Modern Surgery for Esophageal Cancer

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KEYWORDS

• Esophageal cancer • Operative treatment • Review

Primary treatment of carcinoma of the esophagus and cardia rests on surgical resection. Although recent advances have shown the suitability of endoscopic treatment in selected patients with very early cancers, and preliminary studies have suggested that responders to primary chemoradiation may be equivalent to resection in selected patients with squamous cell carcinoma, surgical resection remains the mainstay of therapy, as it has for the past 50 years.[1,2]

National Cancer Institute statistics report that approximately 16,460 people will be diagnosed with esophageal cancer in 2008, and 14,280 or 87% are expected to die from it.[3] These figures increase substantially when data for cancer of the cardia are included. Clearly, curing this disease is a challenge. The clinical biology and presentation of esophageal cancer have changed dramatically in the past 25 years. This has had significant impact on the intent of treatment, resulting in a marked trend favoring curative therapy whenever possible. The liberal use of flexible endoscopy to investigate foregut symptoms and the widespread adoption of Barrett's surveillance programs have markedly increased the proportion of patients in which the cancer is found when the disease may be confined to the mucosa or submucosa.[4] Trends also document an increasing prevalence of adenocarcinoma of the esophagus in younger patients. Large series of those less than 50 years old have been reported.[5] The morbidity and mortality associated with esophageal resection has declined such that dedicated centers routinely achieve 1% to 2% 30-day mortality. Taken together, these changes support highly individualized treatment decisions in which each patient receives the treatment with the best chance of eliminating all disease.

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ASSESSMENT OF THE EXTENT OF DISEASE AND SELECTION OF SURGICAL OPTIONS

At the initial encounter with a patient diagnosed as having carcinoma of the esophagus, a decision must be made as to whether he or she is a candidate for curative surgical therapy, palliative surgical therapy, or nonsurgical palliation. The pros and cons of the use of adjuvant therapy must also be considered, and its timing. Making these judgments can be difficult. Current methods evaluating the pretreatment stage of esophageal carcinoma are imprecise, primarily because of the difficulty of measuring the depth of tumor penetration of the esophageal wall and the inaccessibility of the organ's widespread lymphatic drainage. Even with the modern techniques of CT, MRI, positron emission tomography (PET), endoscopic ultrasound (EUS), and laparoscopic and thoracoscopic technology, pretreatment staging remains inaccurate in many patients.

Esophageal cancer generally presents with dysphagia, although increasing numbers of relatively asymptomatic patients are now identified on surveillance endoscopy or with endoscopy prompted by nonspecific upper gastrointestinal symptoms. Portale and colleagues[5] found a surprisingly high proportion of 213 patients referred for surgical resection before the development of dysphagia (**Table 1**). Twenty-five percent of the 213 patients were enrolled in a surveillance program for Barrett's esophagus or presented with a long history of gastroesophageal reflux disease symptoms, and in another 30% occult bleeding, anemia, or abdominal symptoms, such as pain or discomfort, prompted the physician visit leading to a diagnosis of cancer (**Table 2**). Dysphagia usually presents late in the natural history of the disease and becomes severe only when more than 60% of the esophageal circumference is infiltrated with cancer. Consequently, the cancer is often systemic by the time dysphagia heralds its presence.

The characteristics of esophageal cancer that are associated with improved survival are known. Most studies suggest that only two factors (metastasis to lymph nodes and tumor penetration of the esophageal wall) have significant and independent influence on prognosis. The beneficial effects of the absence of one factor persist even when the other is present. Factors known to be important in the survival of patients with

Table 1
Symptomatic presentation of patients with esophageal cancer

	N = 213
Main symptom at presentation[a]	
Nondysphagia	121 (56.8)
Barrett's surveillance or gastroesophageal reflux disease	44 (24.4)
Bleeding (anemia, hematemesis)	29 (13.6)
Chest and abdominal pain, discomfort	26 (12.2)
Others	14 (6.6)
Dysphagia	92 (43.2)
Duration of dysphagia before diagnosis (mo)[b]	2 (1–3)

Data are expressed as:
[a] N (%).
[b] Median (IQR).
Data from Portale G, et al. Can clinical and endoscopic findings accurately predict early-stage adenocarcinoma? Surg Endosc 2006;20:294–7.

Table 2
Symptomatic-endoscopic-pathologic correlation

	N = 184	Early Stage (PPV)	Lymph Node +
No dysphagia as main symptom at diagnosis	95	51.6	42.1
Tumor length ≤2 cm	67	73.1	20.9
CI ≤25%	62	79	17.7
No dysphagia+tumor length ≤2 cm	55	80	14.5
No dysphagia + CI ≤25%	55	80	16.4
Tumor length ≤2 cm + CI ≤25%	56	80.4	16.1
No dysphagia + tumor length ≤2 cm + CI ≤25%	50	82	14

Data are expressed as *percentage; 29 patients with no visible lesion were excluded from the analysis.

Abbreviations: CI, circumferential involvement; PPV, positive predictive value.

Data from Portale G, et al. Can clinical and endoscopic findings accurately predict early-stage adenocarcinoma? Surg Endosc 2006;20:294–7.

advanced disease, such as cell type, degree of cellular differentiation, or location of tumor in the esophagus, have no effect on survival of patients who have undergone resection for early disease. Although current staging systems fail to take the number of lymph nodes into account, most studies also show that patients having five or less lymph node metastases have a better outcome.

Clinical factors that indicate an advanced stage of carcinoma and exclude surgery with curative intent are recurrent nerve paralysis, Horner's syndrome, persistent spinal pain, paralysis of the diaphragm, fistula formation, and malignant pleural effusion. Factors that make surgical cure unlikely include a tumor greater than 8 cm in length, abnormal axis of the esophagus on a barium radiogram, enlarged paratracheal or para-aortic lymph nodes on CT, a weight loss more than 20%, and loss of appetite. In patients where these findings are not present, staging depends primarily on the length of the tumor as measured with endoscopy, and the degree of wall penetration and lymph node metastasis seen with EUS or other staging modalities. Studies indicate that there are a high number of favorable parameters associated with tumors less than 4 cm in length, there are fewer with tumors between 4 and 8 cm, and favorable criteria for tumors greater than 8 cm in length are uncommon.

EUS has gained popularity over the last 10 years as the modality of choice for pretherapeutic assessment of depth of tumor infiltration into the esophageal wall and lymph node status. Although it provides the best information available regarding both of these important staging parameters, recent data reveal major limitations particularly in differentiating mucosal and submucosal tumors, a key branchpoint in therapeutic decision making. The preoperative locoregional lymph node staging accuracy is improved, however, by performing EUS-guided fine-needle aspiration.[6] Nishimaki and colleagues[7] prospectively assessed the accuracy of preoperative staging using esophagography, esophagoscopy, EUS, and CT in 224 patients with localized esophageal cancer who underwent radical esophagectomy. The study showed that T2 tumors were poorly predicted by endoscopy or esophagography and even though EUS was shown to be the best study for predicting T2 tumors, its accuracy was only 61%, with 33% of patients being overstaged. The overall accuracy of correctly predicting stage I disease before esophagectomy was only 68% and at predicting stage III disease was 70%. The accuracy of clinical staging for predicting stage IIA or IIB disease was less than 50%.

