Comparative Effectiveness in Esophagogastric Cancer

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Abstract

Cancer of the esophagus and the gastroesophageal junction (GEJ) continues to have a dismal prognosis, with the incidence of esophageal cancer increasing in the United States. Although radical resection was initially the primary treatment for this disease process, systemic chemotherapy and radiation have been shown to play a role in prolonging survival in most patient populations. This chapter explores the evidence that guides treatment for esophageal and GEJ cancer today. Chemotherapy and radiation therapy were introduced as treatment modalities for esophageal and GEJ cancers when it became evident that surgical therapy alone provided poor long-term survival rates. A variety of treatment

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strategies have been explored including preoperative (neoadjuvant) and postoperative (adjuvant) chemotherapy, with and without radiation. The evidence suggests that neoadjuvant chemotherapy or chemoradiotherapy provides better outcomes compared to surgery alone for esophageal, GEJ, and gastric cancers. Studies indicate a trend towards improved survival when neoadjuvant chemoradiotherapy is compared to chemotherapy alone. When patients have undergone resection with node-positive disease without receiving neoadjuvant therapy, some form of adjuvant treatment is recommended. This chapter also explores the surgical management of esophageal, GEJ, and gastric cancers including the extent of the gastric lymph node dissection. It also includes a discussion about adherence to national guidelines in terms of gastric cancer treatment and esophageal and gastric lymph node examinations.

Contents

1 Introduction

Esophageal cancer is the eighth most common cancer worldwide with an estimated 482,000 cases diagnosed in 2008. In the United States, it was estimated that in 2013 there would be 17,990 new cases (14,440 for men and 3,550 for women) and 15,210 deaths due to esophageal cancer [1]. The incidence of esophageal adenocarcinoma (EAC) continues to increase drastically in the United States and its incidence surpassed that of squamous cell carcinoma (SqCC) in 1990 [2]. This trend has been attributed to the fact that smoking rates and alcohol consumption are decreasing leading to a decrease in SqCC while obesity is increasing leading to an increase in gastroesophageal reflux disease and therefore increased incidence of EAC. The overall survival of patients with esophageal cancer remains poor with minimal improvement in the last 30 years [3]. The 5-year survival rate for all patients with esophageal cancer during the period of 2001–2007 was 19 % [3].

Radical resection has been the mainstay of treatment for esophageal cancer although frequent local failure and distant metastases have prompted the addition of radiation and systemic chemotherapy. As is evident by the poor survival of patients with esophageal cancer who undergo radical resection and subsequently have disease recurrence, tumor dissemination occurs early in the disease process and because of this systemic chemotherapeutic agents have been the focus of many studies. Despite multiple trials investigating the efficacy of chemotherapy with or without radiation, administered preoperatively, postoperatively, or both, much controversy remains regarding the ideal treatment course. As the cost of target chemotherapeutic agents and radiation modalities rises with only marginal gains in efficacy, the cost effectiveness of treatment is under intense investigation.

Comparative effectiveness research (CER) reached a milestone in 2009 when the American Recovery and Reinvestment Act was signed into law and allotted 1.1 billion dollars to support CER [4]. Two key elements of CER include the direct comparison of effective interventions and the study of these interventions in the typical patient population encountered in typical daily clinical care [4]. CER relies not only upon randomized clinical trials which often include patients in “ideal” circumstances to control for variables, but also upon utilizing large patient databases to draw conclusions from “everyday” patients. This section will focus on the randomized control trials comparing surgery alone to either neoadjuvant or adjuvant therapy in patients with esophageal, gastroesophageal (GEJ), and gastric cancers, as well as how we have used this information in our clinical practice in the United States with our “everyday” patient population. The extent of lymph node dissection will also be addressed in patients with gastric cancer.

2 Role of Radiation Alone

There have been several studies evaluating the role of radiation in the treatment of esophageal cancer. The use of radiation alone has resulted in poor local control and survival with local recurrence rates as high as 77 % [5] and 5-year overall survival rates between 0 and 21 % [6–11]. Clinical trials have also investigated the use of neoadjuvant radiation and surgery compared to surgery alone but there has been a lack of conclusive evidence indicating superiority. A meta-analysis including 1,147 patients from 5 randomized trials evaluated patients with resectable esophageal tumors, the majority with SqCC. These trials compared neoadjuvant radiation and surgery with surgery alone. The overall hazard ratio was 0.89 which suggests a benefit for preoperative radiation although this was not a significant difference [12]. One shortcoming in extrapolating these results to the general population is that most of these trials included patients with SqCC while the incidence of EAC is rapidly increasing in the United States. Further studies would be needed with modern radiotherapy techniques used in both histologies of esophageal cancer.

Postoperative radiation has also been studied and several randomized trials have compared patients with adjuvant radiation to no adjuvant therapy [13, 14]. While these have been small studies, the patients who received radiation did not have increased survival and suffered increased radiation-related complications. In conclusion, radiation has not been shown to be beneficial when used alone pre- or post-operatively in esophageal cancer.

