Thoracoscopic Staging and Surgical Therapy for Esophageal Cancer*

David J. Sugarbaker, MD, FCCP; Michael T. Jaklitsch, MD; and Michael J. Liptay, MD

Esophageal cancer continues to be a major health problem with an associated poor prognosis. New technology is being applied to the staging of this cancer. The new staging system requires assessment of depth of wall penetration and lymph node status prior to resection. To determine penetration and node status with a high degree of accuracy generally requires some combination of chemotherapy, magnetic resonance imaging, endoscopic ultrasound, and/or surgical staging. Several variables need to be considered in planning the surgical approach to the patient with esophageal cancer: the intent of the surgeon to either cure or palliate, the anatomic location of the tumor, and the method of reconstruction. Surgery is optimal for localized esophageal cancer. Neoadjuvant chemoradiation has increased survival in specific subgroups. Phase 2 trials have shown the safety and efficacy of chemoradiation. Randomized multi-institutional trials are needed to verify the encouraging results of recent phase 2 trials.

(CHEST 1995; 107:2185-223S)

Carcinoma of the esophagus accounts for 4% of all cancers in the United States. The American Cancer Society estimates 13,000 new cases will be diagnosed in this country in 1993. Overall survival has remained disappointingly low, with most series reporting 5-year survival rates in the range of 15% regardless of therapy.

In addition to a slight rise in disease incidence over the last 10 years, there has been a dramatic change in the histologic features of esophageal cancer. Historically, more than 75% of such tumors were squamous cell carcinoma. Since the mid-1970s, the incidence of epidermoid squamous cell carcinomas has stabilized, while there has been a greater than 100% rise in the incidence of adenocarcinoma. Most of these adenocarcinomas involve the gastroesophageal junction.

**ESOPHAGEAL STAGING SYSTEMS**

Accurate staging of esophageal cancer is important to assess new treatments and advise individual patients of prognosis. The TNM classification, based on independent measures of primary tumor size, regional lymph node involvement, and distant metastases, forms the basis for stratifying patients with esophageal cancer into prognostic stage groups.

International consensus for esophageal cancer staging was reached in 1987 and in 1988, with worldwide approval from all national TNM committees for the fourth edition of the Union Internationale Contre le Cancer (UICC) classification and the third edition of the American Joint Committee on Cancer (AJCC) Manual for Staging of Cancer. The new system is based on depth of wall penetration and lymph node involvement, these two variables being most predictive of long-term survival. Table 1, adapted from the 1988 manual for cancer staging, summarizes the current TNM classification.

**STAGING TECHNIQUES**

To assess depth of wall penetration and lymph node status with a high degree of accuracy prior to resection generally requires some combination of computed tomography (CT) scan, magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), and/or surgical staging. Surgical-pathologic staging of patients with esophageal cancer, we believe, should form the basis of protocol development, design, and evaluation. It is hoped that refinement of

---

Table 1—Esophageal TNM Staging Classifications*

<table>
<thead>
<tr>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor (T) class</td>
</tr>
<tr>
<td>T1 Invades lamina propria or submucosa</td>
</tr>
<tr>
<td>T2 Invades muscularis propria</td>
</tr>
<tr>
<td>T3 Invades adventitia</td>
</tr>
<tr>
<td>T4 Invades adjacent structures</td>
</tr>
<tr>
<td>Nodal (N) class</td>
</tr>
<tr>
<td>N0 No regional node metastases</td>
</tr>
<tr>
<td>N1 Regional node metastases</td>
</tr>
<tr>
<td>Distant metastases (M) class</td>
</tr>
<tr>
<td>M0 No distant metastases</td>
</tr>
<tr>
<td>M1 Distant metastases</td>
</tr>
<tr>
<td>Stage grouping</td>
</tr>
<tr>
<td>I T1N0M0</td>
</tr>
<tr>
<td>II T2-T3, N0M0</td>
</tr>
<tr>
<td>III T1-T2, N1M0</td>
</tr>
<tr>
<td>IV T3N1M0 or T4</td>
</tr>
</tbody>
</table>

*Adapted from American Joint Committee on Cancer.4

---

*From the Division of Thoracic Surgery, Brigham and Women’s Hospital, Harvard Medical School, Boston.

Reprint requests: Dr. Sugarbaker, Brigham & Women’s Hospital, 75 Francis St, Boston, MA 02115

Multimodality Therapy of Chest Malignancies: Update '94
such protocols will ultimately affect the dismal survival rates reported in this disease over the past 30 years.

