Hypothesis: En bloc esophagectomy (EBE) provides improved survival over transhiatal esophagectomy (THE) in patients with similarly sized transmural tumors (T3) and lymph node metastases (N1).

Design: A retrospective case-control study of 2 methods of esophageal resection for cancer.

Setting: University hospital (tertiary referral center for esophageal disease).

Patients: There were 49 patients (27 who underwent EBE and 22 who underwent THE) with similar T3 N1 disease and the following matched criteria: tumors of similar size and location, more than 20 lymph nodes in the surgical specimen, R0 resection, no previous chemotherapy or radiation therapy, and follow-up until death or for a minimum of 5 years.

Main Outcome Measure: Survival adjusted for differences in demographic and patient characteristics.

Results: The number of nodes harvested was greatest after EBE vs THE (median, 52 vs 29 [range, 21-85 vs 20-60]; P<.001). The median number of involved nodes was similar after EBE vs THE (median, 5 vs 7 [range, 1-19 vs 1-16]). The only 2 independent factors that affected survival in a Cox analysis were the number of involved lymph nodes (P=.01) and the type of resection (P=.03). Patients who underwent EBE had a survival benefit over those who underwent THE (P=.01). The survival benefit of EBE was seen only in patients with fewer than 9 involved lymph nodes (P<.001).

Conclusion: En bloc esophagectomy confers a better survival than THE in patients with T3 N1 disease and fewer than 9 lymph node metastases.

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Controversy persists regarding the extent of resection necessary for cure of esophageal adenocarcinoma. Several retrospective studies1-3 have shown a benefit to the more extensive node dissection accomplished with transthoracic en bloc esophagectomy (EBE) compared with transhiatal esophagectomy (THE). These studies have been criticized as having selection bias and inaccuracy in preoperative staging. Performance of a more complete node dissection also results in the potential for stage migration. A recent prospective randomized controlled trial4 compared transthoracic EBE with THE. The results were inconclusive but showed a trend toward better survival with transthoracic EBE.4 This trial eliminated many of the criticisms of the retrospective studies but included patients with various stages of disease. This broad inclusion may have obscured the benefits of systematic node dissection by the presence of patients with early-stage disease who did not need a formal lymphadenectomy and those with advanced disease and extensive lymph node metastases who were not curable by surgery alone. An alternative approach to compare transthoracic EBE with THE would be to perform a retrospective case-control study between nonrandomized patients with similarly sized transmural tumors (T3) and lymph node metastases (N1). The aim of the present study is to determine whether patients with locally advanced (T3 N1) (according to the American Joint Committee on Cancer TNM staging system) esophageal cancer benefit from transthoracic EBE.
tomy for adenocarcinoma between January 1, 1988, and December 31, 1998, at the university hospital of either Creighton University, Omaha, Neb, or the University of Southern California. Assessment of the extent of disease before surgery included an upper gastrointestinal tract barium roentgenogram, endoscopic examination of the upper gastrointestinal tract, endoscopic ultrasonound of the tumor, and a chest and abdomen computed tomographic scan. Transthoracic EBE was performed in patients who were younger than 75 years and who were free of substantial cardiovascular or pulmonary disease. The criteria used were a forced expiratory volume in 1 second greater than 1.25 L and an echocardiogram that showed an ejec-

tion fraction greater than 40% at rest that increased on exer-

sion owing to surgical and infectious complications and were not available for long-term follow-up. The remaining 49 patients were followed until death or for a minimum of 5 years. Follow-up after surgery was performed by the operating surgeon every 3 months. All deaths were due to cancer. Transthoracic EBE was performed in 27 patients and THE was performed in 22.