3 Role of Definitive Chemoradiotherapy

Due to the poor outcomes when radiation is used alone to treat esophageal cancer, chemoradiation has been extensively used as a treatment modality. The chemotherapy is thought to sensitize the tumor cells to the radiation as well as control micrometastatic disease. Most of the studies evaluating the role of chemoradiation in non-surgical patients have been on those with SqCC. Wong evaluated 19 randomized trials comparing chemoradiation to radiation alone in nonoperative esophageal cancer patients. The study demonstrated significantly improved overall survival when chemotherapy was added to the radiotherapy compared to radiotherapy alone [15]. The Eastern Cooperative Oncology Group (ECOG) used mitomycin C and 5-FU with radiation compared to radiation alone in patients with SqCC esophageal cancer, and found a statistically significant increase in survival in the chemoradiation group. The median survival for the chemoradiation group was 14.5 months compared to 9.2 months for the radiation alone group [16]. These results were replicated when the Radiation Therapy Oncology Group (RTOG 85-01) used cisplatin and 5-FU with radiation (50 Gy) and demonstrated a survival benefit compared radiation alone (60 Gy) [7]. Despite the survival benefit of the chemotherapy with the radiation, there was a 47 % incidence of local failure. Because of this, the INT 0123 trial evaluated increased radiation doses (50.4 vs. 64.8 Gy) combined with chemotherapy. The increased radiation dose did not increase survival or local control and resulted in increased treatment-related mortality, suggesting the ideal radiation dose is 50.4 Gy. The current standard of care for nonoperative patients is 50.4 Gy combined with cisplatin and 5FU [17].

4 Role of Neoadjuvant Chemoradiotherapy

For those patients in which surgical resection is an option, the role of neoadjuvant chemoradiation has been studied. There have been at least eight randomized trials evaluating concurrent use of chemotherapy and radiation (Table 1) [18–25]. Three of those trials enrolled mostly patients with SqCC while the others included a mixture of EAC and SqCC. Out of the eight trials, four demonstrated statistically significant improvement in survival [18, 22, 23, 25]. In the CROSS trial, Dutch investigators

Table 1 Neoadjuvant chemoradiation versus surgery alone

Trial	N	Histology (%)	CRT regimen (Gy)	Median survival	3 year OS (%)	*p* value
Lee et al. [20]	50 S	SqCC 100	Cisplatin, 5FU, 45.6	27.3 m	–	NS
	51 CRT			28.2 m		
Lv et al. [23]	80 S	SqCC 100	Paclitaxel, cisplastin, 40	36 m	51.3, 33.8 (5 year)	0.04 (CRT groups compared to S group at 5 years)
	80 CRT (pre-op)			53 m	63.5, 43.5 (5 year)	
	78 CRT (post-op)			48 m	62.8, 42.3 (5 year)	
Mariette et al. [89][a]	98 S	SqCC 71	Cisplatin, 5FU, 45	43.8 m	48.6	NS
	97 CRT			31.8 m	55.2	
Walsh et al. [18]	55 S	AC 100	Cisplatin, 5FU, 40	11 m	6	0.01
	58 CRT			16 m	32	
Urba et al. [19]	50 S	AC 75	Cisplatin, 5FU, vinblastine, 45	17.6 m	16	NS
	50 CRT			16.9 m	30	
Burmeister et al. [21]	128 S	AC 62	Cisplatin, 5FU, 35	19 m	–	NS
	128 CRT			22 m	–	
Tepper et al. [22]	26 S	AC 75	Cisplatin, 5FU, 50.4	1.8 year	16 (5 year)	0.002
	30 CRT			4.5 year	39 (5 year)	
van Hagen et al. [25]	188 S	AC 75	Carboplatin, paclitaxel, 41.4	24 m	44	0.003
	178 CRT			49.4 m	58	

N number, *CRT* chemoradiation, *S* surgery, *m* months, *OS* overall survival, *NS* not significant, *SqCC* squamous cell carcinoma, *AC* adenocarcinoma, *Gy* gray, *FU* fluorouracil, [a]indicates an abstract

randomly assigned patients with resectable esophageal or gastroesophageal junction (GEJ) tumors (75 % with adenocarcinoma) to surgery alone versus carboplatin, paclitaxel, and concurrent radiotherapy followed by surgery [25]. This study demonstrated similar post-operative complications and in-hospital mortality between the two groups as well as a 29 % pathological complete response in the chemoradiation group. Significantly, there was an overall survival increase in the chemoradiation group with a median survival of 49 months compared to 24 months in the surgery alone group [25]. Walsh et al. [18] also demonstrated a significant survival benefit in the chemoradiation group with a 3-year survival of 32 % compared to 6 % in the surgery alone group. While the two trials mentioned above were mostly EAC, Lv et al. [23] conducted a study in China with only SqCC patients. In this study patients were randomized to one of three arms: preoperative chemoradiation, postoperative chemoradiation, or surgery alone. There was a statistically significant improvement in survival in both the pre- and post-operative chemoradiation groups compared to the surgery alone group [23]. The largest meta-analysis conducted evaluating neoadjuvant chemoradiation included 1,854 patients and found the all-cause mortality HR to be 0.78 ($p < 0.0001$). The study included 12 randomized trials evaluating sequential and concurrent treatment, as well as SqCC and EAC [26]. When the patients were divided into histologic subtypes, the HR for SqCC was 0.80 ($p = 0.004$) and the HR for AC was 0.75 ($p = 0.02$).

In summary, for patients with potentially resectable localized esophageal and GEJ cancers, several randomized trials as well as meta-analyses demonstrate improved survival and efficacy with preoperative chemoradiation therapy compared to local therapy alone (surgery or radiation).