The limits of EUS are particularly evident in the attempt to distinguish intramucosal from submucosal tumors and submucosal from intramuscular ones. In a study from the Cleveland Clinic Foundation, Zuccaro and colleagues[8] directly compared clinical TNM classification with pathologic classification in 266 patients with esophageal cancer who had EUS staging followed directly by esophagectomy. EUS was confirmed to be reasonably accurate in the identification of T3 tumors (83%). T2 tumors were correctly identified by EUS in only 42% of patients; in 54% they were erroneously overstaged to T3. Even less accurate was the identification of T1 or in situ tumors. T1 lesions were correctly classified in 29% of patients and in situ tumors were never correctly identified preoperatively. T1 tumors were overstaged in 46% of cases and understaged in 24%. It is interesting to note that 16 patients with T1 tumors (20%) and 13 patients with Tis tumors (68%) were misdiagnosed as clinical T0.

Endoscopic mucosal resection (EMR), initially used as a definitive resection option for early esophageal cancer and high grade dysplasia, has recently been proposed as a staging tool to determine the depth of invasion of esophageal adenocarcinoma and may become the procedure of choice reliably to differentiate intramucosal from submucosal lesions. Mino-Kenudson and colleagues[9] from Massachusetts General Hospital found that interobserver agreement of EMR for Barrett's esophagus–related superficial neoplasms is significantly higher than for mucosal biopsies.

PET and particularly PET-CT scanning are emerging as both a highly useful staging modality and also as a technique that provides prognostic information, such as predicting the response to neoadjuvant therapy. In a recent meta-analysis, van Vliet and colleagues[10] assessed the diagnostic accuracy of EUS, CT, and PET. The results suggest that each modality plays a distinctive role in staging of esophageal cancer. For detection of regional metastases, EUS seems to be the most sensitive (0.80 versus 0.50 and 0.57 pooled sensitivity with CT and PET, respectively) and PET the most specific (0.85 versus 0.83 and 0.70 pooled specificity for CT and EUS, respectively) diagnostic procedure. For distant metastases combined CT-PET has significantly higher specificity and sensitivity than CT.

Rizk and colleagues[11] from the Memorial Sloan-Kettering Cancer Center evaluated the significance of preoperative PET standardized uptake values (SUV) in predicting survival of 55 patients with adenocarcinoma of the distal esophagus and gastroesophageal junction who underwent esophagectomy alone as primary treatment of their disease. Patients with low SUV less than 4.5 were more likely to have early stage disease, T1-2 disease, and less lymph node involvement than patients with high SUV (90% versus 60% and 8% versus 48%). The overall survival in the low SUV group was significantly better than in the high SUV group (**Fig. 1**).[12] Furthermore, within the subset of patients with early clinical or pathologic stage disease, patients with low preoperative SUV had a significantly better survival. When the SUV was considered as a continuous variable, it correlated with the presence of lymph node metastasis, the number of nodes involved, and the risk of death. The authors concluded that PET SUV could be used to predict clinical or pathologic stage and overall survival in patients with esophageal cancer. High PET SUV also identifies patients with poor prognosis from within a group of patients that would otherwise be considered to have curable early stage disease and could be potentially used to stratify patients for appropriate therapy.

PET has also been proposed as a valuable tool to predict response to preoperative chemotherapy. Investigators from Munich, Germany,[13] reported the results of the MUNICON trial on the use of [^{18}F]fluorodeoxyglucose PET as a predictor of response and patient survival in patients with locally advanced adenocarcinoma of the distal esophagus or cardia (T3NxM0) treated with preoperative chemotherapy. These data suggested that a decrease of tumor metabolic activity (SUV) by more than 35% after

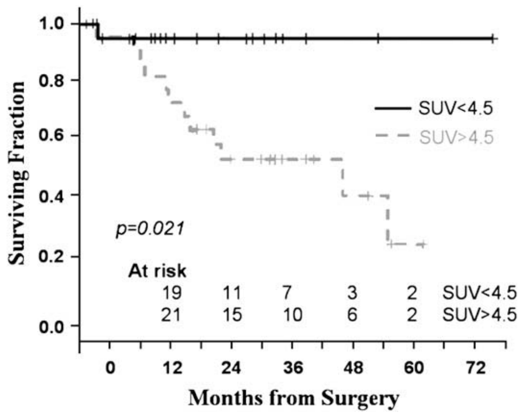

Fig. 1. Survival of esophageal cancer based on standard uptake value (SUV) on positron emission tomography. (*Data from* Swisher SG, Erasmus J, Maish M, et al. 2-fluoro-2-deoxy-D-glucose positron emission tomography imaging is predictive of pathologic response and survival after preoperative chemoradiation in patients with esophageal carcinoma. Cancer 2004 15;101(8):1776–85.)

2 weeks of therapy predicts a high pathologic response rate and is associated with a better survival. Among 110 patients evaluated with [^{18}F]fluorodeoxyglucose PET at baseline and 14 days after chemotherapy was started, 49% of patients were classified as metabolic responders based on tumor uptake and were offered full-dose chemotherapy and then proceeded to surgery. In nonresponders chemotherapy was discontinued and they went directly to surgery. Metabolic response was highly associated with clinical and histopathologic response. Overall survival of metabolic responders was significantly better than nonresponders (**Fig. 2**). Among the 104 patients who underwent surgical resection after completion of neoadjuvant chemotherapy, metabolic response remained a significant prognostic factor.

AN INDIVIDUALIZED SURGICAL APPROACH

At diagnosis, cancer must be either local (confined to the mucosa or submucosa and node negative); regional (node positive without systemic metastasis); or systemic (**Box 1**). It is reasonable to conclude that the extent of operation has little effect on survival of systemic disease but it can have a critical impact on survival for patients with isolated regional disease. The existence of a population of patients with regional disease has been debated in cancer biology, but can be proved by the extensive documentation that cure is possible with surgical resection alone in the presence of positive lymph nodes. The relatively small size of this group and the difficulty in clinically identifying these patients preoperatively account for the difficulty in establishing the benefit of lymphadenectomy as an adjunct to surgical resection.

