingly applied and can induce high degrees of tumor regression, even tumors that invade other adjacent structures, such as aorta, vertebral body, or trachea (T4b tumors), may be considered for resection in selected cases.\textsuperscript{156} Furthermore, it has been reported feasible and beneficial in terms of survival to perform a radical resection combined with off-pump descending aorta replacement and adjuvant chemotherapy in 47 patients with a T4b esophageal tumor invading the aorta.\textsuperscript{157} Additionally, there is evidence that patients with cT4b tumors can be safely treated with RAMIE after long-course chemoradiotherapy and restaging with PET-CT.\textsuperscript{156} A radical resection rate of 90% could be achieved in a case series of 10 patients.\textsuperscript{156}

The selection of patients with oligometastases (<5 metastases) for surgery is of particular interest. The therapeutic approach to these patients is currently undergoing a shift toward a more aggressive treatment including surgical resection.\textsuperscript{158} A radical surgical resection of the primary tumor and the metastases can be performed in patients who respond well to multimodal chemotheraphy. The recently published results of the FLOT 3 study show that patients with limited metastatic disease after four cycles of neoadjuvant chemotherapy followed by routine surgical resection have a favorable survival compared to patients who received eight cycles of chemotherapy and only a surgical intervention for a palliative indication.\textsuperscript{159} Patient selection for surgical resection was based on a realistic chance for R0 resection of the primary tumor and the possibility of at least a macroscopic complete resection of the metastatic lesions as evaluated by endoscopy and CT or MRI scans.\textsuperscript{159} To identify patients who would benefit from such an aggressive treatment, response to systemic treatment and the “test of time” (stable disease during follow-up) are currently the only useful markers.\textsuperscript{160}

Ongoing randomized studies mainly focus on oligometastatic disease in patients with GEJ and gastric adenocarcinoma. The ongoing German FLOT 5 study (NCT02578368) compares chemotherapy followed by surgery versus chemotherapy alone in patients with GEJ or gastric adenocarcinoma on overall survival. The German RENAISSANCE study\textsuperscript{161} (NCT02578368) includes patients with limited metastatic disease, defined as either retroperitoneal lymph node metastases only or a maximum of one organ site that is potentially resectable or locally controllable with or without retroperitoneal lymph nodes. All patients will receive four cycles of FLOT (combined with trastuzumab if HER2-positive) and are randomized to receive additional chemotherapy cycles or surgical resection of primary tumor and metastases followed by adjuvant chemotherapy. Overall survival will be used as primary endpoint. Finally, the GASTRIPEC study (NCT02158988) evaluates the value of intraoperative hyperthermic intraperitoneal chemotherapy in addition to perioperative chemotherapy and gastrectomy for patients with GEJ and gastric cancer with synchronous peritoneal carcinomatosis.\textsuperscript{162}

**Enhanced recovery after esophagectomy in the postoperative setting**

After surgery, patients should first be able to mobilize as freely as possible to facilitate quick return to
an acceptable activity level. To this end, the number of drains is preferably minimized, and pain management should be effectively organized. For gastrectomy, for instance, routine placement of drains and nasogastric tubes is no longer recommended, since their use has no proven benefit. However, esophagectomy usually involves an extensive thoracic procedure, and temporary chest drainage still is considered necessary to prevent pulmonary compression by accumulation of air or fluid. Although direct evidence is lacking for esophagectomy, literature on open pulmonary surgery suggests that the use of a single drain is safe and that drains can be removed when producing less than 200 mL per day. However, owing to the sparsity of literature specifically addressing chest drainage after esophagectomy, postoperative drainage protocols vary widely, and more research is needed to achieve consensus.

Besides limiting the number of drains that potentially hamper mobilization, adequate pain management is essential to facilitate fast recovery. Epidural analgesia is currently the gold standard after esophagectomy, as it was shown to be superior to systemic analgesia after OE in terms of pain relief and pulmonary complications. Nonetheless, this technique can suffer from several potential problems, such as failed placements, catheter occlusions or dislocations, and epidural-related complications (e.g., hypotension, nausea, abscess, and hematoma). With the rise of MIE, alternative techniques have been increasingly investigated and applied in a recent systematic review and meta-analysis, paravertebral analgesia was suggested to be a serious option, as it may provide equal pain control while possibly causing fewer complications, such as hypotension, nausea, and urinary retention, when compared with epidural analgesia. However, well-designed prospective studies are warranted to provide more clarity on the optimal pain management modality.

Early resumption of oral intake is part of ERAS protocols to stimulate the return of bowel function. However, esophagectomy is somewhat unique owing to the construction of a gastric conduit and a necessary vagotomy, which leads to delayed gastric emptying in 10–15% of patients. Previous studies suggested that it may be safe to allow clear liquids from postoperative day 1, but feeding protocols vary widely. Currently, a randomized trial comparing early versus delayed start of oral intake after minimally invasive and hybrid esophagectomy is in its inclusion phase (i.e., the NUTRIENT II trial). The results of this study are expected to provide more clarity regarding the role of early oral intake in the context of enhanced recovery after esophagectomy.

