What's New in Surgical Oncology

A Guide for Surgeons in Training and Medical/Radiation Oncologists

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Preface

The idea for a volume covering those aspects of oncology most relevant to the general surgeon arose when the ACOI (Italian Association of Hospital Surgeons) assigned to me the presidency of the XXXIInd national congress.

This book therefore aims to identify and describe the treatment options for malignancies that are most frequently adopted in general surgery departments, with emphasis on the most innovative and efficient procedures. While, given the importance of financial constraints, issues of cost-effectiveness are not neglected, our main concern has been to approach the topic in a way that will enable new generations of surgeons to apply rapidly emerging techniques and technologies with confidence. Moreover, a multidisciplinary, integrated approach has been emphasized that also involves medical and radiation oncologists, radiologists, and other specialists.

This textbook has been made possible by the fruitful cooperation of leading Italian surgical teams who play a key role in the various fields of surgical oncology. All of them have demonstrated that they are able to follow a broad multidisciplinary approach in the treatment of cancer patients, which is a *sine qua non* for achievement of the best therapeutic outcome.

Our colleagues and friends have also participated enthusiastically in this project. We feel a deep gratitude for their efforts and their intense research. In addition, we would like to thank the staff of Springer Verlag, who have followed and assisted us in our work step by step with outstanding professionalism.

Personally, I wish to thank my coeditors, Ferdinando Agresta, Jacopo Martellucci, and, last but not least, Carlo Bergamini, who has again been a source of strength in bringing this latest project to successful fruition.

Florence, May 2013 Andrea Valeri

Contents

Esophageal Cancer

1

Riccardo Rosati, Giovanni Pallabazzer, Alessandra Melis, Biagio Solito, Maria Grazia Fabrini, Laura Ginocchi, and Stefano Santi

1.1 Introduction

The overall 5-year survival of patients with cancer of the esophagus submitted to resection is 15–34%. Most patients who undergo radical esophagectomy relapse during the course of their disease. In recent years, there has been a growing interest in neoadjuvant treatments, which have produced better results in comparison with adjuvant protocols. There is clear evidence supporting chemoradiotherapy (CRT) for cancers of the esophagus. CRT gives a high rate of complete response (CR), and some researchers have questioned the role of surgery in cases of CR. This has led to trials on definitive chemoradiotherapy (dCRT). These experiences have produced a growing indication for a very demanding procedure: salvage surgery.

Resection of esophageal cancers carries a high rate of morbidity. Efforts have been made in recent years to verify if the application of minimally invasive surgery in this field could be advantageous in reducing the rate of mor-

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bidity (especially in terms of respiratory complications). Also, in recent years, increasing numbers of patients have been selected for endoscopic treatment for early cancers.

The aim of this chapter is to give on overview on these topics (neoadjuvant and adjuvant treatment, dCRT and salvage surgery, minimally invasive surgery and endoscopic resection) in the treatment of esophageal neoplasms.

1.2 Therapeutic Strategies in Esophageal Cancer

Surgery is considered the treatment of choice for patients with localized esophageal cancer in terms of locoregional control and long-term survival. However, 5-year survival in significantly influenced by nodal involvement: 5-year survival for patients who undego radical resection for N+ cancers is ≈25% [1]. Surgery alone is considered inadequate for patients with advanced cancers (T3, N+ and, according to some oncologists, also for T2 esophageal cancers). An increasing number of patients with esophagogastric cancer are treated with preoperative chemotherapy (CT) or CRT.

1.2.1 Neoadjuvant Treatment

The aim of neoadjuvant treatment is to increase the number of R0 resections, to eradicate micrometastases, and to decrease the dissemination of cancer cells during surgery without affecting postoperative morbidity and mortality [2]. In addition, the radio-sensitizing properties [3] of certain chemotherapeutic agents and the increased oxygenation of undisturbed tissue in the tumor bed enhance the effects of perioperative radiotherapy (RT) [4].