**Computed Tomography and Magnetic Resonance Imaging**

Computed tomographic scan of the chest and upper abdomen with oral and intravenous contrast is used to evaluate the primary esophageal tumor, supraclavicular nodes, mediastinal nodes, abdominal nodes, lungs, liver, and adrenal glands. Compared with resection specimens, the accuracy of CT images is 80 to 85% in detecting extent of disease.\(^5\)-\(^9\)

Evaluation of the primary tumor by CT scan is not without limitations. Individual layers of the esophageal wall cannot be discerned with certainty. A wall thickness greater than 5 mm is equated with at least a T2 tumor, and T4 lesions (involving adjacent organs) are difficult to diagnose with certainty.\(^5\)

Computed tomographic accuracy of regional lymph node status is less than 69%.\(^6\),\(^10\),\(^11\) Radiologic criteria for an abnormal lymph node is a transverse axis of 10 mm or greater. Nodes less than 10 mm that are infiltrated by tumor will be falsely interpreted as normal, and swollen inflammatory nodes may be falsely interpreted as abnormal. Furthermore, enlarged nodes adjacent to a tumor may be overlooked on CT scan if such structures are radiographically inseparable. The CT scan is a very accurate tool for the detection of distant metastases in the chest or abdomen. Abdominal metastases in the liver can be detected with 90% accuracy.\(^8\)

**Magnetic Resonance Imaging**

The diagnostic accuracy of CT and MRI has been virtually identical.\(^12\) Assessment of mediastinal node status is accurate only in 56% of patients with either imaging technique. Accuracy of assessing abdominal nodes is even less, with only 45% accuracy for either technique.

**Endoesophageal Ultrasound**

Endoesophageal ultrasound is a relatively new instrument used for staging. It consists of a probe at the end of an endoscope and an inflatable balloon to distend the esophagus and provide an ultrasonic interface between the probe and the mucosa.\(^5\)

Endoesophageal ultrasound is a good tool for the detection of depth of tumor invasion. It has a broad range of accuracy, ranging from 71% overall to 98% of the subset of patients without obstruction.\(^5\),\(^12\)-\(^14\) Endoesophageal ultrasound understages the primary tumor in about 5% of cases and overstates the primary tumor in approximately 6 to 11%,\(^12\),\(^14\) especially in tumors that do not extend through the muscularis propria.

Unlike CT, EUS can assess the shape, margin, and internal structure, as well as the size, of mediastinal and celiac nodes. However, it has been difficult to distinguish inflammatory lymph nodes from metastatic disease by EUS. Quantification of EUS accuracy for node status has generally ranged between 70 and 88%.\(^5\),\(^12\)-\(^14\) Although highly sensitive (85 to 95%), the accuracy of predicting the status of lymph nodes is adversely affected by a low specificity (50 to 60%).\(^12\),\(^14\)

At present, EUS fails to fully visualize the abdominal extent of disease secondary to obstruction of the esophagus in a significant number of patients (21 to 36%). The ultrasonic endoscope is large and cannot be passed through stenotic lesions.\(^13\)-\(^15\)

**Minimally Invasive Surgical Staging**

Approximately 66% of patients presenting with esophageal cancer will have abnormal regional lymph nodes.\(^16\) With the encouraging results of new induction chemotherapy and radiotherapy (RT) protocols, the preresectional identification of this group has become important.

Recent advances in thoracoscopy have opened new vistas for surgical staging of esophageal cancer. Thoracoscopy allows evaluation of the entire thoracic esophagus and periesophageal nodes in the right side of the chest, and the aortopulmonary window nodes, periesophageal nodes, and mid-to-lower thoracic esophagus in the left side of the chest. Occult pleural and pulmonary metastases can be readily identified at thoracoscopy. The minimally invasive surgical staging procedure allows direct visualization of the adventitia of the esophagus and can accurately judge deep wall invasion and involvement of adjacent organs. The location and nature of contiguous spread to important adjacent mediastinal structures can be directly assessed. Regional lymph nodes can be visualized and directly sampled for histologic analysis.

Thoracoscopy can be combined with staging abdominal laparoscopy or minilaparotomy under the same general anesthetic. In a systematic fashion, the peritoneal surface, liver, gastrohepatic ligament, gastric wall, cardia, and undersurface of the diaphragm are inspected. Biopsy specimens are taken from the celiac nodes and perigastric nodes, even when they appear completely normal. Patients deemed candidates for multimodality protocols can then have a central venous catheter port and feeding jejunostomy placed at the end of the staging procedures.