Conclusions and future directions

With the implementation and favorable results of neoadjuvant therapy, curative treatment is possible for an increased number of esophageal cancer patients. However, adequate staging and thorough examination of the general condition are essential to select patients who are eligible for and would benefit from esophagectomy. Over the last decades, minimally invasive techniques have been increasingly used and have shown promising results. However, not only is it important to explore the surgical procedure itself but the entire perioperative care pathway should be effectively organized in order to optimize surgical outcome. With this in mind, treatment of esophageal cancer with curative intent should be performed by a multidisciplinary team that is experienced in providing this type of care.

Competing interests

J.P.R. and R.v.H. are proctoring surgeons for Intuitive Surgical Inc. and train other surgeons in robot-assisted minimally invasive esophagectomy. All other authors have nothing to disclose.

References

1. Lagergren, J., E. Smyth, D. Cunningham & P. Lagergren. 2017. Oesophageal cancer. Lancet 390: 2383–2396.
2. Lordick, F., C. Mariette, K. Haustermans, et al. 2016. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 27(Suppl. 5): v50–v57.
3. van Hagen, P., M.C.C.M. Hulshof, J.J.B. van Lanschot, et al. 2012. Preoperative chemoradiotherapy for esophageal or junctional cancer. N. Engl. J. Med. 366: 2074–2084.
4. Cunningham, D., W.H. Allum, S.P. Stenning, et al. 2006. Perioperative chemotherapy versus surgery alone for resectable gastrooesophageal cancer. N. Engl. J. Med. 355: 11–20.
5. Goense, L., P.S.N. van Rossum, D. Kandioler, et al. 2016. Stage-directed individualized therapy in esophageal cancer. Ann. N.Y. Acad. Sci. 1381: 50–65.
6. Rice, T.W. & E.H. Blackstone. 2013. Esophageal cancer staging. Thorac. Surg. Clin. 23: 461–469.
Surgical treatment of esophageal cancer

Borggreve et al.

7. Findlay, J.M., K.M. Bradley, E.J. Maile, et al. 2015. Pragmatic staging of esophageal cancer using decision theory involving selective endoscopic ultrasonography, PET and laparoscopy. Br. J. Surg. 102: 1488–1499.

8. Zhang, Y.-Q., T. Chen, C. Zhang, et al. 2017. Endoscopic submucosal dissection for superficial proximal esophageal neoplasia is highly successful. Ann. Surg. 266: 995–999.

9. Yang, D., F. Zou, S. Xiong, et al. 2017. Endoscopic submucosal dissection for early Barrett’s neoplasia: a meta-analysis. Gastrointest. Endosc. https://doi.org/10.1016/j.gie.2017.09.038.

10. Schölvinck, D., H. Künzli, S. Meijer, et al. 2016. Management of patients with T1b esophageal adenocarcinoma: a retrospective cohort study on patient management and risk of metastatic disease. Surg. Endosc. 30: 4102–4113.

11. Molena, D., F. Schlottmann, J.A. Boys, et al. 2017. Esophagectomy following endoscopic resection of submucosal esophageal cancer: a highly curative procedure even with nodal metastases. J. Gastrointest. Surg. 21: 62–67.

12. van der Horst, S. & R. van Hillegersberg. 2015. Esophagectomy for patients with esophageal cancer and cervical lymph node metastases (node). https://clinicaltrials.gov/ct2/show/NCT02426879. Accessed on Feb. 5, 2018.

13. Herrmann, E., N. Mertineit, B. De Bari, et al. 2017. Outcome of proximal esophageal cancer after definitive combined chemo-radiation: a Swiss multicenter retrospective study. Radiat. Oncol. 12: 97.

14. Kassis, E.S., A.S. Kosinski, P. Ross, et al. 2013. Predictors of anastomotic leak after esophagectomy: an analysis of the society of thoracic surgeons general thoracic database. Ann. Thorac. Surg. 96: 1919–1926.

15. Schmidt, H.M., S.S. Gisbertz, J. Moons, et al. 2017. Defining benchmarks for transthoracic esophagectomy: a multicenter analysis of total minimally invasive esophagectomy in low risk patients. Ann. Surg. 266: 814–821.

16. Goense, L., P.S.N. van Rossum, T.J. Weijs, et al. 2016. Aortic calcification increases the risk of anastomotic leakage after Ivor–Lewis esophagectomy. Ann. Thorac. Surg. 102: 247–252.

17. van Rossum, P., L. Haverkamp, H.M. Verkooijen, et al. 2015. Calcification of arteries supplying the gastric tube: a new risk factor for anastomotic leakage after esophageal surgery. Radiology 274: 124–132.

18. Lainas, P., D. Fuks, S. Gaujoux, et al. 2017. Preoperative imaging and prediction of oesophageal conduit necrosis after oesophagectomy for cancer. Br. J. Surg. 104: 1346–1354.