5 Role of Adjuvant Chemoradiotherapy for Gastroesophageal Tumors

Several trials have evaluated the role of adjuvant chemoradiation in patients with resectable tumors of the GEJ or stomach. The INT 0116 trial investigated patients with AC of the GEJ or stomach and randomized 556 patients to surgery plus postoperative chemoradiation or surgery alone [27]. The adjuvant chemoradiation included 5-FU and 45 Gy. The median overall survival in the chemoradiation group was significantly improved at 36 months compared with 27 months in the surgery alone group. The survival benefit was confirmed in the 10-year follow-up study [28]. The study conducted by Lv et al. [23] mentioned above with only SqCC patients included a postoperative chemoradiation group which had a statistically improved survival compared with the surgery alone group although the study was not powered to detect differences between the pre-operative chemoradiation group and the post-operative chemoradiation group.

6 Role of Neoadjuvant Chemotherapy

Due to the controversy surrounding radiation therapy and its utility in esophageal and gastric cancers, multiple trials have evaluated chemotherapy prior to surgery compared to surgery alone. At least 9 randomized trials have evaluated this question (Table 2). Similar to neoadjuvant chemoradiation, these trials are a mixture of SqCC and EAC and the results are mixed regarding survival benefit. Six trials did not show a benefit [29–34] while four did show a significant survival benefit [35–38]. One of the largest randomized control trials was the MAGIC trial which randomly assigned patients with resectable AC (stage II or higher with no evidence of metastases) of the stomach (74 %), GEJ (11 %), or lower esophagus (15 %) to either perioperative chemotherapy and surgery (250 patients) or surgery alone (253 patients) [36]. Chemotherapy consisted of three cycles each pre- and post-operatively of epirubicin, cisplatin, and 5-FU. The complication rate and 30-day mortality of both groups was similar. The perioperative chemotherapy group had a statistically increased 5-year survival rate of 36 % compared to 23 % in the surgery alone group. One limitation of the treatment strategy is that only 42 % of the perioperative chemotherapy group actually received the postoperative chemotherapy. A similar trial by Ychou et al. [38] again included only patients with resectable AC of the stomach, GEJ, and distal

Table 2 Neoadjuvant chemotherapy versus surgery alone

Trial	N	Histology (%)	Chemotherapy regimen	Perioperative mortality (%)	3 year OS (%)	*p* value
Cunningham et al. [36]	253 S	AC 100	Epirubicin, cisplatin, 5FU (pre-op and post-op)	5.9	23 (5 year)	0.009
	250 C			5.6	36 (5 year)	
Ychou et al. [38]	111 S	AC 100	Cisplatin, 5FU (pre-op and post-op)	4.5	24 (5 year)	0.02
	113 C			4.6	38 (5 year)	
	19 C			12		
Schlag [30]	24 S	SqCC 100	Cisplatin, 5FU	10	10 m (MS)	NS
	22 C			19	10 m (MS)	
Law et al. [32]	73 S	SqCC 100	Cisplatin, 5FU	8.7	13 m (MS)	NS
	74 C			8.3	16.8 m (MS)	
Kelsen et al. [33]	227 S	AC 53	Cisplatin, 5FU	–	26	NS
	216 C			–	23	
Ancona et al. [34]	48 S	SqCC 100	Cisplatin, 5FU	4.2	22 (5 year)	NS
	48 C			4.2	34 (5 year)	
Allum et al. [37] (MRC)	402 S	AC 67	Cisplatin, 5FU	10	17 (5 year)	0.03
	400 C			10	23 (5 year)	
Boonstra et al. [35]	84 S	SqCC 100	Cisplatin, etoposide	4	17 (5 year)	0.03
	85 C			5	26 (5 year)	
Maipang et al. [31]	22 S	SqCC 100	Cisplatin, vinblastine, bleomycin	–	36	NS
	24 C			17	31	

N number, *S* surgery, *C* chemotherapy, *AC* adenocarcinoma, *SqCC* squamous cell carcinoma, *FU* fluorouracil, *OS* overall survival, *NS* not significant

esophagus and randomized 113 patients to the perioperative chemotherapy group and 111 patients to the surgery alone group. A key difference in this trial compared to the MAGIC trial was the patient population. In the MAGIC trial 74 % of the patients had gastric cancer compared to 25 % in this trial, and GEJ/distal esophageal comprised 26 % in the MAGIC trial compared to 75 % in this trial. The chemotherapy regimen in this trial included two or three cycles of cisplatin and 5FU preoperatively and three or four cycles postoperatively. The perioperative chemotherapy group had a significant increase in 5-year survival of 38 % compared to the surgery alone group at 24 %. Perioperative chemotherapy also significantly improved the curative resection rate from 73 to 84 %. Another large trial by the Medical Research Council (MRC) included 802 patients. This patient population included 67 % with EAC although it did not include gastric cancer [39]. Patients were randomized to preoperative chemotherapy consisting of cisplatin and 5FU followed by surgery or surgery alone. Overall survival was significantly improved in the preoperative chemotherapy group compared to surgery alone with a hazard ratio of 0.79. A follow-up study by Allum verified improved survival for the preoperative chemotherapy group with a 5-year survival of 23 % compared to 17 % for the surgery alone group [37]. This survival benefit held true for both EAC and SqCC. A similar trial by

Kelsen did not show a survival benefit [33]. In this randomized trial 216 patients underwent preoperative chemotherapy with cisplatin and 5-FU and 227 patients underwent surgery alone. The histological type was split 50/50 between EAC and SqCC. There was not a significant difference in survival between the neoadjuvant chemotherapy group and the surgery alone group although there was a survival benefit for those patients that responded to chemotherapy. The reason that there was no difference in survival in this study is unclear as similar chemotherapeutic agents were used. One possibility for the difference was the study size of the MRC trial included almost twice as many patients and another is that the percentage of patients with SqCC versus EAC was different.