The main advantage of the combined thoracoscopic/laparoscopic staging procedure is that it provides greater accuracy in evaluation of regional and celiac lymph nodes. Such information is indispensable in
patient stratification and selection of therapy, especially in the setting of new treatment protocols. Furthermore, for patients who will be receiving RT, the histologic status of thoracic and abdominal lymph nodes is critical for the design of treatment fields. For example, in patients with tumors of the lower esophagus, the supraclavicular lymph nodes may be omitted from the treatment field in the absence of involved nodes. If thoracic nodes are involved, however, treatment fields may be increased to cover the supraclavicular regions since they would represent a high-risk site in this setting. Moreover, RT for celiac nodes is controversial due to the M1 status of these nodes and the potential morbidity of upper abdominal RT. Therefore, some radiation oncologists may choose only to treat perigastric and celiac lymph nodes in the setting of documented involvement. For all these reasons, we believe histologic confirmation of the mediastinal and upper abdominal lymph nodes is an important complement to CT and EUS staging information.

Surgical Therapy

Several variables need to be considered in planning the surgical approach to the patient with esophageal cancer: the intent of the surgeon to either cure or palliate, the anatomic location of the tumor, the method of reconstruction, and the overall clinical setting, ie, the patient’s overall health and ability to comply with complicated regimens.

Palliation

The patient with unresectable esophageal cancer can be surgically palliated by a number of approaches: transhiatal esophagectomy, transthoracic esophagectomy for tumors involving the trachea, bronchus, or major vessels, endoscopic laser therapy with or without photodynamic therapy, endoscopic cautery, and dilation with stenting. Several reports have established the role of esophagectomy with reconstruction for palliation of the progressive dysphagia in the patient with incurable disease. This approach is superior to RT in the relief of dysphagia, although RT may provide similar overall survival. Two thirds of patients treated with palliative RT can be expected to develop symptoms or signs of recurrent stricture, and 11% may receive no palliation. A transhiatal esophagectomy with cervical gastroesophageal or coloesophageal anastomosis is a good operation for this group of patients with low postoperative mortality (6% of patients) and lasting palliation (87%). The lack of exposure and inability to perform a complete lymphadenectomy is not a serious drawback in the palliative setting. However, a transhiatal resection is contraindicated if the primary tumor involves the surrounding mediastinal structures, which is common with tumors of the upper third of the esophagus.

Esophageal bypass with a substernal colon or gastric conduit has also been proposed as a palliative procedure, but it is associated with a higher postoperative morbidity and mortality than the transhiatal approach. These procedures require two or three anastomoses with subsequent increased risk of leakage. Since the primary tumor has not been removed, it frequently progresses to complete obstruction of the native esophagus, thus producing a blind pouch for the collection of food and secretions. Patients in this situation are at high risk for aspiration. Stapling of the most proximal portion of the native esophagus does not solve this problem. Instead, secretions gather within the esophagus, and the proximal, stapled end can blow out, leading to mediastinitis and death.

Cure

Surgical cure of esophageal cancer is possible in selected patients. The goal is a complete resection, including the full extent of the primary tumor and all regional lymph nodes with occult disease. A radical lymphadenectomy is an important part of the operation for three reasons: (1) to cure those few patients in whom the disease is still limited to just the regional lymph nodes; (2) to form the basis for decisions regarding further therapy and follow-up; and (3) to critically assess outcomes of neoadjuvant treatment protocols.

If the surgeon is operating with curative intent, then aggressive preresectional staging must be undertaken. Decisions to utilize neoadjuvant therapies should be based on such staging. At the time of resection, a radical lymphadenectomy should be performed and the regional nodes carefully analyzed by the pathologist. Additional decisions regarding the use of adjuvant therapy should be based on the pathologic analysis. For this reason, we strongly advocate a transthoracic or “three-hole” esophagectomy with cervical gastroesophageal or coloesophageal anastomosis. This offers the greatest sampling of mediastinal nodes.

Anatomic Location

The esophagus is anatomically divided into four areas. The cervical esophagus extends from the cricopharyngeal muscle to the thoracic inlet. The upper third of the mediastinal esophagus extends to the aortic arch. The middle third continues to the inferior pulmonary vein, and the lower third connects with the gastric cardia.