Transthoracic EBE was performed as described in previ-

ous publications.3, 6 In brief, the en bloc dissection was performed through a right posterolateral thoracotomy entering the chest through the seventh intercostal space on top of the eighth rib. The dissection removed en bloc the esophagus, azygos vein, thoracic duct, and surrounding lymph node–bearing mediasti-

nal tissues. The border of the dissection extends superiorly to above the azygos arch; laterally to include the left and right mediastinal parietal pleura; anteriorly to the membranous trachea, pericardium, and diaphragm; posteriorly to the spine and aorta; and inferiorly to the esophageal hiatus and down into the costal vertebral angle. The abdominal dissection was performed through an upper midline incision and removed the proximal stomach and the greater omentum. On the right side of the abdomen, the node-bearing tissue was removed from the lateral surface of the right crus, the porta hepatis, and around the portal vein and the common hepatic, celiac, and left gastric arteries. On the left side, the node-bearing tissue was removed from the lateral surface of the left crus, around the splenic artery, medial to the splenic hilum, and anterior to the adrenal gland. The en bloc dissection provided systematic removal of lymph nodes in the following areas: low paratracheal, subcarinal, perihilar, parasphe
go, parahiatal, costal-vertebral space, porta hepatis, superior retropan-

cratic, and around the portal vein and the hepatic, celiac, and splenic arteries. In 25 patients, reconstruction was performed with an interposed colon between the cervical esophagus in the neck and the retained antrum of the stomach. In 2 patients with limited extension of the tumor into the stomach, a tubed gastric pull-up was used for reconstruction.

Transthiatal dissection was performed as described by Or-

ringer7 through an upper midline incision and a left cervical incision. The lower esophageal dissection was performed through a widened diaphragmatic hiatus using blunt and sharp dissec-

tion. The lymph node dissection in the lower and middle me-
diastinum was not as extensive as with the transthoracic en bloc dissection. However, the transthiatal approach allowed re-

oval of nodes around the distal esophagus and subcarinal area. The node dissection in the upper abdomen was similar to that described herein for transthoracic en bloc dissection. Recon-

struction after THE was performed with the stomach in 18 pa-

patients and with the colon in 4 depending on the degree of tu-

or extension into the stomach.

Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Transhiatal Esophagectomy Group</th>
<th>En Bloc Esophagectomy Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F, No.</td>
<td>18/4</td>
<td>26/1</td>
<td>NS</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>71 (50-80)</td>
<td>57 (25-91)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hospital stay, median, d</td>
<td>18 (11-166)</td>
<td>20 (14-55)</td>
<td>NS</td>
</tr>
<tr>
<td>Barrett esophagus, No.</td>
<td>11</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor size, median, cm</td>
<td>4.0 (1-9)</td>
<td>4.0 (1-9)</td>
<td>NS</td>
</tr>
<tr>
<td>Removed nodes, Total No.</td>
<td>648</td>
<td>1379</td>
<td>.001</td>
</tr>
<tr>
<td>Removed nodes, median (range), No.</td>
<td>29 (20-60)</td>
<td>52 (21-85)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Involved nodes, median (range), No.</td>
<td>7 (1-16)</td>
<td>5 (1-19)</td>
<td>NS</td>
</tr>
<tr>
<td>Distribution of involved nodes, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td>14</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Abdomen</td>
<td>41</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>45</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NS indicates not significant.

Table 2. Factors Included in the Cox Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor size</td>
<td>NS</td>
</tr>
<tr>
<td>Number of nodes removed per patient</td>
<td>NS</td>
</tr>
<tr>
<td>Number of nodes removed according to categories (20-29; n = 17; 30-46; n = 16; 47-85; n = 16)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of metastatic nodes per patient</td>
<td>NS</td>
</tr>
<tr>
<td>Number of metastatic nodes according to categories (1-3; n = 16; 4-8; n = 15; 9-19; n = 18)</td>
<td>.01</td>
</tr>
<tr>
<td>Metastatic chest nodes (yes or no)</td>
<td>NS</td>
</tr>
<tr>
<td>Type of resection (en bloc or transhiatal)</td>
<td>.03</td>
</tr>
<tr>
<td>Type of reconstruction (colon or stomach)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.
In both procedures, all reconstructions were placed in the posterior mediastinum, and the proximal anastomosis was hand sewn in the neck. When the stomach was used for reconstruction, the lesser curve down to the fourth vein along with its lymph node–bearing mesentery was resected by forming, with a gastrointestinal stapler, a narrow gastric tube along the greater curvature.