7 Role of Adjuvant Chemotherapy

Adjuvant chemotherapy is generally only recommended in patients with positive lymph nodes. Studies that have included adjuvant chemotherapy after neoadjuvant chemotherapy and/or surgery include the MAGIC trial and the French trial [36, 38] although in both of these trials only about 50 % of patients intended to receive postoperative chemotherapy actually did. There are a few trials evaluating adjuvant chemotherapy only. Ando randomized 205 patients with esophageal SqCC to either surgery alone or surgery followed by cisplatin and vindesine. The study did not find a statistical significance in 5-year survival between the two groups [40]. A subsequent study by Ando again included patients with esophageal SqCC randomized to surgery alone versus chemotherapy including cisplatin and 5FU. The 5-year survival rates were 52 and 61 % for surgery alone and surgery plus chemotherapy, respectively. This difference was not statistically significant [41]. It is important to realize that both of these studies only included those patients with esophageal cancer and furthermore only SqCC histology.

The question of neoadjuvant chemotherapy compared to adjuvant chemotherapy has been evaluated by a Japanese trial in which patients with esophageal SqCC were randomized to cisplatin and 5FU either pre- or post-operatively. Overall 5-year survival rates were significantly improved in the preoperative chemotherapy group (55 %) compared to the postoperative chemotherapy group (43 %) [42].

8 Summary

In conclusion, the evidence suggests that neoadjuvant chemotherapy or chemoradiotherapy provides better outcomes compared to surgery alone for esophageal cancer, GEJ, and gastric cancers. Meta-analyses indicate a trend towards improved survival in neoadjuvant chemoradiotherapy compared to neoadjuvant chemotherapy. For those patients that have undergone resection for node-positive esophageal cancer without receiving neoadjuvant therapy, some form of adjuvant treatment is generally recommended although there is no evidence supporting chemoradiation versus chemotherapy alone. One of the barriers to using randomized control trials in CER is that to answer certain questions the number of patients needed to enroll would be prohibitive both logistically and financially. Utilization of large databases is often beneficial to examine these questions from a different angle. One important question that must be addressed is how are clinicians using the information from these trials and consensus guidelines to treat their everyday patients?

9 Implementation of Consensus Guidelines for Esophageal Cancer Treatment

It is evident that surgery alone is insufficient for treatment of locally advanced esophageal and GEJ cancers and a plethora of randomized trials indicate that neoadjuvant treatment is superior to surgery alone. Consensus groups such as the National Comprehensive Cancer Network (NCCN) recommend as standard of care neoadjuvant therapy for stage II and III esophageal cancer [43]. Multimodality therapy for esophageal cancer was advocated in the 1980s when it became evident that surgical resection alone resulted in poor outcomes. Neoadjuvant chemotherapy and chemoradiation was implemented into clinical practice after a few large randomized trials demonstrated survival benefits with neoadjuvant treatment in the late 1990s and early 2000s [18, 22]. The ideal treatment regimen including type of chemotherapy, use of radiation, and if so what dose, were largely unknown due to a heterogeneous and unstandardized mix of trials with often conflicting results. Because of this uncertainty Merkow evaluated the national trends for neoadjuvant use in esophageal cancer to determine the effect of these randomized clinical trials on current esophageal cancer treatment. The study evaluated 8,562 patients from the National Cancer Database (NCDB) that were surgically treated for esophageal cancer between 1998 and 2007 [44]. This study demonstrated that for stage I patients neoadjuvant therapy use significantly decreased from 23.5 % in 1998 to 11.2 % in 2007. For stage II and III patients neoadjuvant use significantly increased: from 48 % in 1998 to 72.5 % in 2007 for stage II patients and from 51 % in 1998 to 90 % in 2007 for stage III patients. Factors that were found to be associated with decreased use of neoadjuvant therapy for stage II and III patients were older age, severity of comorbidity, Medicare insurance coverage, clinical stage II disease, and residence in the western United States [44]. An additional factor evaluated using the NCDB was perioperative mortality. In this study evaluating over 1,000 different hospitals, there was no significant difference in perioperative mortality between the patients treated with neoadjuvant therapy compared to those undergoing surgery alone. There was a significant decrease in surgical margin positivity rate as well as lymph node positivity in those patients who underwent neoadjuvant treatment compared to the surgery alone group.