The standard option for patients with localized esophageal cancer, based on the results of several randomized trials, is CRT followed by surgery, A randomized trial [5] comparing preoperative CRT, based on cisplatin and 5-fluorouracil (5FU) *versus* surgery alone demonstrated an increase of survival in patients treated with neoadjuvant therapy (3-year overall survival (OS) 32% *versus* 6%). A similar result was obtained in the Cancer and Leukemia Group B (CALGB) 9781 study [6]. Even though the study was closed prematurely for poor accrual, the results demonstrated a survival advantage for patients treated with neoajuvant treatment. That is, a median survival of 4.48 *versus* 1.79 years in favor of CRT (exact stratified log-rank, $p=0.002$) with a 5-year survival of 39% for CRT followed by surgery *versus* 16% for surgery alone. The Preoperative Chemotherapy or Radiochemotherapy in Esophagogastric Adenocarcinoma Trial (POET) study [7] randomized patients with locally advanced adenocarcinoma of the gastroesophageal junction (GEJ) to CT or CRT followed by surgery. Although the study was stopped early and statistical significance was not achieved, the results indicated a survival advantage for preoperative CRT (3-year OS 47.4% *versus* 27.7%, $p=0.07$). Moreover, patients in the CRT group had a significantly higher rate of pathologic CR (15.6% *vs* 2.0%) or tumor-free lymph nodes (LNs; 64.4% *versus* 37.7%); the rate of postoperative mortality was higher in this group of patients but the difference was not significant (10.2% *versus* 3.8%, p=0.26).

A recent phase-III trial [8] compared CRT (carboplatin and paclitaxel and radiotherapy) plus surgery (178 patients), with surgery alone (188 patients) in patients with squamous cell carcinoma (SCC) or adenocarcinoma of the esophagus. An R0 resection was achieved in 92% of patients in the CRT group comapared with 69% in the surgery group (p<0.001). The rate of pCR was 29%. OS was significantly better in these patients (hazard ratio (HR), 0.657 (0.495–0.871, p=0.003). Postoperative complications and deaths carried a similar rate in the two treatment groups. The most recent phase-III trials [9-11] demonstrated that cisplatin based neoadjuvant CT increased the number of R0 resections in patients with adenocarcinoma of the lower esophagus and GEJ compared with surgery alone. In the MRC Adjuvant Gastric Infusional Chemotherapy Trial (MAGIC) [9], gastric adenocarcinoma and GEJ adenocarcinoma were assigned randomly to three perioperative and three postoperative cycles of ECF (epirubicin, cisplatin and fluorouracil) CT (250 patients) or surgery alone (253 patients). With respect to the latter, the perioperative CT group had a higher likelihood of OS (HR, 0.75; 0.60–0.93, p=0.009) and 5-year survival (36% *versus* 23%). Moreover, the Fédérale Nationale des Centres de Lutte Contre Le Cancer (FNLCC) ACCORD 07/FFCD 9703 phase-III study [10] demonstrated that neoadjuvant CT with cisplatin and 5FU improves OS (HR, 0.69; 0.50–0.95, p=0.02), 5-year survival (38% *versus* 24%) and curative resection (84% *versus* 73%) in stomach adenocarcinoma and GEJ locally advanced adenocarcinoma. A similar benefit was also shown in the OEO2 Allum trial [11] with a HR of 0.84 (0.72–0.98, p=0.03) and a 5-year survival of 23% *versus* 17.1%, in the CT setting for adenocarcinoma and SCC. A recent meta-analysis [12] involving 9 trials for 1981 patients confirmed the benefit of neoadjuvant CT in terms of OS with a HR of 0.87 (0.79–0.96; p=0.005) compared with surgery alone. Four meta-analyses [3,13–15] provided strong evidence for a survival benefit of neoadjuvant CRT or CT over surgery alone. However, a clear demonstration of the advantage of one stratery compared with the other was lacking.

