GENERAL THORACIC SURGERY

NODE STATUS IN TRANSMURAL ESOPHAGEAL ADENOCARCINOMA AND OUTCOME AFTER EN BLOC ESOPHAGECTOMY

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Objective: Adenocarcinoma has replaced squamous cell as the most common esophageal cancer in the United States. The purpose of this study was to determine the prevalence and location of lymph node metastases, the feasibility of performing an R₀ resection, and disease recurrence and survival in patients with transmural adenocarcinoma of the lower esophagus and gastroesophageal junction. **Methods:** Forty-four patients with transmural adenocarcinoma underwent en bloc esophagectomy with systematic thoracic and abdominal lymphadenectomy. They were followed up for a median of 23 months. **Results:** Actuarial survival for the entire group was 26% at 5 years. The most important predictors of the likelihood of recurrent disease and 5-year survival were the presence and number of lymph node metastases and the ratio of involved to total removed nodes. Seven patients (16%) were found to have no lymph node metastases and had an 85% 5-year survival. In contrast, patients with more than 4 involved nodes or a node ratio greater than 0.1 had a high likelihood of recurrence and death. Location of involved lymph nodes did not predict the likelihood of recurrence or death. Despite all patients having transmural tumors, recurrence within the field of the en bloc resection occurred in only 1 patient (2%). **Conclusions:** En bloc esophagectomy in patients with transmural esophageal adenocarcinoma is required to obtain the survival benefit of an R₀ resection, to adequately assess lymphatic tumor burden, and to be able to predict the likelihood of recurrence and death and thereby guide the use of postoperative adjuvant therapy. (J Thorac Cardiovasc Surg 1999;117:960-8)

Adenocarcinoma is now the most common esophageal cancer in the United States. In white men its incidence has risen 10% per year during the past decade, and it now ranks in the top 15 cancers affecting this group.¹ Esophageal adenocarcinoma is one of the

most lethal malignant diseases known to mankind. Within 5 years of diagnosis the majority of patients will die.

Despite liberal endoscopy in patients with reflux symptoms and routine endoscopic surveillance for Barrett's esophagus, most patients who have adenocarcinoma of the esophagus present de novo with dysphagia and have large tumors. Using endoscopic ultrasound, we now have the capability to identify patients with advanced disease, including those with transmural tumors.^{2,3} In many centers these patients are targeted for neoadjuvant therapy. Before this alternative therapy is widely adopted, it is imperative that the results of complete surgical resection alone be defined. Since 1981 our group has used en bloc esophagectomy with systematic mediastinal and abdominal lymphadenectomy to treat patients with esophageal adenocarcinoma. We reviewed our experience with this procedure in

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Fig 1. Boundaries of our standard en bloc resection.

patients with transmural adenocarcinoma of the lower esophagus and gastroesophageal junction to determine the prevalence and location of node metastases, the feasibility of performing an R_0 resection, and the outcome in terms of disease recurrence and survival.

Methods

The study population consisted of 44 patients who underwent en bloc esophagectomy for transmural (T3) adenocarci-

Fig 2. Lymph nodes routinely removed with thoracic and abdominal lymphadenectomy. Location code: 1 = lower paratracheal; 2 = subcarinal; 3 = paraesophageal; 4 = parahilar; 5 = splenic hilum; 6 = splenic artery; 7 = greater curve; 8 = lesser curve; 9 = left gastric; 10 = hepatic; 12 = portal; 13 = right gastric; 14 = retropancreatic.

noma of the lower esophagus or gastroesophageal junction. All operations were performed by one group of surgeons and represent their cumulative experience at three different institutions between 1981 and 1998. There were 40 men and 4 women, with a median age of 58 years (range 25–73 years). None of the patients had received preoperative chemotherapy, radiotherapy, or prior esophageal or gastric resection. All patients had a barium radiograph of the upper gastrointestinal tract, upper gastrointestinal endoscopy with endoscopic ultrasound when feasible, and computed tomography of the chest and abdomen.