10 Implementation of Consensus Guidelines for Gastric Cancer Treatment

In a similar study to the one mentioned above, Sherman examined the implementation of gastric cancer guidelines into clinical practice using the NCDB [45]. In some clinical trials proximal gastric adenocarcinoma, GEJ, and distal esophageal tumors are treated similarly [27, 36, 38]. As mentioned before, the Cuningham (MAGIC), Macdonald (INT-0116), and Ychou trials demonstrated that adjuvant therapy use in gastric AC resulted in a significantly improved overall survival [27, 36, 38]. These trials were published in the early 2000s and it was unclear how the results of these trials translated into generalized clinical practice outside the auspices of a trial. Based on these studies, the NCCN guidelines recommend preoperative chemoradiation for localized GEJ AC and perioperative chemotherapy or postoperative chemoradiation therapy for localized gastric AC [43]. To determine the impact of the studies and guidelines, Sherman identified 30,448 patients from the NCDB who underwent surgical resection for a diagnosis of stage IB-III gastric adenocarcinoma between 1998 and 2007 [45]. The proportion of patients with stage IB-III gastric adenocarcinoma who received systemic therapy (either pre- or post-operatively) increased by 71 % (from 35.7 to 61 %) between 1998 and 2007 while the proportion of patients who underwent surgery alone significantly decreased. The largest annual increase occurred between 1999 and 2000 which coincides with the release of the INT-0116 trial findings. The use of neoadjuvant therapy was also significantly increased between 1998 and 2007 from 6 to 20 %, with the largest increase between 2005 and 2006 which corresponded with the release of the MAGIC trial results. Multivariate analysis identified several factors for predicting systemic therapy use (pre- or postoperative): young age, male, fewer comorbidities, higher income, and private insurance. The most predictive factor for receiving neoadjuvant therapy was tumor location in the gastric cardia.

11 Summary

These studies indicate that clinical treatment of gastroesophageal cancer in the United States is changing. These changes seem to correlate with the release of large randomized trials and consensus guideline updates. While many physicians are altering their treatment based on current literature and studies, many physicians have not yet implemented these changes.

12 Gastric Cancer Lymph Node Dissection

One of the first clinicians to promote extended lymphadenectomies in gastric cancer was a Polish-Austrian surgeon Mikulicz [46]. He believed that aggressive locoregional control was paramount in controlling the orderly step-wise progression of cancer metastases through the lymph nodes. Even today the debate continues: those surgeons that advocate a D2 or D3 resection echo Mikulicz's beliefs for locoregional control, and opponents argue that extensive surgery only adds perioperative morbidity and mortality without a survival advantage. Most patients who present with gastric cancer in the United States have advanced disease and the majority who undergo resection are found to have nodal disease [47, 48]. Controversy continues as Asian countries have been performing extended lymphadenectomies for decades while Western countries have only recently incorporated extended lymphadenectomies (D2) into their guidelines [43, 49]. Gastric cancer lymphatic drainage generally follows the vasculature. The most common locations for nodal metastases are lesser curvature (29 %), infra-pyloric (23 %), greater curvature (22 %), right cardia (19 %) and left gastric artery (19 %) [50]. Generally gastric lymph node dissections can be divided into D1 through D4 and the lymph node stations are numbered (Fig. 1). A D1 dissection involves removal of the stomach and the perigastric lymph nodes. In a D2 dissection, additional lymph nodes are removed including nodes along the left gastric, common hepatic, splenic, and left hepatoduodenal artery. D3 and D4 dissections include posterior hepatoduodenal and para-aortic lymph nodes [51]. Much of the controversy surrounding lymph node dissections in gastric cancer started in the 1980s when stage-specific 5-year survival in Japan was shown to be superior to that in the United States [52]. It was theorized that this difference was due to the extended lymphadenectomies performed in Japan

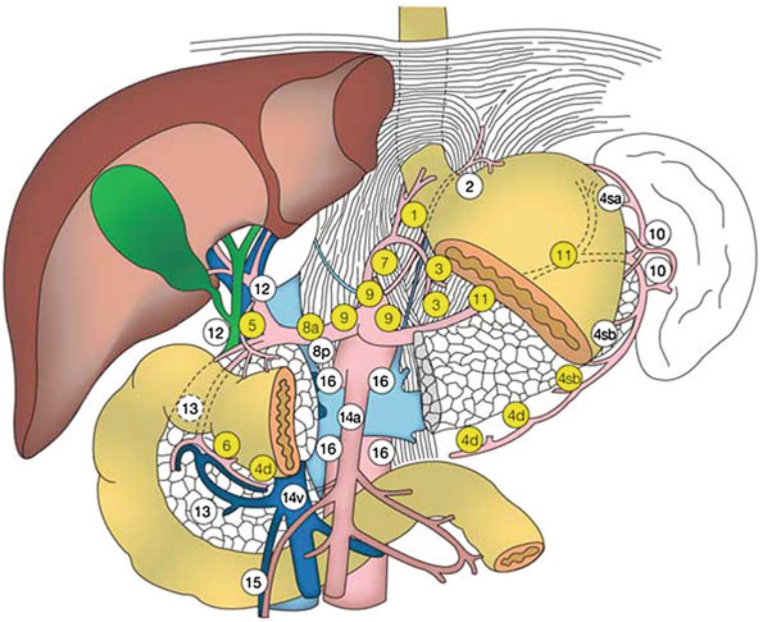

Fig. 1 Gastric lymph node stations [91]

compared to the United States. This stimulated multiple randomized trials comparing the extent of gastric lymphadenectomies.