1.2.2 Adjuvant Treatment

Two trials in the 1980s demonstrated that adjuvant radiotherapy does not elicit any benefit in patients submitted to resection for cancer of the esophagus. Data on adjuvant CT or CRT are limited except for adenocarcinoma of the lower esophagus and GEJ. Although multiple clinical trials [16–20] did not show significantly longer OS, several meta-analysis [21–24] suggested a small relative (12–28%) reduction in the risk of death for esophageal and GEJ adenocarcinoma after adjuvant CT, with an absolute survival benefit of 3–7%. In the US Southwest Oncology Group/Intergroup (SWOG) 9008/INT 0116 trial

[25], 556 patients with resected gastric or GEJ (≈20%) adenocarcinoma were randomly assigned to surgery plus 5FU and leucovorin postoperative CRT or surgery alone. The median OS was longer after complementary CRT (36 months) than after surgery alone (27 months) with a HR for death of 1.35 (1.09–1.66, $p=0.005$) and a HR for relapse of 1.52 (1.23–1.86, $p<0.001$). Although the study by Macdonald et al. elicited positive results, ≈54% of patients underwent a less than D1 resection. Hence, adjuvant CRT could have compensated for insufficient surgery. Three phase-III trials [26–28] on SCC that compared adjuvant CT with surgery alone did not find any benefit in OS. The most recent study among them demonstrated an advantage for 5-year disease-free survival (DFS) for CT compared with surgery alone (55% *versus* 45%, $p=0.037$), but did not demonstrate any significant difference in OS (61% *versus* 52%, $p=0.13$). Five-year survival in patients with LN-positive disease was 52% *versus* 38% ($p=0.041$). It appears that adjuvant CT should be reserved for patients with lymph-node metastases.

In conclusion, there is evidence of an advantage for preoperative CT for esophageal cancer independent from histology. However, this evidence is stronger for adenocarcinoma, which should be treated with preoperative and postoperative CT. Although a meta-analysis and a recent phase-III trial suggested that preoperative CRT confers survival benefit, it is not clear which patients (based on stage, tumor location, histology) will benefit most this treatment. Moreover, the rate of postoperative mortality seems to be increased after this treatment. Data on adjuvant CT/CRT are limited, except for lower esophageal/GEJ adenocarcinoma treated with limited surgery (LN dissection D1 and less) [29].

1.2.3 dCRT

The postoperative rate of mortality for radical esophagectomy is high, ranging from 5.7% to 14%, except in high-volume and dedicated treatment centers. CRT gives a rate of CR of 25–40% depending on tumor stage. Therefore, dCRT has gained interest among oncologists: dCRT is a treatment protocol of combined chemotherapy (mainly consisting of cisplatin and 5-FU) and a radiation total dose of 50–60 Gys, whereas the radiation dose in a neoadjuvant setting is ≈40–45 Gys.

Traditionally, dCRT has been used in patients with cancer of the cervical esophagus (where surgery includes laryngectomy and loss of phonation), in advanced cancers of the thoracic esophagus (either with extended involvement of the LNs) or with non-resectable disease (T4b)) or in patients who are unfit for surgery.

Phase-II trials that investigated the results of CRT alone demonstrated a rate of local control of 40–75%, with a median OS of 12.5–40 months and 3-year survival of 13–37% [30]. More than 70% of patients with a CR after CRT have a complete pathological response, so whether all patients who undergo CRT should also undergo surgery is controversial.

Two randomized studies have been published comparing dCRT with neoadjuvant CRT, and one further study has addressed the comparison between dCRT and surgery alone [1, 7, 29, 31]. dCRT did not give improved survival in comparison with individuals who had undergone resection. However, the rate of morbidity of these treatments was significantly higher for patients undergoing dCRT, even though the mortality (which was mainly postoperative) was significantly higher in resected patients.