Cox proportional hazards analysis was used to compare survival, adjusting for differences in factors that may impact survival between the THE and transthoracic EBE groups. These factors included age, tumor size, number of lymph nodes removed, number of involved nodes, node involvement in the chest, type of resection, and type of reconstruction. The number of nodes was also studied as a categorical variable (20-29, 30-46, and ≥47), as was the number of nodes containing metastatic cancer (1-3, 4-8, and ≥9). Univariate analyses were performed using the Fisher exact test or the χ² test for categorical variables and the Mann-Whitney test for continuous variables. Survival was calculated using the Kaplan-Meier method, with comparisons of survival using the log-rank test. P<.05 was considered statistically significant.

**RESULTS**

The characteristics of the study population are listed in Table 1 according to the type of resection performed. As expected, patients who had a transthoracic EBE were younger and had a greater median number of nodes harvested. The median number and distribution of involved nodes were similar after transthoracic EBE vs THE.

Table 2 gives the results of a Cox analysis of factors that could potentially affect survival in the population studied. Only 2 of the studied factors statistically significantly affected survival: type of resection and extent of lymph node disease characterized by the number of nodes involved (1-3, 4-8, and ≥9). The Figure shows survival according to the type of resection performed and the number of involved nodes. It is important to remember that all patients were followed up for a minimum of 5 years or until death, and all deaths were due to recurrent cancer. Overall survival was better after transthoracic EBE (P=.01, log-rank test) (Figure, A). The survival benefit of transthoracic EBE was limited to patients with 8 or fewer involved nodes (Figure, B), with no difference in outcome between transthoracic EBE and THE when 9 or more lymph nodes were involved (Figure, C).

**COMMENT**

In this study, we showed that transthoracic EBE confers a survival benefit over THE in patients with transmural (T3) esophageal adenocarcinomas when 8 or fewer lymph nodes (N1) are involved. Identifying this difference in survival required a retrospective study of similar patients with pathologic T3 N1 disease. This approach removed the effect of inaccurate preoperative staging and minimized the effect of postoperative stage migration on survival because all patients had N1 disease. The requirement that 20 or more lymph nodes were in the surgical specimen allowed confirmation that the extent of lymph node disease in both groups was comparable. These conditions focused the question of which procedure was associated with a better survival rate. Indeed, the Cox analysis identified only 2 independent factors that affected survival in the studied population: type of resection and extent of lymph node disease categorized by the number of involved nodes. Other attempts have been made to determine whether the extent of resection affects survival (Table 3). Four of these studies were retrospective, and none of them made an attempt to limit the studied population to T3 N1 disease. Consequently, their conclusions, although statistically significant in 3 of the 4 studies, were accepted with caution and reservation. The only prospective randomized controlled study was performed by Hulscher et al1 and showed a nonsignificant trend toward better survival with transthoracic EBE. However, the study was underpowered. The calculations for sample size were based on survival of 30% with
THE, whereas the literature would only support 25% survival at best. Furthermore, they estimated a 15% difference between the procedures but actually observed only a 10% difference. Consequently, the correct sample size required to detect a statistical difference in their study design would be 260 patients per arm, but they enrolled only 110 per arm.

Some would say that although transthoracic EBE provides a better survival rate, the benefit is offset by its increased morbidity and mortality rates. Several studies have evaluated the mortality and morbidity rates of both procedures and have shown that they are similar (Table 4).1-4,8-11 Indeed, the progressive improvements in intraoperative and postoperative care have eliminated mortality and morbidity as factors in the choice of procedures.