Operative approach. En bloc esophagogastrectomy with systematic mediastinal and abdominal lymphadenectomy was performed as previously described.^{4,5} In brief, the esophagus, azygos vein, and surrounding mediastinal tissues were removed in continuity. The thoracic dissection extended superiorly to the carina, laterally to include the left and right mediastinal pleura, anteriorly to the membranous trachea and pericardium, posteriorly to the spine and aorta, and inferiorly to the diaphragm. The abdominal dissection included removal of the proximal two thirds of the stomach, the greater omentum, spleen, left gastric and splenic arteries along with

Fig 3. The frequency of nodal metastases by node location for patients with transmurad adenocarcinoma located at the gastroesophageal junction and distal esophagus who underwent en bloc esophagectomy.

their surrounding fibro-areolar tissue, and nodal tissue along the portal vein, common hepatic artery, and celiac axis (Fig 1). Overall, this dissection allowed a reproducible, systematic removal of all lymph nodes in the following locations: low paratracheal, subcarinal, paraesophageal, parahiatal, porta hepatis, hepatic artery, celiac axis, and the retroperitoneal area of the upper part of the abdomen (Fig 2). In most patients, gastrointestinal continuity was established by an isoperistaltic colon interposition.

Analysis of the resected specimens. For this study, two experienced pathologists re-examined slides from the resected specimens to identify the depth of invasion of the primary tumor and to search for areas of intestinal metaplasia (Barrett's mucosa) adjacent to the tumor. The location of the primary tumor was determined by review of the original pathology report. After the resection the pathologists meticulously searched the specimen for lymph nodes and recorded their locations. We defined local nodes as those in close proximity to the primary tumor and included the parahiatal, lesser curve, left gastric artery, and paraesophageal node groups. Nodes outside these areas, but within the field of the en bloc resection, were considered distant. Node status was also analyzed according to the staging system proposed by Korst and associates.⁶

Follow-up. Patients were followed up by the operating surgeon at 3-month intervals for the first 3 years, twice a year for the next 2 years, and yearly thereafter. Median follow-up was 23 months (range 4-118 months). Each follow-up visit included serum and liver chemistry panels, carcinoembryonic antigen level, and computed tomographic scans of the chest and abdomen. All surviving patients were either seen in person or contacted by telephone within 3 months of the preparation of this manuscript. Recurrent tumor located within the field of the original en bloc resection was considered local recurrence. All patients were included in the survival analysis, including those dying in the perioperative period and those dying of causes other than cancer.

Statistical analysis. The χ^2 and Fisher exact tests were used to compare proportions. Survival probabilities were calculated by the method of Kaplan and Meier, and survival curves were compared by the log-rank method.

Results

All tumors invaded through the esophageal wall but not into adjacent organs. The primary tumor was located in the distal third of the esophagus in 8 patients (18%) and at the gastroesophageal junction in 36

Fig 4. Actuarial survival for patients with transmurial esophageal adenocarcinoma stratified by the number of lymph node metastases.

Fig 5. Actuarial survival for patients with transmurial esophageal adenocarcinoma stratified by the ratio of involved to total number of removed lymph nodes.

(82%). Histologic evidence of intestinal metaplasia was found adjacent to the tumor in 27 patients (61%).

A total of 2340 lymph nodes were excised and examined histologically. The median number of lymph nodes removed per patient after systematic mediastinal and abdominal lymphadenectomy was 51 (range 18-92). Lymph nodes metastases were identified in 37 of the 44 patients (84%). Despite transmural invasion, 7 patients (16%) had no lymph node metastases. Of the 37 patients with lymph node metastases, 16 (43%) had 4 or fewer involved nodes, and in these patients the majority (69%) had only local node involvement. In contrast, the majority (62%) of patients with more than 4 involved lymph nodes were found to have distant node metastases. Thus there was a trend toward an increased likelihood of distant node metastases with increasing number of involved lymph nodes (χ^2 , $P = .13$). The prevalence of metastatic nodes in patients with tumors located at the gastroesophageal junction or in the distal esophagus is shown in Fig 3. We found that the frequency and distribution of nodal metastases was similar for both primary tumor locations.