Patient with a High Probability of Disease Confined to the Mucosa (Localized Disease)

Treatment decisions, efficacy, and importantly prognosis are all highly dependent on making the distinction between dysplasia, intramucosal, and submucosal cancer to the extent possible. Intraepithelial tumors (HGD, carcinoma in situ) have a quite different biologic behavior than intramucosal tumors, which are very different than submucosal tumors (**Fig. 3**). Vascular invasion and lymph node metastasis do not occur in

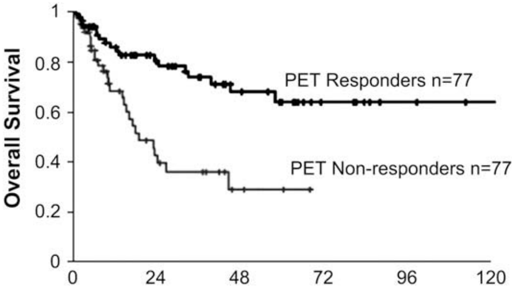

Fig. 2. Overall survival based on metabolic response evaluated by positron emission tomography (PET). (*Data from* Ott K, Weber WA, Lordick F, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. J Clin Oncol 2006;24:4692–8.)

HGD and carcinoma in situ and are uncommon in intramucosal tumors, but occur in more than one quarter of patients with submucosal lesions. As a consequence, the 5-year survival for intramucosal tumors is significantly better than a tumor that has invaded the submucosa. Techniques of curative resection given a high probability of local disease range from endoscopic resection and ablation to standard operative esophagectomy.

Endoscopic treatment

EMR, photodynamic therapy, radiofrequency ablation, and combinations of these have been studied in the setting of HGD and early invasive carcinoma. Photodynamic therapy suffers from a high prevalence of incomplete ablation; a relatively high (30%) prevalence of strictures; and lack of availability and expertise in many locations. As such its application is becoming much less common. EMR has taken its place and in the proper setting is a very viable treatment option, particularly when associated with the addition of radiofrequency ablation. The primary limitation of EMR is the need to "see" the area of interest. Local recurrence or development of metachronous lesions after EMR has been reported in 15% to 30% of patients. The combination of local resection and ablation has been used to reduce this possibility, especially in high-risk patients who may be precluded from undergoing esophagectomy because of multiple comorbidities.[2]

Box 1
Characteristics and estimated prevalence of extent of disease at presentation

Local disease: (15%)

Asymptomatic

Minimal or no visible lesion

Regional disease: (25%)

Minimal symptoms (anemia)

Small (<2–3 cm) noncircumferential

Systemic disease: (60%)

Dysphagia

>3 cm circumferential tumor, plus nodes on EUS

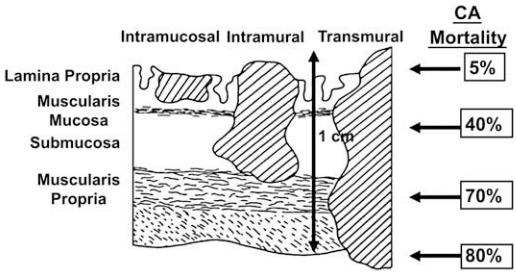

Fig. 3. Relationship of depth of tumor penetration and mortality.

The largest experience to date combining endoscopic techniques in the treatment of early neoplasia has been reported by investigators in Wiesbaden, Germany.[14] The outcome of 100 consecutive patients with low-risk adenocarcinoma of the esophagus arising in Barrett's esophagus patients who underwent EMR was assessed. A total of 144 resections (1.47 per patient) were performed without technical problems. No major complications and only 11 minor ones (bleeding without decrease of Hb >2 g/dL, treated with injection therapy) occurred. Complete local remission was achieved in 99 of the 100 patients after 1.9 months (range, 1–18 months) and a maximum of three resections. During a mean follow-up period of 36.7 months, recurrent or metachronous carcinoma was found in 11% of the patients, but successful repeat treatment with EMR was possible in all of these. The calculated 5-year survival rate was 98%. This report established EMR as a safe and efficacious treatment in highly select patients with HGD and intramucosal adenocarcinoma. In a follow-up publication, results after 5-year follow-up in 349 patients with high-grade intraepithelial neoplasia and intramucosal adenocarcinoma were reported. Endoscopic resection was performed in 279 patients, photodynamic therapy in 55, and both in 13. A complete response was achieved in 96% of the patients; 3.7% required surgery for failed endoscopic treatment. Metachronous disease developed in 21% and the calculated 5-year survival rate was 84%. Risk factors associated with recurrence included piecemeal resection, long-segment Barrett's, no ablative therapy after mucosal resection, multifocal neoplasia, and a time to complete resection of more than 10 months.

The context of the use of EMR is critical, however, and it is important that these data not be extrapolated in the treatment of patients beyond those described in these studies. The described outcomes require a highly selected group of patients, which may be difficult for most centers to reproduce. The 100 patients reported from Wiesbaden were selected out of 667 possible candidates over 7 years. This equates to the referral of nearly 100 patients with very early esophageal adenocarcinoma per year. Most centers see a handful at best. All patients underwent very intensive staging, including EUS and radiographic procedures; high-resolution videoendoscopy with methylene blue chromoendoscopy; detailed morphologic assessment of the lesions according to the Japanese classification for early gastric cancer; an intense biopsy protocol (four quadrants, every 1 cm); routine assessment by two different pathologists; and high-frequency (20 MHz) ultrasound. Equally intense follow-up was required with endoscopy at 1, 2, 3, 6, 9, 12, 16, 24, 30, and 36 months with repeated high-resolution and chromoendoscopy, a routine rigorous biopsy protocol, EUS and abdominal ultrasound, and CT. The rigor of the patient selection should be evident and the difficulty most would have in reproducing it. The persistent neoplastic risk in the remaining Barrett's mucosa is also a concern.

Surgical resection

Options for esophageal resection in early stage cancer include transhiatal or transthoracic simple esophagectomy, vagal-sparing, or minimal invasive esophagectomy. The chance of curative resection with a simple esophagectomy is critically dependent on accurate identification of the location and depth of the tumor or the presence of regional nodal metastases. Because the perfect tool for preoperative staging of esophageal cancer is not yet available, the presence or absence of an endoscopically visible lesion in patients with HGD or intramucosal carcinoma has been proposed as a predictor of tumor depth and nodal metastases. The data indicate that a positive biopsy in the absence of an endoscopically visible lesion almost always corresponds to an intramucosal tumor without nodal metastases. In addition, a number of studies have shown that about 40% to 50% of patients with the preoperative diagnosis of HGD were indeed proved to harbor occult adenocarcinoma at resection. EMR may be the best method to stage the depth of invasion of small esophageal tumors. Currently, patients with documented, confirmed HGD or adenocarcinoma in the absence of a visible endoscopic lesion are appropriate candidates for vagal-sparing or minimally invasive esophagectomy.