Anatomic location influences the choice of surgical procedure. Tumors of the cervical esophagus are best treated with RT or a surgical approach through the right side of the neck. Upper-third lesions of the
thoracic esophagus are best approached through a right anterolateral thoracotomy. Middle-third lesions are approached through a three-hole method, with a midline laparotomy, right posterolateral thoracotomy, and left cervical incision. Primary lesions of the distal third of the thoracic esophagus can be approached through a left sixth-interspace thoracotomy with an intrathoracic gastroesophageal anastomosis.29

**Method of Reconstruction**

In general, the first choice of a conduit for reconstruction is the stomach. The stomach is converted to a tube and based on the right gastroepiploic artery. The tubular stomach has considerable length and will easily reach into the neck. It is passed through the mediastinum in the orthotopic position. There is a single anastomosis in this method of reconstruction, usually just distal to the cricopharyngeal muscle. Gastric emptying is facilitated by an accompanying pyloromyotomy or pyloroplasty. The stomach conduit provides excellent function and is associated with low morbidity.

The colon is an alternative to the stomach for reconstruction. It is based on the middle colic artery and is generally placed in a heterotopic position beneath the sternum. There are generally three anastomoses in this operation: colocolonic to reestablish the continuity of the lower gastrointestinal tract, coloesophageal proximally, and cologastric or coloenteric distally.

Surgical therapy alone has produced disappointing results in the treatment of esophageal cancer. Both local and distant recurrence are common when single-modality therapy is used. There has been great interest in the possible role of induction chemotherapy and RT which may both increase the number of curative resections and prolong survival. Careful patient selection for these protocols is needed to both tailor new treatments and to properly assess their impact.

**Neoadjuvant Therapy**

Preoperative RT has been used in an attempt to improve overall results in patients with esophageal cancer.30-35 Most investigators have used 40 Gy given over 4 weeks, with surgery performed 4 weeks later. Clifton et al35 reported an increase in resectability rate from 58 to 79% with preoperative RT. This observation was confirmed by Akakura et al34 but challenged by Launois et al.32 Preoperative RT does not seem to adversely affect operative mortality or morbidity.30-32 Most series suggest that preoperative RT helps improve local control but makes little difference in overall survival owing to the increased incidence of clinically apparent distant metastases in the radiated groups during follow-up.

Esophageal cancer has been resistant to single-agent chemotherapy with a best response rate of 15%.35 However, the discovery of an efficacious chemotherapy protocol would be helpful in this disease, which is characterized by a high frequency of occult systemic spread at the time of diagnosis.

As previously noted, aggressive surgical resection alone produces a 5-year survival rate of 15 to 35%. Curative RT palliates dysphagia for an average of only 6 months and produces a 17% 5-year survival rate. Both local and distant recurrences are common with both these single-modality therapies.

Preoperative chemotherapy combinations have been more effective than single-agent applications. Most investigators have combined cisplatin with one or more agents with response rates of 40 to 50%.35,36 Roth et al36 reported on a multi-institutional randomized trial of surgery alone (20 patients) vs a preoperative cycle of cisplatin, vindesine, and bleomycin followed by surgery (19 patients) for epidermoid cancer of the middle and lower esophagus. Patients in the chemotherapy arm were given additional cisplatin and bleomycin for 6 months postoperatively. The preoperative response rate to chemotherapy was 47% (one complete response [CR] and seven partial responses) with manageable toxic reactions. There was no difference in resectability rates or morbidity and mortality, but the patients responding to chemotherapy had a median survival advantage (>20 months compared with 8.6 months for those treated with surgery alone). The authors noted a significantly greater response in patients with less than 10% weight loss, which they interpreted as patients with less-advanced disease.

The rationale behind trimodality therapy with preoperative chemotherapy and RT is that there will be simultaneous treatment for both local and occult distant disease. Furthermore, chemotherapy is better tolerated prior to surgery than after surgery. Cisplatin and 5-fluorouracil (5-FU) have been identified as radiation sensitizers.

In 1987, Poplin et al37 reported the Southwest Oncology Group’s efforts to validate the Wayne State single-institution experience with preoperative combined chemoradiation therapy. There were 106 evaluable patients treated with concomitant 5-FU, cisplatin, and RT (30 Gy). Surprisingly, the investigators reported a decreased resectability rate (49%) compared with historic controls. Additionally, there was no improvement in overall survival, although patients with a pathologic CR lived longer with a median survival of 32 months. The surgical mortality rate in this series was 11%.

Better results were obtained by Gignoux and Bosset38 in 1989. After treating 119 patients with two
cycles of cisplatin and 37-Gy RT, they reported a 70% overall response rate and a 24% CR rate with moderate toxic reactions.