Twenty-seven patients (61%) had recurrent disease. The median time to detection of recurrence was 15 months (range 4-32 months). In 26 patients recurrent disease was manifested by systemic metastases. One patient had isolated nodal metastases outside the field of the en bloc dissection. This patient had N0 disease at resection, and paratracheal nodal recurrence subsequently developed 2 years later. The involved paratracheal nodes were resected, and the patient is now disease-free 5 years after the initial resection. No patient in this series had anastomotic recurrence. Only 1 patient had recurrent disease in nodes within the field of the en bloc resection; however, this patient also had systemic metastases. The likelihood of recurrent disease after en bloc esophagectomy, whether systemic or nodal, correlated with the presence and number of lymph node metastases in the operative specimen, but not with location of nodes in relation to the primary tumor (Table I). Median survival after detection of recurrent disease was 7 months.

Actuarial survival for the entire group of 44 patients was 26% at 5 years. Three patients died in the perioperative period (6.8%). The presence and number of lymph node metastases were the most significant predictors of 5-year survival (Fig 4). The ratio of involved to total removed lymph nodes in each patient also predicted 5-year survival. Patients with a node ratio of less than 0.1 had a significantly better survival than those with a ratio of more than 0.1 (Fig 5). Patients with a node ratio of more than 0.25 had a particularly poor

prognosis, with a median survival of 7 months (95% confidence interval: 0-19) and no survival at 5 years. As shown in Table II, the presence of distant node metastases as defined either in this study or in the study by Korst and associates⁶ was not a statistically significant predictor of survival.

Discussion

As one might expect, we found that the majority of patients with transmural adenocarcinoma of the esophagus have lymph node metastases. Surprisingly, 16% of these select patients had no involved lymph nodes and had an 85% 5-year survival. Furthermore, as evidenced by the near absence of anastomotic and in-field recurrence, an R₀ resection was accomplished despite the presence of a transmural esophageal adenocarcinoma in all patients. We found that 5-year survival was 23% in patients with 4 or fewer involved nodes, but decreased to 12% in those with more than 4 lymph node metastases. Correspondingly, the likelihood of recurrent disease increased from 53% to 90%, respectively. Patients with more than 10 involved lymph nodes had a particularly poor prognosis, and all have recurrent disease or have died of their cancer.

A problem with using the absolute number of involved lymph nodes after resection to predict the likelihood of long-term survival is the lack of a measure for the completeness of the lymphadenectomy. Recently, the ratio of involved to total number of nodes removed has been proposed as a more quantitative method to assess the adequacy of a lymphadenectomy. Holscher and colleagues⁷ reported that a ratio of involved to total removed nodes of 0.3 was the most effective prognostic parameter to stratify patients into those likely to die of their disease (>0.3) versus those likely to have better survival. Our data suggest that a ratio of 0.1 is a better predictor. A likely explanation for this apparent discrepancy is that the median number of removed nodes in our series was 51, compared with 26 in the series by Holscher and coworkers.⁷ A more extensive lymphadenectomy results in a greater number of uninvolved nodes removed, thereby driving down the node ratio. This emphasizes that the critical number is not the ratio itself, but instead the total number of involved and removed nodes. Consequently, a systematic lymphadenectomy is fundamental in allowing an accurate assessment of the patient's lymphatic tumor burden and in determining the likelihood of long-term survival. The importance of a complete, systematic thoracic and abdominal lymphadenectomy has been confirmed in our own experience after transhiatal resection in patients with a transmural esophageal adenocarcinoma who are elderly or have poor cardiopul-

Table I. Relationship of the presence, number, and location of lymph node metastases to the likelihood of recurrence and median survival in patients with transmural esophageal adenocarcinoma who underwent en bloc esophagectomy (recurrence analysis excluded the 3 postoperative deaths)

	No. of involved nodes			Node location	
	0	1-4	>4	Local	Distant
Recurrence	1/6 (17%)	8/15* (53%)	18/20* (90%)	14/18† (78%)	12/17† (71%)
Median survival (mo) (95% CI)	NA	33 (28-37)	17 (16-19)	27 (20-34)	20 (5-34)

NA, Not applicable; CI, confidence interval.

* $P = .02$ (χ^2).

† $P = .7$ (χ^2).

Table II. Median and 5-year survivals based on the presence and absence of distant node metastases

	Actuarial survival at 5 years		Median survival (mo)	
	Local	Distant	Local	Distant
Local and distant as defined in this study (95% CI)	14 (0-29)	20* (0-40)	27 (20-34)	20 (5-34)
Korst local and distant (95% CI)	13 (0-34)	8† (0-44)	30 (19-40)	17 (12-23)

CI, Confidence interval.