Vagal-sparing esophagectomy The technique of vagal-sparing esophagectomy was developed by Akiyama and coworkers[15] to avoid the functional morbidity of standard esophagectomy by preserving the vagal trunks while removing all at-risk mucosa (**Fig. 4**). This approach is suitable only given confidence of the absence of regional nodal disease. The operation can be done with either open or laparoscopic techniques. The vagal nerves are identified and the proximal lesser curve is dissected similar to a highly selective vagotomy. Vessel loops are placed around the tissue bundles including both nerves. A gastric conduit is prepared and the stomach is divided below the esophagogastric junction. The left neck is dissected in a standard fashion exposing the cervical esophagus and it is divided at the level of thoracic inlet. A standard vein stripper is passed through the esophagus from abdomen to neck and allowed to exit from the cut end of the cervical esophagus. A blunt “knob” is threaded onto its end and the esophagus is secured around the stripping device using an Endoloop. The stripper is slowly and gently pulled from the abdominal site progressively inverting the esophagus stripping it out of the posterior mediastinum. This maneuver strips the

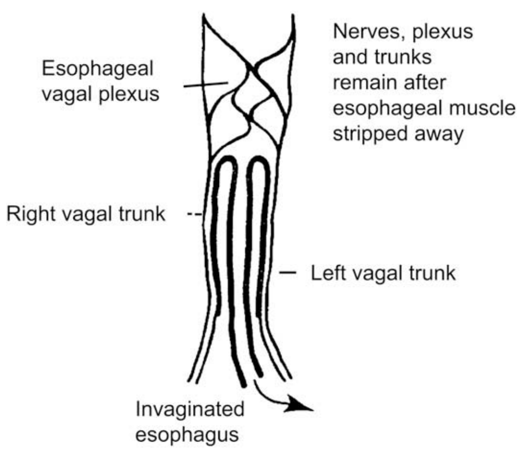

Fig. 4. Illustration of the technique of vagal-sparing esophagectomy.

mucosa, circular, and most of the longitudinal muscle layer but preserves the vagal plexus intact. Gastrointestinal continuity is restored by a gastric pull-up or colon interposition.

Banki and colleagues[16] from University of Southern California reported their initial results of vagal-sparing esophagectomy. Vagal function, assessed by increased acid output and pancreatic polypeptide levels after sham feeding and a preservation of normal gastric emptying, remained intact in 70% of the patients. Follow-up publications showed that the length of hospital stay and the incidence of major complications were significantly reduced when compared with transhiatal or en bloc transthoracic resection.[4,17] Importantly, postvagotomy symptoms, such as dumping and diarrhea, were less common in the vagal-sparing group. Jobe and colleagues[18] reported minimally invasive vagal-sparing methods (**Fig. 5**).

Candidates for vagal-sparing resection are relatively few[19] and include those with high-grade dysplasia or nonvisible invasive cancer. The rationale includes the need for life-long, meticulous, and intensive follow-up required after endoscopic techniques and the small but real prevalence of failure, synchronous and metachronous cancer. Vagal-sparing esophagectomy has the obvious advantage of removing all at-risk mucosa, which obviates the need for rigorous follow-up.

Minimal invasive esophagectomy As in other fields of surgery, with the technical advances of the recent years, minimal invasive esophagectomy became feasible and gained popularity, although concerns have been expressed about its safety and oncologic outcomes. Several methods are available, depending on the chosen combination of abdominal and thoracic procedures. Most published studies are retrospective case series, case reports, and reviews. A recent systematic review of 23 articles on minimal invasive esophagectomy concluded that the available literature is hampered by selection and publication bias.[20] Because direct comparisons with open surgery are lacking (most of the results are compared with historical data from open series), the potential benefit of minimally invasive surgery remains unclear.

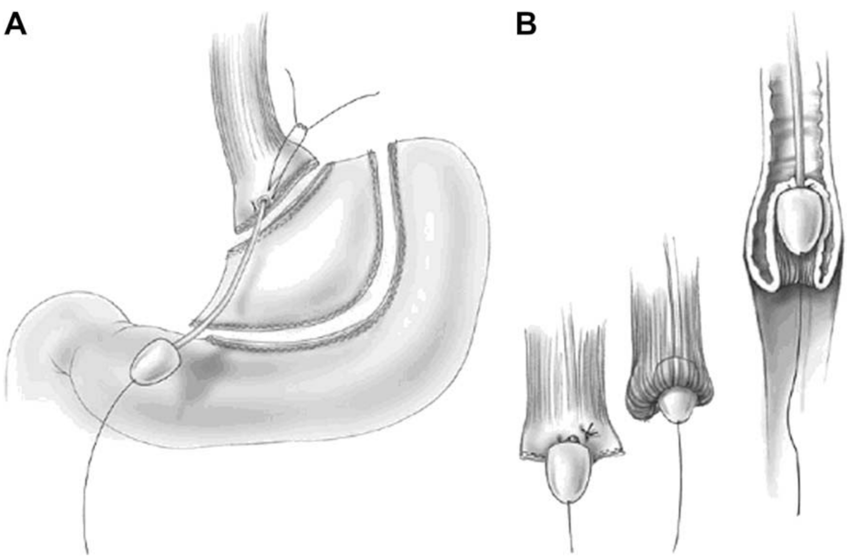

Fig. 5. Laparoscopic vagal-sparing esophagectomy.

Patient with a High Probability of Regional Disease

Although by no means certain, the probability of curable disease limited to regional nodes is high given a patient presenting with or without dysphagia (**Fig. 6**) who on endoscopy has a small (<1–2 cm) noncircumferential visible tumor (**Fig. 7**). It is in this setting that invasion through the muscularis mucosa into the submucosa is likely, along with a 25% or more chance of lymph node metastasis, but a reasonable chance of no systemic spread.[21] Evidence is growing that under these circumstances, which occur in as many as 15% to 25% of patients referred for surgical resection, resection and en bloc lymphadenectomy provides the best chance of cure and should be the treatment of choice (**Fig. 8**). Supporting evidence was recently provided by the randomized study conducted at the University of Amsterdam by Omloo and colleagues[22] in which the 5-year outcome of simple transhiatal and en bloc transthoracic resection for esophageal cancer was reported. Patients with more than one, but less than eight positive nodes benefited from the extended lymphadenectomy. Although no statistical difference in the overall 5-year survival rates was found, subgroup analysis identified that patients with between one and eight positive nodes had significantly improved long-term survival.

The primary rationale for an en bloc resection and extended lymphadenectomy is to minimize the incidence of local and regional recurrences and maximize the chances of long-term survival and cure (**Table 3**). Local recurrence has been shown to be very uncommon (<5%–10%) following en bloc resection, which contrasts with a 35% prevalence of local failure following transhiatal esophagectomy and a 15% to 20% prevalence after Ivor-Lewis resection (**Table 4**). These findings may be explained by the removal of unrecognized, often microscopic, disease with more extensive lymph node dissection. Involved nodes that are left behind during simple esophagectomy are likely the cause of recurrent local disease.