The multicenter trial reported by Bedenne and coworkers demonstrated that the addition of surgery to CRT for locally advanced SCC of the esophagus may give mainly improved local control at the expense of a higher post-treatment rate of mortality [32].

However, a study on a series of patients submitted to esophagectomy for ypT0N0M0R0 in high-quality centers demonstrated that survival and local control were better in patients submitted to surgery, which raised the question of the "quality control" of surgery [33]. Quality of life (QoL) also seems to be improved in in patients treated with surgery compared with patients receiving dCRT [34].

We know that it is very difficult to be sure that a complete clinical response equals a complete pathological response, and accurate predictors of post-treatment response are, at the moment, lacking.

It has also been demonstrated that the pure costs of a therapeutic treatment for cancer of the esophagus (surgery, multimodal therapy or dCRT) are influenced significantly by post-treatment complications, which increase costs by between 9% and 25% [35]. Limiting the rate of treatment-related morbidity is clearly a major factor in controlling costs.

In the absence of level-I evidence to base the decision for the treatment of cancer of the esophagus, it appears that the results of different therapeutic approaches for this cancer are influenced significantly by the postoperative rate of mortality and morbidity in terms of clinical results (survival) and costs.

Therefore, it is crucial that these patients have the treatment and care delivery of their choice in centers that can offer a low rate of morbidity and mortality. Several studies have shown that one parameter that appears to be related to postoperative mortality is hospital volume.

In conclusion, it is thought that patients with resectable tumors (apart those with early neoplasms) should receive neoadjuvant CRT. Elderly or surgical high-risk patients who have achieved a complete clinical response might be considered for dCRT and be submitted to intensive observation.

1.2.4 Salvage Esophagectomy

It is estimated that 40–60% of patients submitted to dCRT will manifest persistent or recurrent neoplasms within 1 year. Salvage esophagectomy is carried out after concurrent dCRT (with a protocol that involves >50 Gy) and is selectively indicated for isolated local failures and recurrences, or for treatment-related complications. Salvage surgery is usually taken into consideration for patients with cancer of the cervical esophagus or for subcarinal cancers. For cancers of the upper thoracic esophagus, the likelihood of direct invasion to neighboring organs is very high and radical resection is seldom possible (Table 1.1)

Surgery after dCRT results in a high rate of morbidity and mortality. Table 1.1 reports the results of some Japanese works comparing the results of salvage surgery with trimodal therapy or surgery alone [36–38].

Salvage surgery results in a high rate of postoperative respiratory and anastomotic complications. The postoperative rate of mortality is significantly higher compared with other treatment strategies. One multivariate analysis has shown that dCRT is an independent factor associated with these complications. The main reasons for postoperative mortality are graft necrosis, anastomotic leaks, perioperative hemorrhage, acute distress respiratory syndrome, and tracheobronchial necrosis.

It has been demonstrated that the rate of morbidity and mortality for salvage surgery is increased significantly if patients receive a total radiation dose >55 Gy. In the series reported by D'Journo et al., [39] hospital mortality increased from 14% to 30% in patients receiving more than this radiation dose, and surgical complications increased from 28% to 60%.

The dose and quality of radiotherapy, therefore, influence significantly the results of salvage surgery.

Radiotherapy also influences the rate of anastomotic leaks. Previously, irradiated tissues may have a compromised the blood supply, which would not promote good anastomotic healing.

Other factors that seem to be associated with the high rate of complications for salvage surgery are malnutrition and immunosuppression. Preoperative treatments seem to induce a significant reduction of immunological parameters such as the activity of natural killer cells and total lymphocyte count. Frequently, patients who are candidates for salvage surgery are malnourished with high preoperative weight loss and low albumin levels. Both factors can lead to a high rate of complications. The role of immunonutrition in patients undergoing multimodal treatment to counteract these negative parameters needs to be evaluated.