19. Zhao, L., G. Zhao, J. Li, et al. 2016. Calcification of arteries supplying the gastric tube increases the risk of anastomotic leakage after esophageal surgery with cervical anastomosis. J. Thorac. Dis. 8: 3551–3562.

20. Kechagias, A., P.S.N. van Rossum, J.P. Ruurda & R. van Hillegersberg. 2016. Ischemic conditioning of the stomach in the prevention of esophagogastric anastomotic leakage after esophagectomy. Ann. Thorac. Surg. 101: 1614–1623.

21. Schröder, W., A.H. Holscher, M. Bludau, et al. 2010. Ivor–Lewis esophagectomy with and without laparoscopic conditioning of the gastric conduit. World J. Surg. 34: 738–743.

22. Li, S.-J., Z.-Q. Wang, Y.-J. Li, et al. 2017. Diabetes mellitus and risk of anastomotic leakage after esophagectomy: a systematic review and meta-analysis. Dis. Esophagus 30: 1–12.

23. Lagarde, S.M., J.B. Reitsma, A.-K.D. Maris, et al. 2008. Preoperative prediction of the occurrence and severity of complications after esophagectomy for cancer with use of a nomogram. Ann. Thorac. Surg. 85: 1938–1946.

24. Wei, R., W. Dong, H. Shen, et al. 2016. Predictive effects of lung function test on postoperative pneumonia in squamous esophageal cancer. Sci. Rep. 6: 23636.

25. Wejs, T.J., J.P. Ruurda, G.A. Nieuwenhuijzen, et al. 2013. Strategies to reduce pulmonary complications after esophagectomy. World J. Gastroenterol. 19: 6509.

26. Inoue, J., R. Ono, D. Makiu, et al. 2013. Prevention of postoperative pulmonary complications through intensive preoperative respiratory rehabilitation in patients with esophageal cancer. Dis. Esophagus 26: 68–74.

27. van Adrichem, E.J., R.L. Meulenbroek, J.T.M. Plukker, et al. 2014. Comparison of two preoperative inspiratory muscle training programs to prevent pulmonary complications in patients undergoing esophagectomy: a randomized controlled pilot study. Ann. Surg. Oncol. 21: 2353–2360.

28. Valkenet, K., J.G. van de Port, J.J. Dronkers, et al. 2011. The effects of preoperative exercise therapy on postoperative outcome: a systematic review. Clin. Rehabil. 25: 99–111.

29. Valkenet, K., J.C. Trappenburg, R. Gosselink, et al. 2014. Preoperative inspiratory muscle training to prevent postoperative pulmonary complications in patients undergoing esophagectomy resection (PREPARE study): study protocol for a randomized controlled trial. Trials 15: 144.

30. Vlacich, G., P.P. Samson, S.M. Perkins, et al. 2017. Treatment utilization and outcomes in elderly patients with locally advanced esophageal carcinoma: a review of the National Cancer Database. Cancer Med. 6: 2886–2896.

31. Niemuehler, H., R. Kunzmann, L. Sisic, et al. 2015. Surgery of gastric cancer and esophageal cancer: does age matter? J. Surg. Oncol. 112: 387–395.

32. Yamamoto, M., M. Yamasaki, K. Sugimoto, et al. 2016. Risk evaluation of postoperative delirium using comprehensive geriatric assessment in elderly patients with esophageal cancer. World J. Surg. 40: 2705–2712.

33. Al-Batran, S.-E., S. Lorenzen, E. Lilly & S. Lorenzen. 2017. Management of locally advanced gastroesophageal cancer still a multidisciplinary global challenge? Hematol. Oncol. Clin. North Am. 31: 441–452.

34. Ychou, M., V. Boige, J. Pignon, et al. 2011. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J. Clin. Oncol. 29: 1715.

35. Shapiro, J., J.I.B. Van Lanschot, M.C.M. Hulshof, et al. 2015. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 16: 1090–1098.

36. Al-Batran, S., N. Homann, H. Schmalenberg, et al. 2017. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin,
cisplatin, and fluorouracil or capecitabine (ECP/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT-AIO). J. Clin. Oncol. 35(15_suppl): 4004.

37. Reynolds, J., S. Preston, B. O’Neill, et al. 2017. ICORG 10–14: NEOadjuvant trial in Adenocarcinoma of the oEsophagus and oesophagealGastric junction International Study (Neo-AEGIS). BMC Cancer 17: 401.

38. Hoepnner, J., F. Lordion, T. Brunner, et al. 2016. ESOPEC: prospective randomized controlled multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (NCT02509286). BMC Cancer 16: 503.

39. Tang, H., L. Tan, Y. Shen, et al. 2017. CMISR1701: a multicenter prospective randomized phase III clinical trial comparing neoadjuvant chemoradiotherapy to neoadjuvant chemotherapy followed by minimally invasive esophagectomy in patients with locally advanced resectable esophageal squamous cell carcinoma (cT3–4aN0–1M0) (NCT03001596). BMC Cancer 17: 450.