The most likely explanation for the improved survival after transthoracic EBE in the present study is better removal of local-regional disease, that is, unrecog-
ized microscopic disease was removed when using en bloc lymph node dissection but was left behind when using transhiatal lymph node dissection. In support of this explanation is the observation that transthoracic EBE, according to the literature, results in better control of local-regional disease (Table 5). Indeed, in clinical trials, neoadjuvant radiochemotherapy has been added to THE in an effort to control local-regional disease, but without great success. A more prudent approach would be to use transthoracic en bloc node dissection to control local-regional disease and to focus neoadjuvant or adjuvant therapy on eliminating systemic disease.

At present, the cure of adenocarcinoma of the esophagus depends on 2 proven principals: early detection and complete surgical removal of disease. Today we have the advantage of early detection in patients with Barrett esophagus who are under surveillance.23 Patients with limited disease can be treated with more limited resection.24 However, based on the results of this study, it seems inappropriate to use limited resection in patients with T3 N1 disease. Instead, these patients should be offered the benefit of complete removal of disease with transthoracic EBE. When 9 or more lymph nodes are involved, the disease is likely to be systemic and the benefit of improving survival with transthoracic EBE is lost. In these patients, efforts should focus initially on the elimination or control of potential systemic disease with appropriately selected chemotherapy (Mary-Beth Moore-Joshi, unpublished data, 2004) removal of the primary tumor and locoregional disease with an EBE, and administration of a program of maintenance chemotherapy. In conclusion, fit patients with transmural adenocarcinoma in the distal esophagus or at the gastroesophageal junction without evidence of extensive (78) lymph node metastasis on computed tomographic scan or endoscopic ultrasound should undergo EBE with the intent to cure.

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REFERENCES


DISCUSSION

Mark Talamonti, MD, Chicago, Ill: This is an important paper, not just because it addresses the surgical controversy regarding the various types of operations used to treat esophageal cancer, but also because it highlights the role of surgery in the treatment of these patients. Remember that among our colleagues in medical oncology and radiation oncology, the role of esophagectomy as the primary treatment of choice for esophageal cancer is currently being challenged. Due to the poor outcomes following surgical resection for patients with locally advanced disease, the question has now arisen among those disciplines as to whether or not surgery need be performed at all for these patients.

Thus, the remarkable survival rates reported here should help to emphasize that esophagectomy remains the standard of care for patients with potentially curable disease. This study addresses the debate within the surgical literature as to what represents the appropriate operation for esophageal cancer and, spe-
cifically, what is the impact of extended soft tissue resections and extended lymph node dissections on overall survival.

My questions for the authors: Your data suggest that at a specific level of lymph node involvement, even a radical operation will have little impact on survival. The survival benefit is greatest when there is limited lymph node disease, and it is lost when 9 or more lymph nodes are positive. If fewer than 9 nodes are involved, then improved local control with an en bloc resection will significantly impact survival. My first question, thus, has to do with the patterns of disease failure. Do you have any data regarding local failure rates in these 2 groups? Was early local failure greater in the transhiatal group, and how did this compare to the local failure rate in the en bloc group? I wonder if you might also postulate why aggressive local surgery for esophageal cancer improved survival when similar studies for other foregut cancers, mainly gastric cancer and pancreatic cancer, have not shown any benefit to extended lymph node dissections or more radical soft tissue en bloc resections.

Secondly, the esophageal cancer group at USC has helped define molecular events important in the development and progression of esophageal cancers. In the current study, even in the most favorable group—those having en bloc resections and less than 9 nodes positive—the 5-year survival rate was about 35%, and, therefore, further improvement in survival will have to address the likelihood of early systemic disease.

Have you, therefore, examined any other biologic or pathologic factors such as flow cytometry, oncogene expression, or tumor suppressor mutations that may help stratify risk in your patients? I know the number of patients was small, but it would seem to me that despite the fact that many of your patients were cured by surgery, most were not. In your current practice, do any or all of these T3 N1 stage III esophageal cancer patients receive postoperative adjuvant therapy? If so, how do you decide who is treated, and what type of treatment do they receive?