The clinical challenge lies in the fact that preoperative diagnostic methods cannot reliably predict patients in which disease is limited to the esophagus and its regional lymphatic basins. Further, current staging systems do not take the extent of lymph node metastases into account, failing to reflect the clinical observation that patients with numerous positive lymph nodes have worse survival than those with limited nodal metastases. Multiple recent reports have challenged the current UICC/AJCC TNM classification as oversimplifying the prognostic effect of lymphatic metastatic disease. Mariette and colleagues[23] reported a retrospective analysis of 536 patients in which a staging system using either the number of resected lymph nodes or the ratio of metastatic to resected lymph nodes offers greater prognostic value and risk stratification. Similarly, Greenstein and colleagues,[24] analyzing the Surveillance Epidemiology and

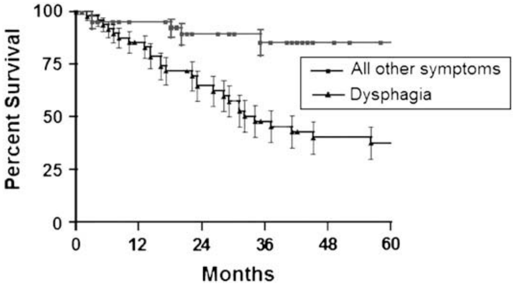

Fig. 6. Kaplan-Meier survival of a cohort of Los Angeles patients presenting with dysphagia compared with those with none or nonspecific symptoms.

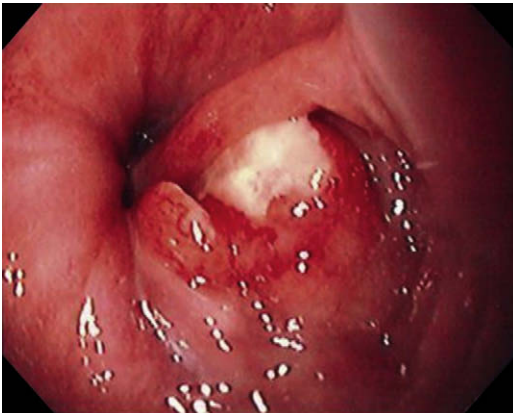

Fig. 7. Endoscopic view of a noncircumferential adenocarcinoma of the lower esophagus in which there is a high likelihood of regional disease.

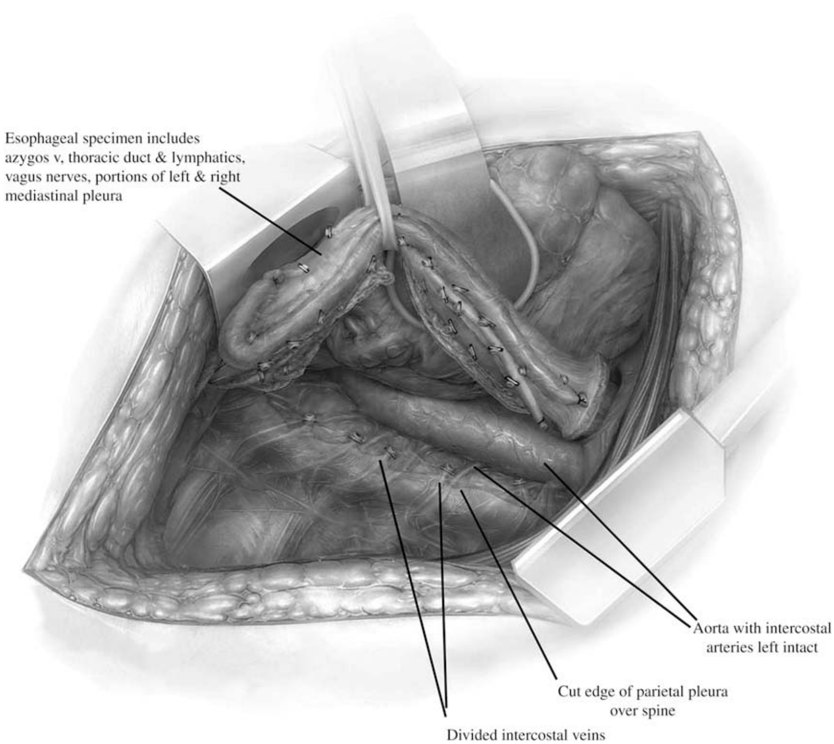

Fig. 8. Artist illustration of the transthoracic portion of an en bloc esophagectomy. The aorta, pericardium, and right and left bronchi are skeletonized with a complete infracarinal posterior mediastinal lymphadenectomy. The azygous venous system and the thoracic duct are both taken in the resection specimen.

Table 3
Local recurrence after varied or surgical resections

Surgical Resection	N	% Local Recurrence within Operative Field
En bloc[a]	94	1
Ivor-Lewis[b]	100	14
Transhiatal[c]	144	35
Chemotherapy + surgery[d]	124	32
Chemotherapy + radiotherapy + surgery[e]	50	19

[a] *Data from* Hagen JA, DeMeester SR, Peters JH, et al. Curative resection for esophageal adenocarcinoma: analysis of 100 en bloc esophagectomies. Ann Surg 2001;234:520–30 [discussion 530–1].

[b] *Data from* King RM, Pairolero PC, Trastek VF, et al. Ivor Lewis esophagogastrectomy for carcinoma of the esophagus: early and late functional results. Ann Thorac Surg 1987;44:119–22.

[c] Hulscher et al. J Am Coll Surg 2000,191:143–8.[42]

[d] *Data from* Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 1998;339:1979–84.

[e] *Data from* Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001;19:305–13.

End Results (SEER) database from 1988 to 2003, reported that the ratio of metastatic to resected lymph nodes was independently associated with worse survival. A similar study by the same authors showed that the disease-specific survival increased with the higher number of negative lymph nodes.[25] Based on their data the authors suggest that at least 18 lymph nodes should be removed for correct risk stratification.

Peyre and colleagues[26] recently reported the results of an international multicenter study of the benefit of lymphadenectomy from centers in Asia, Europe, and North America. All had R0 resections and a minimum of 5-year follow-up. The frequency

Table 4
Reported ability of transthoracic enbloc esophagectomy and transhiatal esophagectomy to control local-regional disease

Author and Reference	No. of Subjects	Local Recurrence (%)
En bloc esophagectomy		
Matsubara, et al[43]	171	10
Altorki and Skinner[35]	111	8
Hagen, et al[36]	100	1
Collard, et al[44]	324	4
Swanson, et al[45]	250	5.6
Range		1–10
Transhiatal esophagectomy		
Hulscher, et al[42]	137	23
Becker, et al[46]	35	31
Gignoux, et al[47]		47
Nygaard, et al[48]	186	35
Range		23–47

Data from Johansson J, DeMeester TR, Hagen JA, et al. En bloc vs transhiatal esophagectomy for stage T3 N1 adenocarcinoma of the distal esophagus. Arch Surg 2004;139:627–31.

of systemic recurrence ranged from 16% for those without nodal involvement to 94% in patients with greater than or equal to nine involved lymph nodes. Absolute survival was 86% in patients without nodal metastases. Analysis suggested that if at least 23 lymph nodes are removed during the operation a marked increase in survival was observed. Patients with T1N0 stage disease had an absolute improvement in survival of 11%, whereas patients with T3N1 had even more striking improvement (26% versus 11%). The probability of systemic disease was 49% with one to four involved nodes, 73% with five to eight involved nodes, and 92% with greater than nine involved nodes. Schwarz and Smith[27,28] analyzed the SEER National Cancer Database and found that a total lymph node count greater than 30 and a negative lymph node count greater than 15 after esophagectomy was associated with the lowest 90-day mortality. These studies, taken together with the inability precisely to predict those patients who will not gain benefit, support the use of a more extensive resection in any patient where cure is a possibility.[26]

Patient with a High Probability of Systemic Disease

Patients, who present with dysphagia and large (>3–5 cm) circumferential lesions on endoscopy or have five or more positive nodes on staging CT or EUS usually have a more advanced disease and a high probability of developing systemic disease after surgery. These patients are unlikely to be cured. They may benefit from neoadjuvant or adjuvant chemotherapy but no definitive survival benefit has been shown to date using combined modality therapy.