40. Mukherjee, S., C.N. Hurt, S. Gwynne, et al. 2015. NEOSCOPE: a randomised phase II study of induction chemotherapy followed by either oxalaplatin/capecitabine or paclitaxel/carboplatin based chemoradiation as preoperative regimen for resectable oesophageal adenocarcinoma. BMC Cancer 15: 48.

41. Messager, M., X. Mirabel, E. Tresch, et al. 2016. Preoperative chemoradiation with paclitaxel-carboplatin or with fluorouracil-oxaliplatin—folic acid (FOLFOX) for resectable esophageal and junctional cancer: the PROTECT-1402, randomized phase 2 trial. BMC Cancer 16: 318.

42. Pasquali, S., A. Guang Yim, R.S. Vohra, et al. 2017. Survival after neoadjuvant and adjuvant treatments compared to surgery alone for resectable esophageal carcinoma: a network meta-analysis. Ann. Surg. 265: 481–491.

43. Burt, B.M., S.S. Groth, Y.H. Sada, et al. 2017. Utility of adjuvant chemotherapy after neoadjuvant chemoradiation and esophagectomy for esophageal cancer. Ann. Surg. 266: 297–304.

44. Noordman, B.J., B.P.L. Wijnhoven, S.M. Lagarde, et al. 2017. Active surveillance in clinically complete responders after neoadjuvant chemoradiotherapy for esophageal or junctional cancer. Dis. Esophagus 30: 1–8.

45. Oppedijk, V., A. van der Gaast, J.J. van Lanschot, et al. 2014. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J. Clin. Oncol. 32: 385–391.

46. Alnajj, R.M., W. Du, E. Gabriel, et al. 2016. Pathologic complete response is an independent predictor of improved survival following neoadjuvant chemoradiation for esophageal adenocarcinoma. J. Gastrointest. Surg. 20: 1541–1546.

47. Donahue, J.M., F.C. Nichols, Z. Li, et al. 2009. Complete pathologic response after neoadjuvant chemoradiation for esophageal cancer is associated with enhanced survival. Ann. Thorac. Surg. 87: 392–399.

48. Berger, A.C., J. Farma, W.J. Scott, et al. 2005. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. J. Clin. Oncol. 23: 4330–4337.

49. van Rossum, P.S.N., L. Goene, J. Meziani, et al. 2016. Endoscopic biopsy and EUS for the detection of pathologic complete response after neoadjuvant chemoradiotherapy in esophageal cancer: a systematic review and meta-analysis. Gastrointest. Endosc. 83: 866–879.

50. Kwee, R.M. 2010. Prediction of tumor response to neoadjuvant therapy in patients with esophageal cancer with use of 18F FDG PET: a systematic review. Radiology 254: 707–717.

51. van Rossum, P.S.N., D.V. Fried, L. Zhang, et al. 2016. The incremental value of subjective and quantitative assessment of 18F-FDG PET for the prediction of pathologic complete response to preoperative chemoradiotherapy in esophageal cancer. J. Nucl. Med. 57: 691–700.

52. Aoyagi, T., K. Shuto, S. Okazumi, et al. 2011. Apparent diffusion coefficient values measured by diffusion-weighted imaging predict chemoradiotherapeutic effect for advanced esophageal cancer. Dig. Surg. 28: 252–257.

53. De Cobelli, F., F. Giganti, E. Orsenigo, et al. 2013. Apparent diffusion coefficient modifications in assessing gastroesophageal cancer response to neoadjuvant treatment: comparison with tumour regression grade at histology. Eur. Radiol. 23: 2165–2174.

54. van Rossum, P.S.N., A.L.H.M.W. van Lier, M. van Vulpen, et al. 2015. Diffusion-weighted magnetic resonance imaging for the prediction of pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer. Radiother. Oncol. 115: 163–170.

55. Wang, L., L. Liu, C. Han, et al. 2016. Chemoradiotherapy of esophageal cancer. The diffusion-weighted magnetic resonance imaging (DWI) predicts the early response of esophageal squamous cell carcinoma to concurrent chemoradiotherapy. Radiother. Oncol. 121: 246–251.

56. Heethuis, S.E., P.S.N. van Rossum, I.M. Lips, et al. 2016. Dynamic contrast-enhanced MRI for treatment response assessment in patients with oesophageal cancer receiving neoadjuvant chemoradiotherapy. Radiother. Oncol. 120: 128–135.

57. Ljungqvist, O., T. Young-Fadok & N. Demartines. 2017. The history of enhanced recovery after surgery and the ERAS Society. J. Laparoendosc. Adv. Surg. Tech. A 27: 860–862.

58. Gustafsson, U.O., M.J. Scott, W. Schwenk, et al. 2012. Guidelines for perioperative care in elective colon surgical: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. Clin. Nutr. 31: 783–800.

59. Lassen, K., M.M. Coolsen, K. Slim, et al. 2012. Guidelines for perioperative care for pancreatoduodenectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. Clin. Nutr. 31: 817–830.

