Esophageal Carcinoma: Current Controversies

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The incidence of esophageal adenocarcinoma and adenocarcinoma of the gastric cardia has increased so substantially in the last two decades that adenocarcinoma now accounts for approximately one half of esophageal malignancies seen in the United States and Europe. The reasons for this histological change may be related to a parallel increase in the incidence of gastroesophageal reflux disease in the Western world and the subsequent development of Barrett’s metaplasia. Controversies surrounding carcinoma of the esophagus that are currently the focus of study are the relationship of Barrett’s esophagus to the development of adenocarcinoma; whether adenocarcinoma of the esophagus and cardia is the same disease; the correct way to stage the disease; the treatment of disease confined to the mucosa; the extent of surgical resection to cure disease beyond the mucosa; the role of adjuvant chemotherapy in the treatment of the disease; and the methods of palliating patients with incurable disease. Semin. Surg. Oncol. 13:217–233, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: Barrett esophagus; esophageal neoplasms; adenocarcinoma; squamous cell carcinoma; cardia; stomach neoplasms; neoplasm staging; epidemiology/etiology/surgery/pathology; differential diagnosis; adjuvant chemotherapy; adjuvant radiotherapy; brachytherapy; laser surgery; palliative care

INTRODUCTION

Carcinoma of the esophagus, by some estimates, is the most common malignancy affecting humans. It is frequent in China, Japan, the former USSR, Iran, and in parts of South America, South Africa, and France. It is relatively uncommon in the United States and Europe. Approximately two decades ago, the most common histological type of esophageal malignancy in the United States was squamous cell carcinoma, and it was associated with abuse of alcohol and tobacco. Over the last two decades, however, the incidence of distal esophageal adenocarcinoma and adenocarcinoma of the gastric cardia has increased substantially in the Western world [1–6]. This increase exceeds that seen for other tumors and is likely to make esophageal adenocarcinoma a common clinical problem in the future. Consequently, in the United States and Western Europe, adenocarcinoma now accounts for approximately 50% of esophageal malignancies. The reason for this change in histology in the Western world remains unclear, but probably is related to a parallel rise in the incidence of gastroesophageal reflux disease in the same part of the world and the subsequent development of Barrett’s metaplasia.

The controversies surrounding carcinoma of the esophagus that are currently the focus of study are the relationship of Barrett’s esophagus to the development of adenocarcinoma; whether adenocarcinoma of the esophagus and cardia is the same disease; the correct way to stage the disease; the treatment of disease confined to the mucosa; the extent of surgical resection to cure disease beyond the mucosa; the role of adjuvant chemotherapy in the treatment of the disease; and the methods of palliating patients with incurable disease.

RELATIONSHIP OF BARRETT’S ESOPHAGUS TO ESOPHAGEAL ADENOCARCINOMA

Barrett’s esophagus is an acquired condition [7,8] in which the squamous epithelium of the distal esophagus is injured by the reflux of gastric juice and is replaced by columnar epithelium [9]. It is a peculiar type of healing which can occur at any stage in reflux disease [10]. About 18% of patients with chronic reflux disease develop Barrett’s esophagus [11,12].

The columnar epithelium that replaces injured squamous epithelium may be classified histologically as fundic, junctional (cardiac), or specialized [13]. Fundic-type epithelium is normally found in the fundus and body of the stomach. Junctional-type epithelium is reported to be

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present for a variable distance between the squamocolumnar junction and the fundic epithelium. Fundic and junctional-type columnar epithelia are differentiated by the cellular constitution of their associated glands. The classical definition of a junctional gland is one composed entirely of mucus cells. In contrast, mucus cells in the fundic gland are confined to the neck of the gland with the distal part composed of parietal and oxytic cells. Specialized intestinal epithelium is thought not to be normally found in the esophagus or stomach and is characterized by the presence of goblet cells. Goblet cells can usually be recognized on sections stained with hematoxylin and eosin, but if there is doubt, specific staining with periodic acid–Schiff/alcan blue, pH 2.5, or with mucicarmine will confirm the presence of their characteristic mucins. When specialized intestinal epithelium is present in the esophagus, the diagnosis of Barrett’s esophagus can be made with confidence [14].

The significance of Barrett’s esophagus is that it is the initiating step in a sequence of metaplasia-to-dysplasia-carcinoma. This links the common condition of gastroesophageal reflux to one of the most lethal malignancies. The risk of malignant degeneration is most likely to occur when specialized intestinal metaplasia is present, and is lower or absent when only fundic or junctional-type epithelium is found [15–19].

The main evidence linking Barrett’s esophagus to esophageal adenocarcinoma may be summarized as: 1) the carcinoma is an adenocarcinoma indicating an origin from glandular epithelium such as specialized intestinal epithelium; 2) specialized intestinal metaplasia and dysplasia are frequently found adjacent to an adenocarcinoma; 3) several investigators have followed patients with Barrett’s metaplasia who have progressed subsequently to dysplasia and invasive cancer; and 4) patients with Barrett’s metaplasia have an increased risk of developing adenocarcinoma.