My final question has to do with my own current surgical practice and, I suspect, that of many other surgeons in the room who currently perform either transthoracic esophagectomy or a standard transthoracic esophagectomy. I emphasize that the presentation you heard today is not a transthoracic vs a transhiatal comparison. The en bloc resection described by DeMeester and his colleagues is a much more radical resection of mediastinal lymph nodes and soft tissues in the chest and in the upper abdomen. So despite the lack of any overwhelming advantage to neoadjuvant chemoradiation, most of us who see these patients at tertiary referral centers continue to enter patients on either single-institution pilot studies or larger multiinstitutional clinical trials. As I listened to the presentation and after reading the manuscript, the question I asked myself was whether this operation should be done or needs to be done at all after a patient has had preoperative chemoradiation. Would the complication rates be prohibitive? Few data were presented today on the complication rates between the 2 groups. Would the effects of local control be negated by the addition of preoperative radiation therapy? Perhaps the failures of previous clinical trials were not due to ineffective chemotherapy or radiation therapy but perhaps to inadequate surgery.

Dr T. R. DeMeester: I also would like to underscore your remarks about the current medical oncologist’s view that surgery may not be necessary for esophageal cancer. The main reason for this attitude is that surgery commonly performed for esophageal cancer is plagued with a high local recurrence rate. Unless we improve our ability to control local disease, surgery will be in trouble as a therapy. You asked a question about local control with the 2 procedures. Although this was not the focus of our presentation, failure of local control with the operative field following an en bloc resection is 1%. Following transthiatal resection it is around 25%. The big difference between the 2 procedures is obtaining local control of the dis- ease. Failure to obtain good local control with transthiatal resection was one reason for adding radiation to the neoadjuvant therapy used in treating this disease. The real message is surgeons need to do better surgery.

Your second question was: Is control of local disease the reason for success of the en bloc? I believe it is. The en bloc dissection removes more unrecognized disease with its more extensive lymph node dissection. Involved nodes are left behind with the transthiatal resection, even though we make attempts to try to remove as much lymph node disease as possible. Eventually, unremoved involved nodes result in recurrent local disease.

You asked about the biomarkers. We are looking for biomarkers with great intensity. Obviously, the next step is to identify patients who are likely to be free of lymph node metastasis or who are likely to respond to chemotherapy. Markers such as p53 and methylation are being investigated in our department. We have published on the effect of these markers already, but their specificity is insufficient to use them routinely.

You asked about the use of the en bloc resection after preoperative chemoradiation. We are currently investigating that combination. We do have patients who are referred after preoperative chemoradiation, and we have a group in whom en bloc resection was done. Eventually, we hope to show that even with neoadjuvant therapy, an en bloc resection is necessary and beneficial in controlling local disease.

Raymond J. Joehl, MD, Hines, Ill: I enjoyed the paper and, as usual, it tends to ask more questions than it answers. I noted that there may have been an age difference between the 2 groups of patients. Is the en bloc resection one reason for adding radiation to the neoadjuvant therapy? Perhaps the failures of preoperative chemotherapy, and we have a group in whom en bloc resection was done. Eventually, we hope to show that even with neoadjuvant therapy, an en bloc resection is necessary and beneficial in controlling local disease.

Dr T. R. DeMeester: This study extends from 1988 to 1998 to provide at least a 5-year follow-up in all of the patients. Our policy during our initial experience with the en bloc was not to do an en bloc in a patient over age 75. We also backed away from an en bloc in patients with comorbidity. It just doesn’t make sense to be more aggressive under those conditions. Out of that population came the study population we presented today. For this reason, we performed a Cox regression analysis between the similar groups to identify factors that influence survival. And as you saw in our study population, there were only 2 factors that affected survival regarding patients with similar extent of disease: the number of lymph node metastases and the type of resection. Age and comorbidities did not affect survival. Also, patients were followed until death or for 5 years, and all deaths were due to tumor recurrences.