60. Nygren, J., J. Thacker, F. Carli, et al. 2013. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS((R))) Society recommendations. World J. Surg. 37: 285–305.

61. Nygren, J., J. Thacker, F. Carli, et al. 2012. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. Clin. Nutr. 31: 801–816.
Surgical treatment of esophageal cancer

Borggreve et al.

62. Mortensen, K., M. Nilsson, K. Slim, et al. 2014. Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. Br. J. Surg. 101: 1209–1229.

63. Thorell, A., A.D. MacCormick, S. Awad, et al. 2016. Guidelines for perioperative care in bariatric surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. World J. Surg. 40: 2065–2083.

64. Findlay, J.M., R.S. Gilles, J. Millo, et al. 2014. Enhanced recovery for esophagectomy: a systematic review and evidence-based guidelines. Ann. Surg. 259: 413–431.

65. Markar, S.R., H. Schmidt, S. Kunz, et al. 2014. Evolution of standardized clinical pathways: refining multidisciplinary care and process to improve outcomes of the surgical treatment of esophageal cancer. J. Gastrointest. Surg. 18: 1238–1246.

66. Aarts, M.A., A. Okrainec, A. Glicksman, et al. 2012. Adoption of enhanced recovery after surgery (ERAS) strategies for colorectal surgery at academic teaching hospitals and impact on total length of hospital stay. Surg. Endosc. 26: 442–450.

67. Younis, J., G. Salerno, D. Fanto, et al. 2012. Focused preoperative patient stoma education, prior to ileostomy formation after anterior resection, contributes to a reduction in delayed discharge within the enhanced recovery programme. Int. J. Colorectal Dis. 27: 43–47.

68. Huddy, J.R., F.M.S. Huddy, S.R. Markar & O. Tucker. 2017. Nutritional optimization during neoadjuvant therapy prior to surgical resection of esophageal cancer—a narrative review. Dis. Esophagus 31: 1–11.

69. Grotenhuis, B.A., B.P. Wijnhoven, F. Grune, et al. 2010. Preoperative risk assessment and prevention of complications in patients with esophageal cancer. J. Surg. Oncol. 101: 270–278.

70. Zhong, J.X., K. Kang & X.L. Shu. 2015. Effect of nutritional support on clinical outcomes in perioperative malnourished patients: a meta-analysis. Asia Pac. J. Clin. Nutr. 24: 367–378.

71. Nozoe, T., Y. Kimura, M. Ishida, et al. 2002. Correlation of pre-operative nutritional condition with post-operative complications in surgical treatment for oesophageal carcinoma. Eur. J. Surg. Oncol. 28: 396–400.

72. Watzberg, D.L., H. Saito, L.D. Plank, et al. 2006. Post-surgical infections are reduced with specialized nutrition support. World J. Surg. 30: 1592–1604.

73. Mariette, C., M.L. De Botton & G. Piessen. 2012. Surgery in esophageal and gastric cancer patients: what is the role for nutrition support in your daily practice? Ann. Surg. Oncol. 19: 2128–2134.

74. Mueller, C., C. Compher & D.M. Ellen. 2011. A.S.P.E.N. clinical guidelines: nutrition screening, assessment, and intervention in adults. J. Parenter. Enter. Nutr. 35: 16–24.

75. Arends, J., P. Bachmann, V. Baracos, et al. 2017. ESPEN guidelines on nutrition in cancer patients. Clin. Nutr. 36: 11–48.

76. Kingma, B.E., E. Steenhagen, J.P. Ruurd & R. van Hillegersberg. 2017. Nutritional aspects of enhanced recovery after esophagectomy with gastric conduit reconstruction. J. Surg. Oncol. 116: 623–629.

77. Jenkins, T.K., A.N. Lopez, G.A. Sarosi, et al. 2017. Preoperative enteral access is not necessary prior to multimodality treatment of esophageal cancer. Surgery. https://doi.org/10.1016/j.surg.2017.09.046.

78. Yoshida, N., Y. Baba, Y. Hiyoshi, et al. 2016. Duration of smoking cessation and postoperative morbidity after esophagectomy for esophageal cancer: how long should patients stop smoking before surgery? World J. Surg. 40: 142–147.

79. Mantziari, S., M. Hübner, N. Demartines & M. Schäfer. 2014. Impact of preoperative risk factors on morbidity after esophagectomy: is there room for improvement? World J. Surg. 38: 2882–2890.

80. Steenhagen, E. 2016. Enhanced recovery after surgery: it's time to change practice! Nutr. Clin. Pract. 31: 18–29.

81. Smith, M.D., J. McCall, L. Plank, et al. 2014. Preoperative carbohydrate treatment for enhancing recovery after elective surgery. Cochrane Database Syst. Rev.: CD009161.

82. Ljungqvist, O. 2009. Modulating postoperative insulin resistance by preoperative carbohydrate loading. Best Pract. Res. Anaesthesiol. 23: 401–409.