When dealing with salvage surgery, there are some technical aspects that might act as protective measures for ischemic tracheobronchial lesions and for pulmonary complications during esophagectomy. Care should be taken to preserve the right posterior bronchial artery whenever possible; dissection around the airways should be very carefully managed; and neck dissection should be minimized as much as possible to preserve the blood supply from the inferior thyroidal artery to the trachea [40].

Median survival after salvage esophagectomy has been reported to vary between 7 months and 25 months, with 5-year survival between 0% and 37% [38]. Some parameters appear to influence survival after salvage surgery. The most important is prediction of R0 resection: in case of R1–2 salvage surgery, no survival is reported beyond 13 months. In this respect, Triboulet et al. [41] report-

Table 1.1 Results of some Japaneses work comparing the results of salvage surgery with trimodal therapy or surgery alone [9–11]

		n.	Compl	Pulm	Anast	M
Morita [36]	Surgery alone Preoperative CRT Salvage surgery	253 197 27	24,5% 40,1% **59,3%**	9,9% 14,7% **29,6%**	13% 23,4% **37%**	2,4% 2,0% **7,4%**
Miyata [37]	Preoperative CRT Salvage surgery	112 33		22% **33%**	22% **39%**	4% **12%**
Tachimori [38]	No/Preoperative Salvage surgery	553 59		20% **32%**	25% **31%**	2% **8%**

Compl, complications; *Pulm*, pulmonary complications; *Anast*, anastomosis; *M*, mortality.

ed that criteria for R0 prediction are tumor length <5 cm and limited aortic coverage. Other parameters that favorably influence survival are recurrent instead of persistent disease and a longer free interval compared with earlier relapse.

In conclusion, it appears that salvage esophagectomy is technically feasible but at the expense of a high rate of morbidity and mortality. However, it may be the only established treatment strategy that offers any chance of long-term survival. Due to the high rate of complications and results in terms of survival, it should be attempted only if R0 resection is deemed possible. The selection of patients for salvage esophagectomy should be very meticulous. Among selected patients, 5-year survival of ≤25% can be achieved. The selection and treatment of patients forf salvage surgery should be undertaken only in referral centers.