One of the first trials was performed in South Africa by Dent in the late 1980s. In this study 22 patients were randomized to a D1 resection and 21 patients to the D2 resection group. While the morbidity was found to be higher in the D2 group, the survival at 3 years was similar between the two groups [53]. A larger trial was performed in the United Kingdom with a total of 400 patients who were randomized to a D1 or D2 lymphadenectomy [54]. For tumors in the middle and upper third, a distal pancreaticosplenectomy was performed to obtain the splenic hilar nodes and retropancreatic nodes. There was no significant difference in 5-year survival between the two groups: 35 % compared to 33 % for D1 versus D2 groups respectively. Although there was no overall survival difference, on multivariate analysis, those patients who underwent a D2 resection but did not undergo a distal pancreaticosplenectomy did have an improved survival rate compared to the D1 group. A similar trial performed in the Netherlands accrued patients with gastric cancer from 80 Dutch hospitals and randomized 380 patients to a D1 lymphadenectomy and 331 to a D2 lymphadenectomy [55]. The 5-year survival rates were not significantly different: 45 % for the D1 group and 47 % for the D2 group. There was a significant increase in complications (25 % vs. 43 %) and postoperative deaths (4 % vs. 10 %) in the D2 group compared to the D1 group. When the study was followed out to 11 years the survival for the two groups remained similar: 30 % versus 35 % for the D1 and D2 groups respectively [56]. When subgroups were analyzed, it was determined that a D2 lymphadenectomy may benefit those patients with N2 disease and that a pancreatectomy/splenectomy seemed to be the biggest risk factor of postoperative morbidity and mortality.

One of the main concerns regarding the two prior studies was a lack of surgeon training in D2 resections and variations between individual surgeons at different hospitals. Because of this the next trial performed in Italy included specialized surgeon training. In this study, 267 patients with gastric cancer were randomized to a D1 or D2 resection [57]. Unlike the previous studies, there was not a significant difference in morbidity in the D1 versus D2 groups (12 % vs. 18 %) or operative mortality (3 % vs. 2.2 % respectively) [58]. Similar to the previous studies, there was not a significant difference in 5-year survival between the D1 and D2 groups: 66.5 % versus 64.2 % respectively. When the subgroups were analyzed, it was found that patients with T2-T4 tumors and positive lymph nodes who underwent a D2 resection had a significantly improved 5-year survival rate compared to those in the D1 group: 59 % versus 38 %.

To determine the outcome of extended lymphadenectomies in Eastern patients, a randomized trial in Taiwan was performed at a single institution with 3 well-trained surgeons [59]. Patients were randomized to a D1 resection or a D3 resection. A D1 resection was defined as dissection of the perigastric lymph nodes in close proximity to the tumor along the greater and lesser curvatures [59]. A D3 dissection was defined as additional lymph node dissection around the blood vessels supplying the stomach such as the left gastric, common hepatic, and splenic, as well as lymph nodes in the hepatoduodenal ligament and retropancreatic region. Overall 5-year survival was significantly improved in the D3 resection group at 60 % compared with the D1 group at 53.6 %. Quality control for the surgeons was attempted by having only 3 surgeons perform the operations and each completed at least 25 D3 resections prior to the study. This study implies that in gastric cancer a D3 resection by well-trained surgeons offers a survival benefit compared to a D1 resection. A Japanese study evaluated whether an even more extensive lymphadenectomy known as a para-aortic lymph node dissection (PAND) was superior to the standard D2 lymphadenectomy with gastric resection [60]. The trial was performed in 24 hospitals and 523 patients with curable gastric cancer were randomized to either the standard D2 resection or a D2 resection plus PAND. There was a trend toward increased complications in the D2 plus PAND group with 28 % compared to the D2 group at 21 %. There was no significant difference in 5-year survival between the two groups: 70.3 % for the D2 plus PAND group compared to 69.2 % for the D2 alone group.

13 Gastric and Esophageal Lymph Node Examination in the United States

Regardless of one's opinions about the ideal lymphadenectomy, what has been shown is that lymph node metastases are an important prognostic factor after gastric resection [61–64]. An adequate lymphadenectomy is necessary to allow for accurate pathologic staging. Several studies have investigated this issue and current consensus guidelines recommend a minimum of 15 lymph nodes to allow for reliable staging [43, 65–67]. Similar to esophageal and gastric cancer guidelines, it was unclear how treatment across the United States reflected these recommendations. Bilimoria evaluated how hospital type and volume effected the adequacy of the lymph node resection in gastric cancer [68]. The NCDB was used to identify 3,088 patients who underwent resection for gastric cancer. Of these patients, only 23.2 % had greater than or equal to 15 lymph nodes resected for pathologic evaluation, with an average of 7 lymph nodes [68]. The study also demonstrated that patients were significantly more likely to have greater than 15 lymph nodes examined if they underwent resection at an NCCN-NCI center compared to other academic or community hospitals. Patients were also significantly more likely to have greater than 15 lymph nodes examined if they underwent resection at the highest volume centers compared to high, moderate, or low volume centers.

Like gastric cancer, the NCCN guidelines recommend examining greater than 15 lymph nodes for adequate staging. The adequacy of lymph node resections following esophageal resection in the United States was unknown prior to a study by Merkow which evaluated this question. The study identified 13,995 patients from the NCDB of which 23.5 % had a least 15 lymph nodes examined [69]. During the most recent period of study from 2005 to 2007, greater than 15 lymph nodes were examined in 39 % of academic hospitals compared to 28 % at community hospitals, and in 44.1 % at high-volume centers compared to 29.3 % at low-volume centers.