* $P = .1$ (log-rank test: local versus distant).

† $P = .2$ (log-rank test: local versus distant).

Table III. Summary of multimodality therapy randomized trials for esophageal adenocarcinoma

First author	Arm	No.	Three-year survival (%)	Median survival (mo)	Local recurrence (%)
Walsh ¹²	Surgery	55	6	11	NA
	Multimodality	58	32	16	NA
Urba ^{11*}	Surgery	50	15	18	39
	Multimodality	50	32	17	19

NA, Not applicable.

*Data published in abstract form only.

monary physiology. In these patients, despite a complete abdominal lymphadenectomy, the node ratio was unable to predict the likelihood of survival.

We found that adenocarcinomas of the gastroesophageal junction and lower esophagus tend to metastasize to similar lymph node regions and that distant or celiac nodal involvement occurred with primary tumors in either location and did not preclude long-term survival. We did note that patients with distant node metastases tended to have more involved nodes and, as a consequence, were more likely to have a recurrence and die of their disease. However, in the absence of a greater number of involved nodes, distant nodal metastases per se were not predictive of the likelihood of survival and should not deter resection.

Comparing outcomes between various reports in the

literature is difficult because of the confusion in staging. However, the 26% 5-year survival in our series compares favorably with the 25% to 33% 5-year survival reported by others for esophagectomy with limited lymphadenectomy.^{8,9} The survival in our series is particularly noteworthy in that it involved exclusively patients with transmural disease, whereas the other series included a variety of stages. Altorki and colleagues¹⁰ have recently reported favorable results similar to ours, with a 34.5% 4-year survival after en bloc resection in patients with advanced (stage III) esophageal cancer. They concluded, and we would agree, that en bloc resection improves survival compared with lesser resections.¹⁰ In our center, during the same period as this study, we performed 40 transhiatal resections in patients with transmural adenocarcinoma because of advanced

age or compromised physiologic condition. In this group survival at 5 years was 7%, and recurrent local disease developed in 15% of the patients.

Of importance, survival after an en bloc resection for transmural esophageal adenocarcinoma in this series compares favorably with published results for various stages of resectable esophageal cancer treated with neoadjuvant therapy followed by surgery. The two most widely quoted randomized trials both report a 3-year survival of 32% in the neoadjuvant group, with the best survival occurring in the 20% with complete pathologic response (Table III).^{11,12} Three-year survival for the group of patients with transmural tumors treated only by en bloc resection in this series was 36%. Given our results with en bloc surgical resection alone, one must question the utility of routine neoadjuvant therapy. However, we found that the subgroup of patients with a transmural tumor and more than 4 lymph node metastases had a 90% likelihood of developing systemic disease after resection alone. In our opinion, these patients should be targeted for neoadjuvant therapy. Furthermore, despite the lack of improvement in survival reported with previous trials, consideration should be given to early adjuvant postoperative chemotherapy in those patients found on pathologic review of the specimen to be at high risk for recurrence. Perhaps aggressive chemotherapy directed at a group of patients known to have a 90% likelihood of recurrence would demonstrate an improvement in survival.

A striking benefit of en bloc resection in patients with advanced disease was the excellent local control produced by this operation. Only 1 of the 44 patients in this study had recurrent disease develop within the field of the en bloc resection, giving a local failure rate of 2% in this homogeneous population of transmural tumors. Similarly, Altorki, Girardi, and Skinner¹⁰ reported recurrent local disease in 5.4% of patients after en bloc resection for stage III esophageal cancer. In contrast, Urba and colleagues¹¹ noted that local failure occurred in 39% of patients who had transhiatal esophagectomy alone and in 19% of patients after multimodality therapy that included the same type of resection. It is interesting to speculate whether, with better surgical therapy in these trials, the difference in outcome would vanish, or perhaps even be in favor of complete surgical resection alone.