1.2.5 Minimally Invasive Esophagectomy (MIE)

R0 surgery represents the "gold standard" multimodal treatment of tumors of the esophagus because it offers the best chance of cure even though esophagectomy (despite the significant technical improvements and advances in surgical technique and perioperative management) is associated with significant morbidity and mortality. Minimally invasive surgery has been developed to reduce the complications related to esophagectomy, especially respiratory diseases (which represent the main cause of mortality). Although minimally invasive surgery for esophageal cancer started in the early 1990s, debate continues regarding its safety, efficacy, and benefits (contrary to the situation, for example, with colorectal surgery). Thus, in recent years, minimally invasive surgery for esophageal cancer has spread worldwide. However, this spread has been slower compared with other laparoscopic and thoracoscopic procedures, mainly due to the technical difficulties that this surgery entails and the lack of consensus in the literature. The reason for this is multifactorial and based on the relative rarity of esophageal tumors (which limits randomized studies) and the great variety of minimally invasive surgical approaches more or less associated with traditional surgery. A recent international survey involving 269 surgeons indicated that 78% of them continued to favor open approaches, 14% indicated a preference for minimally invasive resection, and 8% had no preference [42]. What emerges from numerous studies is that MIE is definitely a time-consuming process, as confirmed by the meta-analyses of Butler et al. [43] and Watanabe et al., [44] with a steep learning curve, but with a significant reduction in blood loss. In these studies, the percentage of conversion differs widely and is closely dependent on the experience of the surgeon, so in high-volume centers the rate of conversion is 0–7.3% [45–48], whereas in low-volume centers it is 10–36% [43,49,50]. In the meta-analysis of Butler et al., [43] the median mortality in total minimally invasive transthoracic esophagectomy was 1% (range, 0–6.5%), and in minimally invasive transhiatal esophagectomy (THE) it was 0% (range, 0–4.6%). The rate of mortality of MIE was similar to that for open surgery in the meta-analysis of Nagpal et al. [51] ($p = 0.26$) and in the meta-analysis of Uttley et al. [52], in which mortality was 2.4% for MIE and 3.8% for open surgery. The possible role of MIE in the reduction of morbidity in general and for respiratory complications in particular has been investigated by many retrospective and prospective studies as well as meta-analyses (Table 1.1). In particular, the meta-analysis of Nagpal et al. [51], which took into account 12 studies involving 672 patients (MIE and hybrid mininvasive esophagectomy [hMIE]) compared with 612 patients (open esophagectomy [OE]), showed a reduction of morbidity, including respiratory complications ($p = 0.04$). However, the same authors pointed out that there may be a bias in the analysis related to the inclusion of studies involving THE. Conversely, in the meta-analysis of Watanabe et al. [44], 10 of the 17 retrospective cohort studies did not show substantial differences in respiratory complications. Many authors [46,53–55] believe that the prone position (PP) could reduce pulmonary complications and have technical and physiological advantages. Regarding the former, certainly the visualization of anatomical structures is better because the lungs do not obscure the surgical field, even with one-lung ventilation. Moreover, the esophagous does not lie in the most declivous portion of the chest and is not obscured by overlying blood. Trauma to the lung is also reduced because it does not need to be retracted; the surgeon operates in a plane parallel to the camera with a similar view to that enabled by abdominal laparoscopic surgery. Finally, mobilization of the esophagus and lymphadenectomy become easier, especially at the level of the aortopulmonary window and close to the recurrent nerve, also on the left side. The undoubted physiological advantage in the prone position is the ability to operate without the excluded lung or a partially desufflated lung, thereby avoiding the pulmonary insufflation and desufflation that causes the release of mediators of inflammation and, even if not clinically tested [56], could be responsible for respiratory complications. The limits of the PP are an increase in operating time, and the difficulty in conversion to thoracotomy in case of massive bleeding. Only one randomized trial between MIE carried out in the PP and open surgery has been published, by Biere et al. [57]. They studied 115 patients randomized to an open esophagectomy or total MIE in the PP and esophagogastric anastomosis in the neck. Pulmonary infections in the first 2 weeks were 29% in the open group and 9% in the minimally invasive group ($p = 0.005\%$). The rate of anastomotic leaks and re-operation was greater for minimally invasive surgery (7% *vs*. 4%, $p = 0.390$ and 14% *vs*. 11%, $p = 0.641$ respectively), whereas the rate of vocal-cord paralysis was higher in the open group (14% *vs*. 2%, $p = 0.012$). The duration of hospital stay was shorter in the MIE group compared with the open group (14% *vs*. 11 days, $p = 0.044$).

The goal of surgery is to obtain an R0 resection. Since the advent of minimally invasive surgery there has been a debate as to whether this approach could be similar for open surgery for oncological outcomes. Some studies have focused on the margins of resection, lymph-node retrieval as well as short- and long-term survival. In the meta-analysis of Butler et al., [43] the positive resection margins have been reported in 0–14% of cases. Martin et al. [58] reported that 13.9% (5/36 patients) of patients, who underwent a transthoracic three-stage esophagectomy had involved margins. In the study of Smithers et al., [53] there was no difference in the resection margins between open, total minimally invasive, and hMIE (19%, 14% and 20%, respectively); however in patients referred to surgery alone, the lateral margin involvement was greater in the open group compared with the assisted thoracoscopic group (15% *vs*. 8%).