These patients, given the absence of metastatic disease, are best suited for palliative transhiatal esophagectomy. A prospective longitudinal study from the European Organization for Research and Treatment of Cancer evaluating quality of life in patients after esophagectomy or other palliative procedures showed that quality-of-life scores returned to preoperative levels within 9 months after surgery. Dysphagia improved in both groups after treatment but the improvement was maintained until death or for the duration of the study in the surgical group, whereas it gradually deteriorated until death in the palliative group. Quality of life after palliative resection was shown to be comparable with that observed after curative resection in terms of quality and quantity of food intake, sleep patterns, and enjoyment of day-to-day living. In patients with high surgical risk, systemic metastases, or unresectable local disease, promising results have been shown in palliation of symptoms with the use of coated self-expanding metal stents.

OUTCOMES OF SURGICAL RESECTION

Morbidity and Mortality of Resection

Although esophagectomy remains a major surgical undertaking with significant morbidity and mortality, both complications and perioperative death have improved significantly over the past 15 to 20 years. Reasons for this include the use of epidural analgesia, improved respiratory therapy, and decreased prevalence of smoking (**Table 5**). Mortality, in high-volume centers with stable and experienced teams and structured care algorithms, has been reported to be as low as 0% to 1% (**Fig. 9**).[29] It averages 4% to 5% in most centers of excellence.

Also important, but often overlooked, is the fact that surgical mortality varies considerably with the type and extent of disease. It approaches zero in patients with HGD; averages 2% to 3% in those with adenocarcinoma; and is highest (8%–10%) in patients with squamous cell carcinoma. These very different patient populations have markedly different underlying tumor burdens and comorbid conditions, and

Table 5
Correlation of changes in perioperative variables with decreased hospital death rate

Factor	*P* Value
Epidural analgesia	0.0001
Bronchoscopy	0.0001
History of smoking	0.005
Blood loss <1000 mL	0.03
PaO_2 (kPa)	0.2
Pulmonary disease	0.3
Albumin (m/L)	0.5
Advanced stage (III/IV)	0.7
FEV (% predicted)	0.7

Data from Whooley BP, Law S, Murthy SC, et al. Analysis of reduced death and complication rates after esophageal resection. Ann Surg 2001;233:338–44.

are often lumped together when reporting mortality statistics. Esophagectomy is arguably the most sensitive surgical procedure to volume-outcome relationships. With less than 4000 esophagectomies per year being performed in the United States, many have argued that the time has come to limit esophageal resection to high-volume centers.

Birkmeyer and colleagues[30,31] in two landmark studies emphasized the relationship between hospital volume and surgical mortality of esophagectomy. Analyzing SEER - Medicare files, mortality decreased with increasing volume in all of the 14 analyzed operative procedures studied. The relative impact of volume varied markedly, however, according to the type of procedure. Esophagectomy was one of the most sensitive procedures to hospital volume; those with less than two resections per year had over 20% surgical mortality compared with 8.4% for those with more than 19 per year. A subsequent study assessed the relative effects of the hospital and the individual surgeon volume. Surgeon volume was inversely related to operative mortality for all analyzed procedures and accounted for 46% of the effect of the hospital volume following esophagectomy. Mortality rate of low-volume surgeons

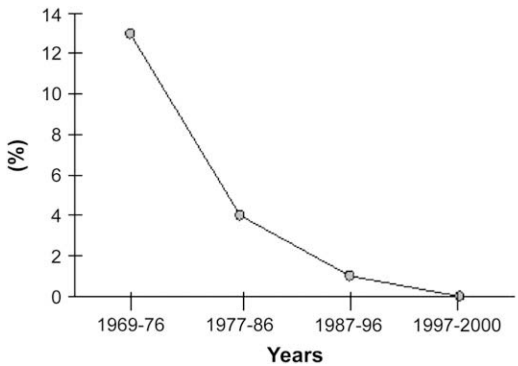

Fig. 9. Trends over time in 30-day operative mortality rate after esophageal cancer resection. (*From* Ohga T, Kimura Y, Futatsugi M, et al. Surgical and oncological advances in the treatment of esophageal cancer. Surgery 2002;131(Suppl 1):S28–34; with permission.)

was higher than high-volume surgeons, regardless of the surgical volume of the hospital in which they practiced.[31]

Orringer and colleagues[32] reported his 22 year experience with over 1000 patients who underwent transhiatal esophagectomy for either benign or malignant disease. Seventy-four percent of the patients were treated for esophageal cancer, 69% of which were adenocarcinoma and 28% squamous cell carcinoma. The stomach was used for reconstruction in 96% of patients, and the colon was used as a substitute when the stomach was not available. Mortality was 4%, significantly declining over the years. The major postoperative complication was anastomotic leak occurring in 13% and was more common after retrosternal placement of the stomach, previous radiation therapy, or prior operations at the gastroesophageal junction. Nearly always, the leak was successfully managed conservatively; takedown of the anastomosis and cervical esophagostomy was necessary in nine patients because of necrosis of the upper stomach. Median hospital stay was 7 days, 90% of patients had no or mild dysphagia after a mean follow-up of 29 months, and only 2% had severe dysphagia requiring regular dilation. Symptoms of gastroesophageal reflux disease were present in 21% of patients but only 3.6% of them had nocturnal reflux or aspiration-related pneumonia.

Representing outcomes from multiple centers with varying volumes, Bailey and colleagues[33] reported an analysis of 1777 esophagectomies at 109 Veterans Administration medical centers entering data into the National Surgical Quality Improvement Program. The procedures were performed in the 1990s; 85% were for malignancy. Thirty-day mortality was 9.8% and complications occurred in 49.5% of patients. The most frequent complications were pneumonia (21%); respiratory failure (16%); and the need for more than 48-hour ventilator support (22%). The National Surgical Quality Improvement Program data allow analysis of risk factors predisposing to death and complications. Predictors of mortality included neoadjuvant therapy, blood-urea-nitrogen greater than 40, alkaline phosphatase greater than 125 U/L, diabetes, alcohol use, decreased functional status, ascites, and advanced age.