Kelsen et al.\(^{39}\) reported on a phase 3 trial comparing two cycles of preoperative cisplatin, vindesine, and bleomycin with preoperative RT (55 Gy). Although survival was not analyzable owing to a crossover design, the authors found no significant differences in response, operability, resection, or operative mortality rates. They concluded that chemotherapy trials should continue, since chemotherapy was as effective as RT in treating local disease while potentially treating systemic disease. They added, however, that more effective chemotherapy was needed before an impact on survival could be expected.

The best results to date (and to our knowledge) have been reported by Forastiere et al.\(^{40}\) Forty-three patients with cancer of the esophagus or cardia were treated with concomitant cisplatin, vinblastine, 5-FU, and 45-Gy RT. The authors reported a 95% operability rate, 84% resectability rate, and a pathologic CR rate of 24%. Median survival was 29 months, and the overall 5-year survival rate was 34%. The subgroup of patients with a pathologic CR did remarkably well, with a median survival of 70 months and a 5-year survival rate of 60%. For patients with residual tumor in the pathologic specimen, median survival was 26 months and the 5-year survival rate was 32%. This latter group still had improved survival compared with other cohorts treated with preoperative chemoradiation alone, suggesting that surgical resection may be beneficial to this group.

Trimodality therapy for esophageal cancer is difficult to administer successfully. It consists of a series of physiologic insults to a patient who is already nutritionally depleted and suffering from a malignancy. Multiagent chemotherapy is combined with intermediate-dose RT and followed by extensive surgery in two major body cavities. In the chemotherapy arm of the study by Kelsen et al.\(^{39}\) there was a 12% mortality rate. Two patients died as a consequence of an anastomotic leak, and five died of adult respiratory distress syndrome. There was believed to be a significant incidence of pulmonary toxic reactions related to the use of bleomycin. In the Forastiere et al.\(^{40}\) series, 98% of patients suffered severe leukopenia, 63% had febrile neutropenia, 23% developed thrombocytopenia, and 33% acquired anemia severe enough to justify transfusion. In addition, there were two deaths secondary to sepsis.

The difficulty of trimodality therapy notwithstanding, the encouraging results reported by others substantiated our personal experience with neoadjuvant cisplatin-based chemotherapy. Between November 1988 and September 1993, 45 selected patients were treated at the Brigham and Women's Hospital with a multimodality approach. The mean age of this cohort was 63 years. Fifteen patients had squamous cell histologic features, and 30 patients had adenocarcinoma. Induction therapy consisted of two cycles of cisplatin and 5-FU given with concomitant RT (35 Gy). Forty-two patients progressed to three-hole esophagectomy, while 3 patients had a transhiatal esophagectomy. The 30-day operative mortality rate was 4%, and there was a 7% anastomotic leak rate. Twenty-seven percent of the patients had a pathologic CR. Median survival was 33 months. The 2-year survival rate for those patients with a pathologic CR was 74%. Patients with residual tumor in the specimen had a 2-year survival rate of 33%. There was no difference in overall 2-year survival rates based on cell type: 54% for adenocarcinoma and 53% for squamous cell carcinoma.

In this ongoing series, concomitant cisplatin/5-FU and RT have not adversely affected surgical morbidity and mortality. There has been an excellent response to induction therapy, with a trend toward improved survival in those patients responding to therapy.

**CONCLUSIONS**

Esophageal cancer continues to be a major health problem with an associated poor prognosis. New technology is being applied to the preresectional staging of this cancer. Accurate pathologic staging allows the identification of subgroups of patients who may benefit most from new combined-modality treatments.

Surgery is optimal for localized esophageal cancer. Neoadjuvant chemoradiation has increased survival in specific subgroups. Phase 2 trials have demonstrated the safety and efficacy of chemoradiation.

The field of neoadjuvant therapy for esophageal cancer continues to progress. Randomized multiinstitutional trials are needed to verify the encouraging results of recent phase 2 trials. Additionally, optimal combinations of chemotherapeutic agents need to be found. More importantly, a method is needed to clearly identify the subgroup of patients expected to benefit from neoadjuvant therapy.

**REFERENCES**

23 Orringer MB. Substernal gastric bypass of the excluded esophagus: results of an ill-advised operation. Surgery 1984; 96:467–70
29 Lu YK, Li YM, GY YZ. Cancer of esophagus and esophagogastric junction: analysis of results of 1,025 resections after 5 to 20 years. Ann Thorac Surg 1987; 43:176–81