LN retrieval during esophagectomy correlates directly with long-term survival, and several studies have confirmed this aspect [59–60] with a possible cutoff of 23 LNs [60]. Case series studies show no differences between open, MIE and hMIE in terms of LN retrieval (MIE *vs*. open, $p = 0.83$ and hMIE *vs*. open $p = 0.62$) [53]. In the meta-analysis of Dantoc et al., [61] the median (range) number of LNs found in the open group, MIE and hMIE groups was 10 (3–32.8) 16 (5.7–33.9) and 17 (17–17.15) respectively. There was a significant difference between the MIE and open groups ($p = 0.032$) but not between MIE and hMIE ($p = 0.25$). The explanation provided by several authors is that the increased visualization of LNs by thoracoscopic methods has led to a greater yield of LNs [54,62]. Despite numerous retrospective studies and meta-analyses, few authors have also evaluated the prognosis of patients who underwent MIE and if this technique gives the same oncological outcomes compared with open surgery. In the study of Dantoc et al., [61] there are no significant differences in survival to 5 years between MIE *vs*. OE and hMIE *vs*. OE ($p = 0.33$ and 0.41, respectively). Thus, based on this meta-analysis, minimally invasive surgery seems to have no advantage or disadvantage in terms of long-term survival. Similar results were reported by Osugi et al. [63] who compared 77 patients who underwent video-assisted thoracoscopic (VATS) esophagectomy *vs* 72 OE patients who underwent three-stage esophagectomy. Survival at 3 years and 5 years showed no significant differences (70% and 55% and 60% and 57%, respectively).

One of the major technical difficulties of minimally invasive esophageal surgery is intra-thoracic anastomoses, which may explain (at least in part) the choice of some authors to carry out three-stage esophagectomy and anastomosis in the neck even in patients with tumors of the distal esophagus and cardia. It is hard to compare the different studies in the literature with regard to the location (thoracic or cervical) and type of anastomoses (manual or mechanical and end-to-end, side-to-side, end-to-side). Maas et al. [64] conducted a review of 12 studies reporting on total minimally invasive Ivor Lewis esophagectomy in which the anastomotic leaks ranged from 0% to 10% and anastomotic stenoses from 0% to 27.5% (Table 1.2). Anastomotic stenoses were more common with the transoral technique. Based on these data, we believe that minimally invasive intrathoracic anastomoses should be undertaken only in controlled trials.

In conclusion, although >20 years have passed since the first MIE, and despite numerous studies, there are many unresolved issues. First, the multiple studies in the literature are, for the most part, retrospective and case series, with a limited number of patients, and are hard to compare with each other with respect to stage of disease, surgical technique, and adjuvant treatments. In addition, most studies have methodological limitations that reduce the statistical significance (e.g., authors at the beginning of their surgical experience may have selected patients with early-stage disease or with a better performance status). For these reasons, MIE, although achieving similar results in terms of oncological outcomes, has not demonstrated a clear advantage with respect to traditional surgery and, even if it is a safe alternative, it cannot be considered the procedure of choice. Second, it is very difficult to carry out randomized trials because, in most cases, it is preferable to choose a tailored surgery centered on patient need and not on a surgical technique that some authors consider better than another. Third, minimally invasive surgery should be totally consistent with the open approach (including surgical indications), so tumors of the cardia and distal esophagus should be approached using the Ivor Lewis procedure. In fact, it is well known that anastomoses in the neck have a higher percentage of fistulas and a greater number of recurrent nerve injuries. Moreover, in esophageal adenocarcinoma, laparoscopy may change the management strategy for up to 20% of patients with occult peritoneal or hepatic metastases. For this reason, carrying out the thoracoscopic stage first could make surgery become palliative. Robotic technology, in which three-dimensional vision and articulated arms facilitate surgical dissection, could have, especially in anatomically confined spaces, an important role in this very challenging type of surgery. We must emphasize that MIE is an advanced procedure requiring knowledge of advanced laparoscopic and thoracoscopic techniques and experience in conventional esophageal surgery. Therefore, it should be undertaken only in centers with vast experience in esophageal surgery.