83. Amer, M.A., M.D. Smith, G.P. Herbison, et al. 2017. Network meta-analysis of the effect of preoperative carbohydrate loading on recovery after elective surgery. Br. J. Surg. 104: 187–197.

84. Awad, S., K.K. Varadhan, O. Ljungqvist & D.N. Lobo. 2013. A meta-analysis of randomised controlled trials on preoperative oral carbohydrate treatment in elective surgery. Clin. Nutr. 32: 34–44.

85. Ljungqvist, O. 2014. ERAS—enhanced recovery after surgery: moving evidence-based perioperative care to practice. J. Parenter. Enter. Nutr. 38: 559–566.

86. Pimenta, G.P. & J.E. de Aguilar-Nascimento. 2014. Prolonged preoperative fasting in elective surgical patients: why should we reduce it? Nutr. Clin. Pract. 29: 22–28.

87. Maltby, J.R. 2006. Fasting from midnight—the history behind the dogma. Best Pract. Res. Anaesthesiol. 20: 363–378.

88. Mendelson, C.L. 1946. The aspiration of stomach contents into the lungs during obstetric anesthesia. Am. J. Obstet. Gynecol. 52: 191–205.

89. Brady, M., S. Kinn & P. Stuart. 2003. Preoperative fasting for adults to prevent perioperative complications. Cochrane Database Syst. Rev.: CD004423.

90. American Society of Anesthesiologists Committee. 2011. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. Anesthesiology 114: 495–511.

91. Hulscher, J.B.F., J.W. van Sandick, A.G.E.M. de Boer, et al. 2010. Extended transthoracic resection compared with limited transthiatal resection for adenocarcinoma of the esophagus. N. Engl. J. Med. 347: 1662–1669.