Conclusions

We found that the presence and number of lymph node metastases and the ratio of involved to total removed nodes are important predictors of recurrent disease and the likelihood of long-term survival in patients with transmural adenocarcinoma of the esoph-

agus. In our opinion, an en bloc esophagectomy with systematic thoracic and abdominal lymphadenectomy is required to reliably obtain an R₀ resection, to achieve excellent local control, to adequately assess lymphatic tumor burden, and to predict the likelihood of recurrence and cancer-related death.

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Discussion

Dr Alex G. Little (*Las Vegas, Nev*). Adenocarcinoma of the gastroesophageal junction is becoming more prevalent and therefore is of increasing importance. This paper adds

useful data to the data pool from which decisions and recommendations will be made about two unsettled and important issues. One is the surgical approach—transthoracic, transhiatal, extended en bloc, two-field, three-field, four-field—and therapy, so your group has performed a valuable service in providing this information. However, I am not fully persuaded. Clearly the only way these issues are going to be settled is by prospective randomized comparisons. Despite the enthusiasm that one surgical group may develop for its way of doing things, whether it be the operative technique or the use or nonuse of adjuvant therapy, continuing to simply present an experience is no longer going to be sufficient to persuade thoracic surgeons or thoracic oncologists.

I have a few questions that reflect my skepticism about the validity of this study to really prove its point about the role of en bloc esophagectomy.

First, I noticed that you had accrued 44 patients over 17 years, but the median follow-up was under 2 years, which suggests that you are comparing patients accrued very recently with patients distributed over a significant amount of earlier time. I think everyone believes that the biologic behavior of adenocarcinoma has changed. Does that disturb you at all or do you think this is a homogeneous patient population?

Dr Nigro. Undoubtedly the epidemiology of esophageal cancer has changed over the past 20 years and patients are now referred for treatment with earlier disease. This may be partially due to our more substantial understanding of those groups at risk and the recognition of the relationship between gastroesophageal reflux disease and esophageal adenocarcinoma. But there is no evidence that the biologic behavior of esophageal adenocarcinoma has changed. Since all of these patients had transmural disease, they should be relatively comparable.

Dr Little. It would seem so, but I am concerned. I do not think that adenocarcinoma of the gastroesophageal junction is behaving now the way it did 17 years ago, so that is at least a concern.

The second question has to do with the fact that even though all patients have transmural primary tumors, a surprisingly high number had no nodes involved, which actually makes them have somewhat early disease, certainly stage II. Since your paper does not address the symptoms in this patient group, were some of these patients actually identified in surveillance approaches, rather than being taken care of because of symptoms?

Dr Nigro. All of the patients in this study presented with transmural tumors and had symptoms of dysphagia and weight loss; none of these patients were discovered during Barrett's surveillance. In our experience those cancers found during surveillance tend to have mucosal or submucosal invasion only, and we now consider these (tumors) to represent early disease.

Dr Little. My final comment and question have to do with the crux of interpretation of these data. My conclusion continues to be that survival is more a function of the biologic behavior and the stage at which the disease is detected rather

than the operative technique, as much as I would like to believe the latter. For example, survival was excellent in patients with N0 disease, as one would expect. I understand the theory that you may detect some micrometastatic deposits in lymph nodes. Nonetheless, in patients with N0 disease, extended dissection does not seem to be very beneficial. My other observation is that patients who had 5 or more lymph nodes involved did very badly and their 5-year actuarial survival was just over 10%. I would argue that those patients did not benefit significantly from an extended resection.

Finally, the survival in the patients with 1 to 4 involved nodes was 23%, which is certainly good, but not obviously or dramatically better than what has been reported with the so-called standard techniques. If you follow the argument that in that case there is no benefit to going beyond what you call local nodes, the hiatal, left gastric artery, lesser curve, and periesophageal nodes, which I think most surgeons would routinely resect, then there is no benefit to going beyond that. That allows you to keep the greater curvature and use the stomach for reconstruction, which is a much less complicated and a much less morbid operation than routinely using the colon.

Do you really believe you have established the role for routine radical en bloc esophagogastrectomy with removal of two thirds of the stomach in all patients with adenocarcinoma of the gastroesophageal junction?

Dr Nigro. We believe that this operation provides for good survival, excellent local disease control, and accurate stratification for subsequent adjuvant therapy. With more limited resections we have observed a lower survival, a high local recurrence rate, and inability to accurately stratify patients for risk of recurrence and cancer-related death.