Several studies have evaluated the mortality and morbidity of en bloc and transhiatal resections and have shown that they are similar (**Table 6**). Connors and colleagues[34] compared transhiatal and transthoracic resections using data available from the Nationwide Inpatient Sample of 17,395 patients who underwent esophagectomy from 1999 to 2003. Overall morbidity and mortality was 50.7% and 8.8%, respectively. There was no significant difference between the in-hospital mortality or in any of the reported complications (including mediastinitis, pulmonary, wound, and cardiovascular) and transhiatal and transthoracic esophagectomy. Furthermore, the data showed that high-volume centers (more than 10 esophagectomies per year) have significantly less morbidity and mortality than low-volume hospitals. Based on these data one can conclude that progressive improvements in intraoperative and postoperative care have largely eliminated mortality and morbidity as a factor in the selection of patients for one procedure versus another.

Survival Data

Long-term survival following esophagectomy for cancer has improved from a dismal 10% to 15% in the 1960s and 1970s to 20% to 25% in the 1980s and 1990s (**Fig. 10**), and to a remarkable 40% to 50% in recent publications using an individualized approach and en bloc resections. Altorki and Skinner[35] have reported a 40% 5-year survival after en bloc resection of unselected cancers in the distal esophagus. Hagen and colleagues[36] in a review of 100 consecutive en bloc esophagectomies for esophageal adenocarcinoma has shown a 52% actuarial survival at 5 years. Most recently,

Table 6
Mortality and morbidity as reported in the literature for transthoracic en bloc esophagectomy and transhiatal esophagectomy

Author and Reference	N	% Mortality	% Morbidity	LOS
En bloc esophagectomy				
[a]Putnam[49]	134	8	75	20 days
[a]Horstmann[50]	41	10	n.s.	23 days
[a]Altorki[51]	78	5.1	24	n.s.
[a]Hulscher[42]	114	4	57	19 days
Swanson[45]	250	3.6	33	13 days
Hagen[36]	100	6	71	14 days
Range		3.6–10	24–75	13–23 days
Transhiatal esophagectomy				
[a]Putnam[49]	42	5	69	19 days
[a]Horstmann[50]	46	11	n.s.	26 days
[a]Altorki[51]	50	6	26	n.s.
[a]Hulscher[42]	106	2	27	15 days
Orringer[52]	417	5	32	11–14 days
Rentz J[53]	385	9.9	49	n.s.
Range		2–11	26–69	11–26 days

Abbreviation: LOS, length of hospital stay.

[a] Indicates that both en bloc esophagectomy and transhiatal esophagectomy are included in the study.

Data from Johansson J, DeMeester TR, Hagen JA, et al. En bloc vs transhiatal esophagectomy for stage T3 N1 adenocarcinoma of the distal esophagus. Arch Surg 2004;139:627–31 [discussion 631–3].

Portale and colleagues[5] in Los Angeles reported an overall 5-year survival of 47% for all patients after esophagectomy including 81% for stage I, 51% for stage II, and 14% for stage III disease (**Fig. 11**).

The evidence strongly suggests that transthoracic en bloc resection results in better survival than simple resections (**Table 7**). This is in contrast to the widespread practice

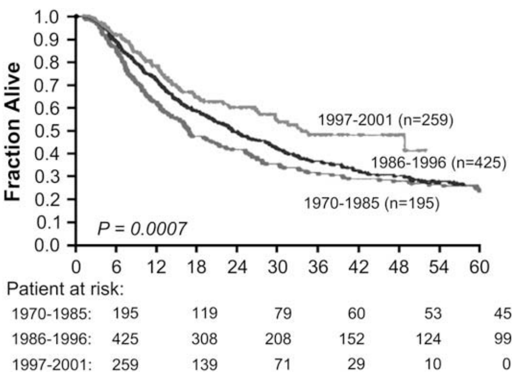

Fig. 10. Improved survival in esophageal cancer over 1950 to 2000. (*From* Hofstetter W, Swisher SG, Correa AM, et al. Treatment outcomes of resected esophageal cancer. Ann Surg 2002;236:376–84 [discussion 384–5]; with permission.)

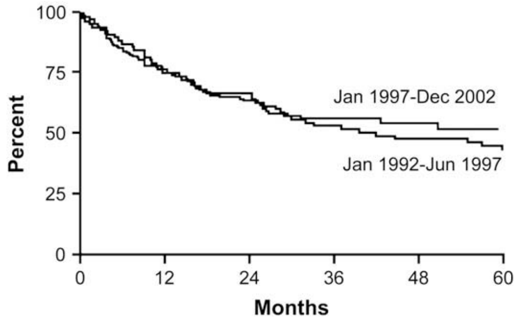

Fig. 11. Survival after esophagectomy for adenocarcinoma. According to reference. (*Data from* Portale G, Hagen JA, Peters JH, et al. Modern 5-year survival of resectable esophageal adenocarcinoma: single institution experience with 263 patients. J Am Coll Surg 2006;202(4):588–96.)

of relying on adjuvant radiochemotherapy to improve local control, which has not seen great success (**Table 8**). Johansson and colleagues,[37] examining the Los Angeles experience, reported a comparison of transthoracic en bloc resection with transhiatal simple resection in a case control series of patients with transmural (T3) esophageal adenocarcinomas with eight or fewer lymph nodes involved (N1). The aim was to compare survival in similar patients with pathologic T3N1 disease. This approach removes the influence of inaccurate preoperative staging and minimizes the influence of postoperative stage migration on survival because all patients had N1 disease. The authors required that 20 or more lymph nodes were in the surgical specimen to provide confirmation that the extent of lymph node disease in both groups was comparable. As much as possible these study conditions focused the question as to which procedure was associated with a better survival. Indeed, the Cox analysis identified only two independent factors that affected survival in the studied population: the type of resection and extent of lymph node disease categorized according to the number of involved nodes (**Fig. 12**).

Table 7
Comparison trials between transhiatal esophagectomy and transthoracic en bloc esophagectomy on long-term survival

Author and Reference	Type of Trial	N	% THE	% EBE	*P* Value
Hagen[54]	Retro	30 EBE / 39 THE	14 (5 y)	41 (5 y)	*P*<.001
Putnam[49]	Retro	102 EBE / 30 THE	12 (4 y)	30 (4 y)	0.02
Horstmann[50]	Retro	41 EBE / 46 THE	18 (3 y)	17 (3 y)	n.s.
Altorki[51]	Retro	78 EBE / 50 THE	11 (4 y)	35 (4 y)	0.007
Hulscher[39]	RCT	114 EBE / 106 THE	27 (5 y)	39 (5 y)	0.08

Abbreviations: EBE, en bloc esophagectomy; RCT, randomized controlled trial; retro, retrospective clinical study; THE, transhiatal esophagectomy.

Data from Johansson J, DeMeester TR, Hagen JA, et al. En bloc vs transhiatal esophagectomy for stage T3 N1 adenocarcinoma of the distal esophagus. Arch Surg 2004;139:627–31 [discussion 631–3].