14 Surgical Treatment for Esophageal and Gastric Tumors

Another source of controversy in esophageal cancer is the surgical management. Esophagectomy is the surgical treatment of esophageal cancer. The type of esophageal resection is dictated by the location of the tumor, the available choices for conduit, and surgeon experience. Surgical therapy remains the mainstay for patients with localized lesions who are fit for major resection, and in the absence of metastatic disease, resection with negative microscopic margins offers the best chance for long-term survival [70, 71]. Appropriate surgical resection depends upon the location and extent of the primary tumor. Surgical strategy should provide the optimal cancer operation with minimal morbidity. For patients with GEJ or proximal gastric lesions, the surgeon will have to make a choice between performing a transabdominal total gastrectomy with esophagojejunal anastomosis versus a combined transthoracic and transabdominal resection of the distal esophagus and proximal stomach with intrathoracic esophagogastric anastomosis (traditional Ivor-Lewis procedure) or transhiatal esophagectomy with cervical esophagogastric anastomosis. In general, if the tumor is limited to the proximal portion of the stomach with minimal extension past the GEJ, a total gastrectomy with intraabdominal esophagojejunal anastomosis is our procedure of choice. We recognize that a longer (>5 cm) negative distal margin will not enhance survival for patients with proximal lesions, but this procedure may minimize post-gastrectomy complications compared to proximal subtotal gastrectomy.

15 Transhiatal Versus Transthoracic Esophagectomy

In an effort to obtain an adequate esophageal margin for more proximal esophageal lesions, an esophagectomy is often required. While there is debate as to whether a transhiatal approach versus a transthroacic approach is preferred, there is no clear evidence indicating the ideal approach [72, 73]. In a meta-analysis by Rindani comparing those two techniques, esophagectomy data from 5,500 patients (44 series) were analyzed [74]. The results demonstrated similar rates of postoperative respiratory and cardiovascular complications. A higher incidence of anastomotic leaks and recurrent laryngeal nerve injuries was found in the transhiatal group [74]. While the 30-day mortality was 6.3 % in the transhiatal group compared to 9.5 % in the transthoracic group, the 5-year survival was similar [74]. In a landmark study, Hulscher et al. [75] assigned 220 patients with adenocarcinoma of the mid-to-distal esophagus or gastric cardia involving the distal esophagus either to transhiatal esophagectomy or to transthoracic esophagectomy with extended en bloc lymphadenectomy. Both operative time and estimated blood loss (EBL) were significantly lower with the transthoracic esophagectomy: 3.5 h versus 6 h and 1 L versus 1.9 L respectively [75]. Although pulmonary complications and chylous leakage were higher after transthoracic esophagectomy (57 % vs. 27 % and 10 % vs. 2 %

respectively) the in-hospital mortality was not significantly different. Duration of mechanical ventilation, ICU and hospital time was shorter in the transhiatal group. Furthermore, there was no significant difference in overall or disease free survival for patients who underwent transhiatal esophagectomy versus those who underwent transthoracic esophagectomy. In 2008, Chang published data from a large population-based study comparing both approaches through the Surveillance, Epidemiology and End Results (SEER) and found a lower operative mortality after transhiatal esophagectomy; 6.7 % versus 13.1 % [76]. Although a higher 5-year survival was noted after transhiatal esophagectomy, after adjusting for other variables, no significant difference was found.

16 Minimally Invasive Approaches of Esophagectomy

16.1 Ivor Lewis Esophagectomy

The minimally invasive Ivor Lewis esophagectomy begins with five-port laparoscopy in supine position. After gastric mobilization and abdominal lymphadenectomy the gastric conduit is created by use of an endoscopic linear stapler. Once the phrenoesophageal ligament is divided, the abdominal part of the procedure is complete and the patient is repositioned in either the left lateral decubitus position or the prone position. The procedure is continued with four-port thoracoscopy. The first thoracic step is the division of the pulmonary ligament followed by circumferential mobilization of the esophagus, division of the azygos vein and dissection of paraesophageal, lower and middle mediastinal, subcarinal and right-sided paratracheal lymph nodes. When the gastric conduit is mobilized into the thorax, the esophagus is divided just superior to the level of the carina and an intrathoracic anastomosis can be accomplished with transoral and transthoracic staplers. Based on a recent review comparing open and minimally invasive esophagectomy in terms of anastomotic leakage and stenosis rates, both techniques can be considered equally safe and effective [77, 78]. However, a hybrid minimally invasive technique combining the open and endoscopic techniques for transthoracic resection has also been described.

17 McKeown Esophagectomy

The 3-incisional McKeown esophagectomy combines features of the transhiatal and the Ivor-Lewis transthoracic technique. The abdominal and thoracic stages of the procedure are comparable to the previously described Ivor-Lewis technique and allow the surgeon to perform the same two-field (upper abdominal and mediastinal) lymphadenectomy under direct vision. The main difference however, is the addition of a left cervical incision to allow a cervical anastomosis. Although robust scientific evidence is lacking, cervical reconstruction is considered to have clinical advantages compared to an intrathoracic anastomosis. The advantages include improved leak management in the event of an anastomotic breakdown, and wider proximal resection margins. A high rate of anastomotic leakage and stenosis are the disadvantages of this technique [79, 80]. The thoracoscopic and laparoscopic portion of the minimally invasive McKeown technique are comparable to the descriptions above. However, the procedure usually begins with a thoracic stage to avoid the need for extra repositioning. Removal of the resection specimen and construction of the gastric conduit usually occurs through an accessory upper midline incision of 5 cm. Subsequently the gastric conduit is delivered to the cervical region where again a hand-sewn or stapled anastomosis can be performed. Similar to the minimally invasive Ivor Lewis approach, hybrid minimally invasive McKeown procedures can be performed.