Dr Gundry. Do you plan to continue this approach or are you going to investigate some adjuvant therapy or multiple-modality protocols?

Dr Nigro. One of the main objectives of our work with esophageal adenocarcinoma has been to establish the relationship between depth of tumor invasion, node status, and survival. This information was available only after performing a resection that included a systematic abdominal and thoracic lymphadenectomy. Our results indicate that patients with transmural tumors and more than 4 involved lymph nodes are at especially high risk for recurrence and are unlikely to be cured with surgery alone. We have incorporated these results into our treatment protocol and believe that this group of patients should be targeted for neoadjuvant and adjuvant therapy.

Dr Little. I would like to make one complimentary comment in closing. This paper based survival statistics on all deaths, perioperative deaths as well as the late deaths due to cancer, and that is the way these data should be presented. It is the most honest way, and I hope that others will adopt this method as well.

Dr Douglas E. Wood (*Seattle, Wash*). I had some of the same comments and questions that Dr Little had. The recurrence rate and survival of patients after esophagectomy for esophageal cancer is related to the biology of the tumor. One of your early slides showed that the majority of your survivors

had N0 disease. If those patients are the long-term survivors, it is hard to imagine that an extended procedure is going to benefit them. In fact, there is no good evidence in any series that a more radical resection does result in better survival. I would urge us all to participate in developing prospective trials to examine the role of neoadjuvant and adjuvant therapies and different surgical techniques rather than multiple parochial case studies within each of our institutions.

You had mentioned in the conclusion a potential role for adjuvant therapy. No data have been presented that show that postoperative or adjuvant therapy improves survival in esophageal cancer. Can you tell me what you mean by selecting patients for adjuvant therapy?

Dr Nigro. We believe that patients with N0 disease will not benefit from neoadjuvant or systemic therapy. We now know that those patients with greater than 4 involved nodes have an extremely poor prognosis, and we believe that it would be more appropriate to target this group for systemic therapy in a manner analogous to the application of adjuvant therapy in colon adenocarcinoma.

Dr Wood. If you could identify that before resection, would you prefer to avoid resection in those patients and treat them nonoperatively? I would point out that not only did patients with more than 4 positive lymph nodes do poorly, but the patients with any lymph node metastases as a group did not do well in your study.

Dr Nigro. The presence of lymph node metastases is a poor prognostic indicator, but it remains difficult to determine this preoperatively. Although patients with involved nodes have a poor prognosis, local disease control remains an important goal that is rarely obtained with nonoperative therapy. In our opinion, surgical resection provides the best palliation for patients with advanced tumors and is the only therapy that is potentially curative.

Dr Wood. Have you used endoscopic ultrasound, computed tomographic scanning, or any of the laparoscopic methods of sampling lymph nodes before resection?

Dr Nigro. Currently our preoperative assessment includes a computed tomographic scan of the abdomen and pelvis and endoscopic ultrasound. As we all know, endoscopic ultrasound is able to determine depth of tumor invasion in approximately 80% of cases, but it does not always accurately reveal node status. We do not believe it is beneficial to add additional invasive procedures such as thoracoscopy and laparoscopy to stage the disease when we can obtain accurate disease staging, along with local disease control and good survival, with one primary operation.

Dr John R. Benfield (*Sacramento, Calif*). I think there is no better place than The Western Thoracic Surgical Association to recognize that thoracic surgery is a family affair. Dr John Nigro is the son of one of my close friends who is also a thoracic surgeon.

Dr Nigro, I think you said that one of your patients who had a peritracheal recurrence had a second resection and then became a long-term survivor. Did I hear that correctly?

Dr Nigro. That is correct.

Dr Benfield. Is it your practice to reoperate on patients who have recurrence? Did this patient have additional nonoperative therapy? If so, do you think the resections or the nonoperative treatment was more important in achieving long-term survival after reresection?

Dr Nigro. We are in the process of reviewing our experience with these patients. We now have a series of 5 to 7 patients with isolated lymph node recurrence who have undergone a second resection and now have no evidence of disease. We believe that these patients can benefit from surgery. The patient you referred to received no therapy other than surgery.

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