Table 8 Combined-modality therapy for esophageal cancer; patterns of failure				
	High Dose (64.8 Gy) (N = 109)		Standard Dose (50.4 Gy) (N = 109)	
	No.	%	No.	%
Alive, no failure	21	19	27	25
Any failure	88	81	82	75
Persistent local disease	36	33	37	34
Local failure	10	9	13	12
Regional failure	8	7	8	7
Distant failure	10	9	17	16
Regional and distant failure	0	0	2	2
Total local or regional persistence or failure	54	50	60	55
Treatment-related death	11	10	2	2
Second primary cancer	4	4	1	1
Cancer death, or not specified	3	3	0	0
Dead of intercurrent disease	6	6	2	2

Two further studies deserve mention. The first is a population-based retrospective case control study comparing survival following transhiatal and en bloc resection in Finland,[38] and the second a prospective randomized trial of simple versus extended esophagectomy from the Netherlands.[39] Sihvo and colleagues[38] compared the fate of 42 patients following esophagectomy with two-field lymphadenectomy with 129

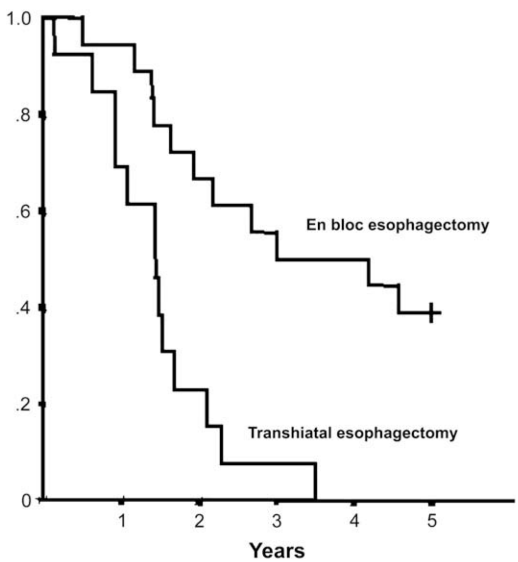

Fig. 12. Survival of T3N1 patients with one to eight metastatic lymph nodes who had a transthoracic en bloc lymph node dissection (N = 18) and those who had a transhiatal lymph node dissection (N = 13). Log rank test, $P = .0006$. (*From* Johansson J, DeMeester TR, Hagen JA, et al. En bloc vs transhiatal esophagectomy for stage T3 N1 adenocarcinoma of the distal esophagus. Arch Surg 2004;139(6):627–31.)

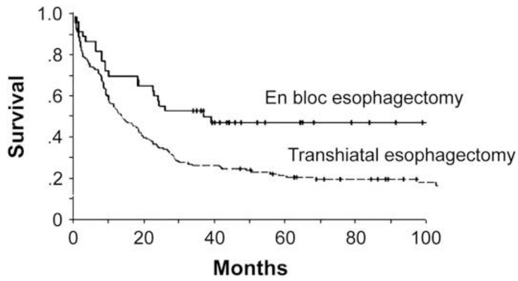

Fig. 13. Five-year survival of patients following esophagectomy with two-field lymphadenectomy versus standard esophagectomy. Log rank test, $P = .005$. (*Data from* Sihvo EI, Luostarinen ME, Salo JA. Fate of patients with adenocarcinoma of the esophagus and the esophagogastric junction: a population-based analysis. Am J Gastroenterol 2004;99(3):419–24.)

patients following standard esophagectomy. Slightly less than half (42.5%) of all cancers of the esophagogastric junction underwent resection. Similar to the reports outlined previously, the 5-year survival was significantly better in patients with two-field lymphadenectomy (50%) than in those with less extensive resections (23.2%, $P = .005$) (**Fig. 13**). Eight-year survival rates were also better (43% versus 21%), suggesting that the effect is long lasting. The authors concluded that in centers with experience, "radical surgery" should be favored for patients eligible for major surgery.

The only prospective randomized controlled study was performed by Hulscher and colleagues[39] in the Netherlands. This study showed a trend toward better survival with the en bloc resection (**Fig. 14**). Unfortunately, the study was underpowered. Their calculations for sample size were based on a survival of 30% following simple transhiatal dissection, whereas the literature supports a 25% survival rate at best. Further, they estimated a 15% difference between the procedures but actually observed only a 10% difference. Given these data, the correct sample size required to detect a statistical difference is 260 patients per arm, whereas they enrolled 110 per arm.

An important common finding in all these studies is the correlation between survival and number of positive nodes on pathology. Survival decreased significantly with nine or more positive nodes in the study by Altorki and Skinner,[35] 80% of patients with five or more involved nodes developed systemic disease in the study by Hagen and colleagues,[36] and 5-year survival was significantly better when the ratio of involved nodes to the total number of nodes removed was less than 10% in the study by Portale

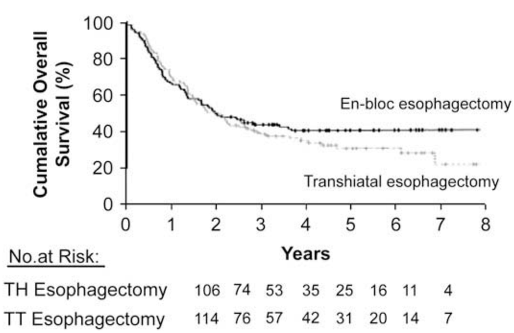

Fig. 14. Overall survival of patients with esophageal adenocarcinoma after transhiatal or transthoracic en bloc esophagectomy. (*Data from* Hulscher JB, van Sandick JW, de Boer AG, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 2002;347(21):1662–9.)

and colleagues.[5] In a multivariate analysis of prognostic factors for esophageal cancer, Bollschweiler and colleagues[40] showed that patients with less than five regional positive nodes had significant better prognosis than those with more than five lymph nodes involved. Also, patients with negative nodes and more than 15 nodes examined showed better prognosis than those with fewer examined nodes. This finding again confirms the regional nature of the disease and underscores the role of lymphadenectomy for improving survival.

Taken together, these studies, which encompass retrospective series, case control studies, population-based studies, and a prospective randomized trial, from around the world strongly suggest that for early cancers of the lower esophagus and cardia, en bloc esophagogastrectomy results in significantly better survival rates than transhiatal esophagogastrectomy. This finding is unlikely to be caused by bias in the stage of disease resected, a difference in operative mortality, or death from nontumor causes. Rather, it seems to be caused by the type of operation performed.

Functional Outcomes

In general, the functional outcome after esophagectomy is good. Twenty-five percent to 50% of patients suffer mild to moderate alimentary disabilities. Orringer and colleagues[41] evaluated alimentary outcome in 242 patients following esophagectomy and gastric pull-up. Most (68%) were either asymptomatic or had mild symptoms that required no treatment. Sixty-five percent were free of dysphagia eating an unrestricted diet, and 60% had no regurgitation. The most satisfactory esophageal replacement may be achieved when a vagal-sparing esophagectomy can be performed, as mentioned previously.

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