18 Robotic Esophagectomy

A robot-assisted esophagectomy has also been described, allowing three-dimensional visualization, improved magnification, and a greater range of instrument motion. Robotic assistance has been described for gastric mobilization (in both transhiatal and transthoracic resections), mediastinal lymphadenectomy, dissection of the esophagus and generation of an intrathoracic anastomosis. The need for single-lung ventilation is a potential limitation. However, preliminary studies showing equality with above-mentioned techniques in terms of safety and efficacy have led to the ROBOT trial, comparing open and robot assisted esophagectomy [81, 82]. A combination of randomized controlled trials (RCT) and meta-analyses have compared open versus minimally invasive esophagectomy with the goal of determining the most effective approach for esophageal cancer [77, 83, 84]. The following section will compare open versus minimally invasive esophagectomy in terms of their respective outcomes.

19 Outcomes

Nagpal et al. [85] addressed intraoperative outcomes based on five comparative studies and found that blood loss was significantly lower in the minimally invasive group. This beneficial effect of minimally invasive surgery was confirmed by the recent TIME trial by Biere, comparing minimally invasive versus open esophagectomy for patients with esophageal cancer. There was a significant decrease in blood loss in the minimally invasive group (200 mL) versus the open esophagectomy group (475 mL) [77]. Comparative studies evaluating operative time have demonstrated decreased operative times in the laparoscopic group compared to the open transhiatal esophagectomy group [85]. In a recent systematic review, seven out of nine included studies (including the TIME trial) showed a significantly increased operative time in case of thoracoscopic resection [77]. Additional studies comparing a minimally invasive approach to an open approach are listed in Table 3.

Table 3 Minimally invasive esophagectomy versus open esophagectomy

Authors	Study design	Sample size/number of study	MIE	Open techniques	EBL (ml)	Pulmonary complications/nerve injury	Oncologic adequacy (R0) MIE versus open	30 day mortality MIE versus open
Nagpal et al. [85]	Meta-analysis	216/5	TTE	TTE	**268.5	*OR 0.58 $P = 0.04$/OR 0.76 $P = 0.71$	NR	OR = 0.55 $P = 0.26$
Biere et al. [77]	Randomized control trials	115/NA	TTE (59)	TTE (56)	200 versus 475	9 % versus 29 % $P = 0.005$/2 % versus 14 % $P = 0.012$	NS	NS
Sgourakis et al. [83]	Meta-analysis	163/5	TTE	TTE	NR	OR 1.31 $P = 0.73$/OR 0.57 $P = 0.52$	NR	RR = 1.45 $P = 0.47$
Schoppman et al. [86]	Cohort	62	TTE (31)	TTE (31)	NR	OR 0.15 $P = 0.001$/OR 0.0095 $P = 0.005$	NS	NS
Sihag et al. [87]	Prospective	114	TTE (38)	TTE (76)	200 versus 250	NR/NR	NS	0 % versus 2 %
Braghetto et al. [90]	Prospective	166	TTE (47)	TTE (60) THE (59)	NR	NR/NS	NR	6.3 % versus 10.9 %

TTE transthoracic esophagectomy, *THE* transhiatal esophagectomy, *MIE* minimally invasive esophagectomy, *OR* odds ratio, *EBL* estimated blood loss, *NR* not recorded, *RR* relative risk, *NS* not significant, *OR in favor of MIE, **EBL in favor of MIE

The most significant factor for the decreased overall morbidity after minimally invasive esophagectomy is the reduction in pulmonary complications. This is reflected by significant differences demonstrated in the meta-analyses of Nagpal, the TIME trial, and to a lesser extent by an observed trend in the meta-analysis by Sgourakis et al. [83]. The evidence about laryngeal nerve palsy is contradictory. The TIME trail showed a significantly lower rate of recurrent laryngeal nerve palsy after minimally invasive resection, which is in accordance with the study by Schoppmann although this contradicts the findings in a meta-analysis [77, 86]. Patients treated in the minimally invasive arm of the TIME trial reported a significantly higher short-term quality of life in terms of physical status, global health and in relation to common postoperative symptoms like pain and speech impediment [77]. Based on the discussed literature, minimally invasive esophagectomy should be regarded as a safe alternative to open resection with proven short-term advantages with respect to pulmonary status, vocal cord function and quality of life.

One of the most controversial issues in the surgical treatment of esophageal cancer is the oncological adequacy of a minimally invasive resection. A major factor in oncologic adequacy is the proportion of R0 resections. Unfortunately, comparisons of R0 resection rates between open- and minimally invasive esophagectomy are rarely reported. In three recent comparative studies R0 resection rates were reported [77, 87, 88]. In the TIME trial an insignificant difference of 8 % (92 % vs. 84 %) in favor of minimally invasive esophagectomy was observed [77]. Two similar studies by Sihag and Sundaram, comparing perioperative outcomes following open versus minimally invasive Ivor Lewis esophagectomy, found no significant differences in R0 resection: (100 % vs. 93.4 %) and (93.6 % vs. 92.3 %) respectively [87, 88]. Contrary to R0 resection rates, the total number of retrieved lymph nodes is a commonly reported outcome measure. One of the three meta-analyses on this topic reported a significant increase in median number of nodes, 16 versus 10, in favor of minimally invasive esophagectomy [84]. In the same review the described increase in lymph node retrieval did not seem to translate to a survival benefit as no significant differences were found in one-, two-, three- and five-year survival [84]. Currently available data imply that oncologic outcomes of minimally invasive esophagectomy are not inferior to those of open esophagectomy.

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