92. McKeown, K.C. 1976. Total three-stage oesophagectomy for cancer of the oesophagus. Br. J. Surg. 63: 259–262.
93. Lewis, I. 1946. The surgical treatment of carcinoma of the oesophagus; with special reference to a new operation for growths of the middle third. Br. J. Surg. 34: 18–31.
94. Haverkamp, L., M.F. Seesing, J.P. Ruurda, et al. 2017. Worldwide trends in surgical techniques in the treatment of esophageal and gastroesophageal junction cancer. Dis. Esophagus 30: 1–7.
95. Lennard, T.W., B.K. Shenton, A. Borzotta, et al. 1985. The influence of surgical operations on components of the human immune system. Br. J. Surg. 72: 771–776.
96. Maas, K.W., S.S. Biere, I.M. van Hoogstraten, et al. 2014. Immunological changes after minimally invasive or conventional esophageal resection for cancer: a randomized trial. World J. Surg. 38: 131–137.
97. Veldkamp, R., E. Kuhry, W.C. Hop, et al. 2005. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol. 6: 477–484.
98. Sauerland, S., T. Jaschinski & E.A. Neugebauer. 2010. Laparoscopic versus open surgery for suspected appendicitis. Cochrane Database Syst. Rev.: CD001546.
99. Bendixen, M., O.D. Jorgensen, C. Kronborg, et al. 2016. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. Lancet Oncol. 17: 836–844.
100. Smithers, B.M., D.C. Gotley, I. Martin & J.M. Thomas. 2007. Comparison of the outcomes between open and minimally invasive esophagectomy. Ann. Surg. 245: 232–240.
101. Luketich, J.D., M. Alvolo-Rivera, P.O. Buenaventura, et al. Minimally invasive esophagectomy: outcomes in 222 patients. Ann. Surg. 2003;238: 485–486.
102. Biere, S.S., M.I. van Berge Henegouwen, K.W. Maas, et al. 2012. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. Lancet 379: 1887–1892.
103. Straatman, J., N. van der Wielen, M.A. Guesta, et al. 2017. Minimally invasive versus open esophageal resection: three-year follow-up of the previously reported randomized controlled trial: the TIME trial. Ann. Surg. 266: 232–236.
104. Sihaq, S., A.S. Kosinski, H.A. Gaissert, et al. 2016. Minimally invasive versus open esophagectomy for esophageal cancer: a comparison of early surgical outcomes from the Society of Thoracic Surgeons National Database. Ann. Thorac. Surg. 101: 1281–1289.
105. Seesing, M.F.J., S.S. Gisbertz, L. Goense, et al. 2017. A propensity score matched analysis of open versus minimally invasive transthoracic esophagectomy in the Netherlands. Ann. Surg. 266: 839–846.
106. Takeuchi, H., H. Miyata, S. Ozawa, et al. 2017. Comparison of short-term outcomes between open and minimally invasive esophagectomy for esophageal cancer using a nationwide database in Japan. Ann. Surg. Oncol. 24: 1821–1827.
107. Mamidanna, R., A. Bottle, P. Aylin, et al. 2012. Short-term outcomes following open versus minimally invasive esophagectomy for cancer in England: a population-based national study. Ann. Surg. 255: 197–203.
108. van Workum E, Stenstra, M.H.B.C., G.H.K. Berkelmans, et al. 2017. Learning curve and associated morbidity of minimally invasive esophagectomy: a retrospective multicenter study. Ann. Surg. https://doi.org/10.1097/SLA.0000000000002469.
109. Briez, N., G. Piessen, F. Bonnetaïn, et al. 2011. Open versus laparoscopically-assisted esophagectomy for cancer: a multicentre randomised controlled phase III trial—the MIRO trial. BMC Cancer 11: 310.
110. American Society of Clinical Oncology. 2017. ESMO 2017: MIRO trial: 3-year outcomes favor laparoscopic surgery for esophageal cancer. Accessed December 15, 2017. http://www.ascopost.com/News/58020.
111. Glatz, T., G. Marjanovic, B. Kulemann, et al. 2017. Hybrid minimally invasive esophagectomy vs. open esophagectomy: a matched case analysis in 120 patients. Langenbecks Arch. Surg. 402: 323–331.
112. Rinieri, P., M. Ouattara, G. Brioude, et al. 2017. Long-term outcome of open versus hybrid minimally invasive Ivor Lewis oesophagectomy: a propensity score matched studydagger. Eur. J. Cardiothorac. Surg. 51: 223–229.
113. Metcalfe, C., K. Avery, R. Berrisford, et al. 2016. Comparing open and minimally invasive surgical procedures for oesophagectomy in the treatment of cancer: the ROMIO (Randomised Oesophagectomy: Minimally Invasive Or Open) feasibility study and pilot trial. Health Technol. Assess. 20: 1–68.
114. van Hillegersberg, R., J. Boone, W.A. Draaisma, et al. 2006. First experience with robot-assisted thoracoscopic esphagolymphadenectomy for esophageal cancer. Surg. Endosc. 20: 1435–1439.
115. Ruurda, J.P., P.C. van der Sluis, S. van der Horst & R. van Hillegersberg. 2015. Robot-assisted minimally invasive esophagectomy for esophageal cancer: a systematic review. J. Surg. Oncal. 112: 257–265.
116. van der Sluis, P.C., J.P. Ruurda, R.J. Verhage, et al. 2015. Oncologic long-term results of robot-assisted minimally invasive thoraco-laparoscopic esophagectomy with two-field lymphadenectomy for esophageal cancer. Ann. Surg. Oncol. 22(Suppl. 3): S1350-S1356.
117. van der Horst, S., T.J. Wejs, J.P. Ruurda, et al. 2017. Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy for esophageal cancer in the upper mediastinum. J. Thorac. Dis. 9(SuppI. 8): S834-S842.
118. van der Sluis, P.C., J.P. Ruurda, S. van der Horst, et al. 2012. Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer, a randomized controlled trial (ROBOT trial). Trials 13: 230.
119. Chassery, V.M., G.K. Kiroff, J.L. Buard & B. Launois. 1989. Cervical or thoracic anastomosis for esophagectomy for carcinoma. Surg. Gynecol. Obstet. 169: 55–62.
120. Okuyama, M., S. Motoyama, H. Suzuki, et al. 2007. Hand-sewn cervical anastomosis versus stapled intrathoracic anastomosis after esophagectomy for middle or lower thoracic esophageal cancer: a prospective randomized controlled study. Surg. Today 37: 947–952.
121. Walther, B., J. Johansson, F. Johnsson, et al. 2003. Cervical or thoracic anastomosis after esophageal resection and gastric tube reconstruction. Ann. Surg. 238: 803–814.
151. Talsma, K., B. Wijnhoven, J. van Lanschot & M. van Berge Henegouwen. 2015. Impact of neoadjuvant chemoradiation on lymph node status in esophageal cancer. *Ann. Surg.* **266**: e52–e53.

152. Noordman, B.J., D. Van Klaveren, M.I. Van Berge Henegouwen, *et al*. 2017. Impact of surgical approach on long-term survival in esophageal adenocarcinoma patients with or without neoadjuvant chemoradiotherapy. *Ann. Surg.* https://doi.org/10.1097/SLA.0000000000002240.

153. Visser, E., P.S.N. van Rossum, J.P. Ruurda & R. van Hillegersberg. 2017. Impact of lymph node yield on overall survival in patients treated with neoadjuvant chemoradiotherapy followed by esophagectomy for cancer. *Ann. Surg.* **266**: 1.

154. Schandl, A., A. Johar, J. Lagergren & P. Lagergren. 2016. Lymphadenectomy and health-related quality of life after oesophageal cancer surgery: a nationwide, population-based cohort study. *BMJ Open* **6**: e012624.

155. Robb, W.B., E. Maillard & C. Mariette. 2017. Lymph node status after neoadjuvant chemoradiotherapy for esophageal cancer. *Ann. Surg.* **266**: e53-e54.

156. van Hillegersberg, R., M.E.J. Seesing, H.J.F. Bremkamp & J.P. Ruurda. 2017. Robot-assisted minimally invasive esophagectomy. *Dort. Chir.* **88**: 7–11.