Anton J. Bilchik, MD, Santa Monica, Calif: Has PET [positron emission tomographic] scanning or endoscopic ultrasound influenced the type of operation performed, particularly if you are seeing a difference in prognosis between patients who have fewer than 3 nodes and more than 9?

Dr T. R. DeMeester: Yes, we do an ultrasound examination ourselves, and it is very helpful in determining if a patient has a transmural tumor. On the other hand, it is not very helpful in determining how deep a tumor extends when it is confined to the wall, that is, an intramural tumor. It is also helpful in identifying patients who have a high number of enlarged nodes. We are about maybe 80% successful in detecting lymph node metastasis, but it is clearly beneficial when you see a large number of enlarged nodes. In such a patient, we would resist performing an en bloc resection. Rather, we would proceed with preoperative neoadjuvant therapy. But if there are less than say 4 or 5 enlarged nodes, we would go ahead with a transthoracic en bloc procedure without neoadjuvant therapy.
Kevin G. Billingsley, MD, Seattle, Wash: I would like to return just for a moment to the question of patient selection and ask if you have applied any of the well-known risk stratification protocols to this group of patients. I am obviously thinking of something like the VA [Veterans Affairs] National Surgical Quality and Improvement Program, which lays out some very specific predictors of comorbidity in surgical risk, things like albumin and ASA [American Society of Anesthesiologists] classification, which may provide a little bit more specificity in adjusting for the comorbidity piece of the study.

Dr T. R. DeMeester: We do look at FEV1 [forced expiratory volume in 1 second] and cardiac ejection fraction; we prefer that patients have an FEV1 greater than 1.25 L and an ejection fraction greater than 40% that increases on exercise without evidence of a wall motion defect. When we have these abnormalities, we manage the patient more conservatively.

Again, this is the reason why we focused our study the way we did so that only the effect of the extent of the resection could be evaluated. The results indicate that when a patient has between 1 and 9 lymph nodes, an en bloc resection provides better survival. Obviously, if you have no lymph nodes involved, you can just take the esophagus out. Our experience with the en bloc resection has shown almost a direct relationship between the number of nodes and the probability of systemic disease 2 years later. When a patient has 9 or 10 involved nodes, the incidence of systemic disease is 100%. It’s interesting that the results of the current study came to a similar conclusion, that is, between 0 and 9 involved nodes, the en bloc resection is of benefit; beyond that number, the benefit is lost because of the high incidence of systemic disease. I concur that if you have 1 or 2 nodes, you are likely to remove them with a transhiatal resection, but making that determination before surgery is difficult.

Katherine J.-M. Liu, MD, Chicago, Ill: I am interested in your findings because they corroborate with some of the observations we made for gastric cancer. In patients with gastric cancer, the greater the number of lymph nodes removed, the better the patient survival. That is also true when the ratio of positive resected lymph nodes is low.

I have noticed in your study that your median number of lymph nodes removed in a transhiatal resection was 29, which is remarkable because in most of the transhiatal resections, we do not find such a high number due to the type of the surgical resection as well as possibly a lack of pathologist’s efforts. My question for you is whether you have looked at the number of nodes removed and how that affects your overall survival in this group of patients, especially when the number of lymph nodes identified in the surgical specimen is less than 29.

Dr T. R. DeMeester: We have to look at the percentage vs number of involved nodes removed. The critical cutoff seems to be about 10%, that is, survival is less favorable if the number of involved nodes is greater than 10% of the total number of nodes removed. So there seems to be a trend that the more nodes you remove the better the survival, but that did not hold for this small study group. What appears to be important is that you remove the involved nodes, and your chances of doing so are greater with an en bloc resection.