Early retrospective studies showed a high prevalence of adenocarcinoma in patients presenting for the first time with Barrett’s esophagus. This led to an overestimation of the risk of adenocarcinoma in Barrett’s esophagus before it was realized that there are many patients in the general population with Barrett’s esophagus who do not seek medical attention [20]. Consequently, a better estimate of the risk of benign Barrett’s esophagus progressing to adenocarcinoma may be obtained from surveillance data (Table I). The actual risk of adenocarcinoma in patients with benign Barrett’s esophagus is about 500 adenocarcinomas per 100,000 patients per year [27]. In an effort to diagnose cancer progression at an early stage, endoscopic surveillance of patients with Barrett’s esophagus has been recommended [28–29], based on the following reasons: 1) there is an increased risk of cancer in patients with Barrett’s esophagus; 2) the esophagus is easily and safely accessible for inspection and biopsy; 3) prognosis in esophageal adenocarcinoma following surgical resection is linked to the stage of disease; 4) detection of high-grade dysplasia or early esophageal cancer on surveillance permits early referral to surgery; and 5) patients operated upon for high-grade dysplasia or cancer detected during surveillance have a better prognosis than patients who present for the first time with a cancer [29].

**TABLE I. Risk of Benign Barrett’s Esophagus Progressing to Adenocarcinoma**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. of patients followed</th>
<th>Mean duration of follow-up (years)</th>
<th>No. of cases of adenocarcinoma</th>
<th>Incidence (patient-years)</th>
<th>Increased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spechler et al. [21]</td>
<td>105</td>
<td>3.3</td>
<td>2</td>
<td>1:175</td>
<td>40</td>
</tr>
<tr>
<td>Sprung et al. [22]</td>
<td>41</td>
<td>—</td>
<td>2</td>
<td>1:81</td>
<td>—</td>
</tr>
<tr>
<td>Cameron et al. [23]</td>
<td>104</td>
<td>8.5</td>
<td>2</td>
<td>1:441</td>
<td>30</td>
</tr>
<tr>
<td>Robertson et al. [24]</td>
<td>56</td>
<td>2.8</td>
<td>3</td>
<td>1:56</td>
<td>62</td>
</tr>
<tr>
<td>Van der Veen et al. [25]</td>
<td>155</td>
<td>4.4</td>
<td>4</td>
<td>1:170</td>
<td>30</td>
</tr>
<tr>
<td>Hameeteman et al. [16]</td>
<td>50</td>
<td>5.2</td>
<td>5</td>
<td>1:52</td>
<td>125</td>
</tr>
<tr>
<td>Iftikhar et al. [26]</td>
<td>102</td>
<td>4.4</td>
<td>4</td>
<td>1:115</td>
<td>30</td>
</tr>
</tbody>
</table>

**IS ADENOCARCINOMA OF THE ESOPHAGUS AND CARDIA THE SAME DISEASE?**

There are similarities in adenocarcinoma of the esophagus and cardia. The incidence of both is increasing in a parallel fashion [5]. Both are more common in white males. The age of diagnosis is similar. Both tumors present at a late stage and have a similarly poor prognosis. Pathological features are similar; both are associated with specialized intestinal metaplasia and have similar gross morphological features. In particular, both tumors stain positive for acid mucins, indicating an origin from specialized intestinal metaplasia [2].

The prevalence of specialized intestinal metaplasia in adenocarcinoma of the esophagus is 79%, of the cardia 42%, and of the upper stomach 5% [30]. The length of Barrett’s epithelium on endoscopy in patients with adenocarcinoma of the cardia is shorter than in patients with esophageal adenocarcinoma (2.7 cm vs. 7.4 cm, \( P < 0.01 \)) [18,19,30]. The lesser chance of finding specialized metaplasia in tumors of the cardia may be that the shorter lengths of Barrett’s allow the tumors to “overgrow” the specialized epithelium.

Eighty-five percent of patients with adenocarcinoma of the cardia or esophagus are white. In contrast, only 30%
of patients with adenocarcinoma of the gastric body or antrum are white [5,30,31]. The average male to female ratio for adenocarcinoma of the cardia is 5.5:1. The ratio is slightly higher for adenocarcinoma of the esophagus, 9.2:1 [30]. This marked male preponderance for tumors of the cardia or esophagus is in contrast to tumors of the distal stomach which have an almost equal sex distribution [30].