157. Cong, Z., Q. Diao, J. Yi, *et al*. 2014. Esophagectomy combined with aortic segment replacement for esophageal cancer invading the aorta. *Ann. Thorac. Surg.* **97**: 460–466.

158. Schmidt, T. & S.P. Mönig. 2017. Therapeutisches Vorgehen beim oligometastasierten Magen- und Ösophaguskarzinom. *Chirurg* **88**: 1024–1032.

159. Al-Batran, S.-E., N. Homann, C. Pauligk, *et al*. 2017. Robot-assisted minimally invasive esophagectomy. *JAMA Oncol.* **3**: 1237.

160. Chiapponi, C., F. Berlth, P.S. Plum, *et al*. Oligometastatic disease in upper gastrointestinal cancer—how to proceed? *Visc. Med.* **18(9)**: 31–34.

161. Mueller, D., S. Moenig, A. Vogel, *et al*. 2017. The “RENAISSANCE” trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer. *JAMA Oncol.* **3(5_suppl)**: TPS4140.

162. Rau, B., M. Loeffler, H. Rau, *et al*. 2015. Perioperative chemotherapy and cytoreductive surgery with versus without HIPEC in gastric cancer with limited peritoneal metastases: a randomized phase III study (GASTRIPEC). *J. Clin. Oncol.* **33(15_suppl)**: TPS4132.

163. Johansson, J., C.G. Lindberg, F. Johnsson, *et al*. 1998. Active or passive chest drainage after oesophagectomy in 101 patients: a prospective randomized study. *Br. J. Surg.* **85**: 1143–1146.

164. Gomez-Caro, A., M.J. Roca, J. Torres, *et al*. 2006. Successful use of a single chest drain postlobectomy instead of two classical drains: a randomized study. *Eur. J. Cardiothorac. Surg.* **29**: 562–566.

165. Richardson, J., S. Sabanathan, A.J. Mearns, *et al*. 1994. Efficacy of pre-emptive analgesia and continuous extrapleural intercostal nerve block on post-thoracotomy pain and pulmonary mechanics. *J. Cardiovasc. Surg.* **35**: 219–228.

166. Davies, R.G., P.S. Myles & J.M. Graham. 2006. A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy—a systematic review and meta-analysis of randomized trials. *Br. J. Anaesth.* **96**: 418–426.

167. Cense, H.A., S.M. Lagarde, K. de Jong, *et al*. 2006. Association of no epidural analgesia with postoperative morbidity and mortality after transthoracic esophageal cancer resection. *J. Am. Coll. Surg.* **202**: 395–400.

168. Hermanides, J., M.W. Hollmann, M.F. Stevens & P. Lirk. 2012. Failed epidural: causes and management. *Br. J. Anaesth.* **109**: 144–154.

169. Brown, D.L. 2005. *Spinal, Epidural, and Caudal Anesthesia*. In Miller’s Anesthesia, R.D. Miller, Ed.: 1653–1683. Philadelphia, PA: Elsevier Churchill Livingstone.

170. Visser, E., M. Marsman, P.S.N. van Rossum, *et al*. 2017. Postoperative pain management after esophagectomy: a systematic review and meta-analysis. *Dis. Esophagus* **30**: 1–11.

171. Poghosyan, T., S. Gaujoux, M. Chirica, *et al*. 2011. Functional disorders and quality of life after esophagectomy and gastric tube reconstruction for cancer. *J. Visc. Surg.* **148(e)**: e327–e335.

172. Weijs, T.J., G.H. Berkelmans, G.A. Nieuwenhuijzen, *et al*. 2016. Immediate postoperative oral nutrition following esophagectomy: a multicenter clinical trial. *Ann. Thorac. Surg.* **102**: 1141–1148.

173. Eberhard, K.E., M.P. Achiam, H.C. Rolff, *et al*. 2017. Comparison of “nil by mouth” versus early oral intake in three different diet regimens following esophagectomy. *World J. Surg.* **41**: 1573–1583.

174. Giacopuzzi, S., J. Weindelmayer, E. Treppiedi, *et al*. 2017. Enhanced recovery after surgery protocol in patients undergoing esophagectomy for cancer: a single center experience. *Dis. Esophagus* **30**: 1–6.

175. Berkelmans, G.H., B.J. Wilts, E.A. Kouwenhoven, *et al*. 2016. Nutritional route in oesophageal resection trial different diet regimens following esophagectomy. *Nutrition* **35**: 266: 1–11.

176. Lordick, F., K. Ott, B.J. Krause, *et al*. 2007. PET to assess early response of esophageal cancer: the MUNICON phase II trial. *Ann. Oncol.* **18(9)**: 797–805.

177. zum Bshopf, C.M., K. Herrmann, T. Schuster, *et al*. 2007. (18)F-FDG PET-guided salvage neoadjuvant radiochemotherapy of adenocarcinoma of the esophagogastric junction: the MUNICON II trial. *J. Nucl. Med.* **52**: 1189–1196.