The marked similarity between adenocarcinoma of the cardia and esophagus has led to the hypothesis that they are the same disease. The origin of the specialized intestinal metaplasia in the cardia is unknown, but is likely to be the same as its pathogenesis in the esophagus. Evidence suggests that duodenogastric reflux plays a role in the genesis of specialized metaplasia in the stomach and esophagus and probably in the cardia. The data on the esophagus come from in vitro work on isolated esophageal preparations which show that duodenal contents injure the esophageal mucosa [32]; from a nitrosamine-treated rat model where esophageal exposure to duodenal juice increases the frequency of tumors with a change in histology from squamous cell carcinoma to adenocarcinoma [33–37]; and from clinical reports that show an increased esophageal exposure to duodenal juice in patients with Barrett’s esophagus [38]. The latter is based on the spectrophotometric detection of bilirubin, and on ambulatory esophageal aspiration studies [39–41]. It is hypothesized that the specialized intestinal epithelium that occurs at the cardia or in the esophagus is from repeated exposure to and is injured by a mixture of gastric and duodenal contents. The reason the process is limited to the cardia in some patients—while in others it involves the esophagus—is due to the ability of the lower esophageal sphincter to limit the injurious agent to the cardia in the former and mechanical failure of the sphincter in the latter. Recently, molecular biological studies have shown a similar prevalence of p53 gene mutations in patients with adenocarcinoma of the cardia and esophagus [42]. Further, the spectrum of mutations is similar but differs from adenocarcinoma located in the stomach proper. Consequently, at the molecular level, adenocarcinoma of the esophagus and cardia appears to be the same disease and results from the malignant degeneration of the specialized epithelium.

**STAGING OF THE ESOPHAGEAL CARCINOMA**

At the initial encounter with a patient diagnosed with carcinoma of the esophagus, a decision must be made as to whether the patient is a candidate for curative surgical therapy, palliative surgical therapy, or nonsurgical palliation. This decision is difficult to make because the pretreatment stage of this disease is imprecise due to the inability to measure the depth of tumor penetration of the esophageal wall and the inaccessibility of the organ’s widespread lymphatic drainage. Despite the modern techniques of computed tomography and magnetic resonance imaging, pretreatment staging still remains imprecise.

Experience with esophageal resections in patients with early disease has identified characteristics of esophageal cancer that are associated with improved survival [43]. This analysis showed that only metastasis to lymph nodes and tumor penetration of the esophageal wall had a significant and independent influence on prognosis. That is, the beneficial effects of the absence of one factor persisted even when the other was present. Factors known to be important in the survival of patients with advanced disease, such as cell type, degree of cellular differentiation, or location of tumor in the esophagus, had no affect on survival of patients who had resections for early disease. The analysis also showed that patients having four or less lymph node metastases had a similar outcome as those with no lymph node metastases. From this experience the wall node metastases (WNM) system for staging was developed by Skinner et al. [44].

The WNM system differed somewhat from the previous efforts to develop a satisfactory staging criteria for carcinoma of the esophagus. Most surgeons agreed that the TMN system described in the 1983 *Manual for Staging of Cancer* left much to be desired [45]. In the 1988 third edition of this manual, the American Joint Committee on Cancer (AJCC) made an effort to provide a finer discrimination between stages than was true of the previous edition [46]. Table II shows the definitions for the primary tumor, regional lymph nodes, and distant metastasis as listed in the 1988 manual. Recently, in a study comparing different staging criteria, Ellis et al. [47] showed that the new staging criteria of the AJCC provided no better discrimination of the stages according to survival than was true of the earlier version. The 5-year survival of stage IIA patients was similar to that of stage IIB patients and the survival of stage IIB patients was similar to that of stage III patients. Similarly, Ellis et al. [47] showed that there was no difference between the 5-year survival of patients with T1 and T2 disease; nor was there a difference between those with a T3 and T4 disease. He did confirm the observation that the depth of wall penetration and extent of lymph node involvement were reliable independent predictors of survival [2,47].

Ellis et al. [47] proposed adoption of Skinner’s WNM staging system with some modifications (Table II). In their proposal, tumors limited to above the muscularis mucosa would be equivalent to Skinner’s W0 designation, T1 and T2 tumors would equate with the W1 classification, and T3 and T4 tumors to the W2 classification. These classifications are illustrated in Figure 1. They further reported a clear distinction between the 5-year survival of patients with negative nodes, and those with less than five nodes involved. Table II shows the definitions for the primary tu-
DeMeester

TABLE II. Esophageal Cancer: Classification and Staging

<table>
<thead>
<tr>
<th>1988 TNM system</th>
<th>Modified Skinner WNM system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor (T)</td>
<td>Primary tumor (T)</td>
</tr>
<tr>
<td>TX</td>
<td>W0 Tumor limited to above the muscularis mucosa (intramucosal)</td>
</tr>
<tr>
<td>TO</td>
<td>W1 Tumor limited to the esophageal muscularis propria</td>
</tr>
<tr>
<td>Tis</td>
<td>W2 Tumor extending through the esophageal wall (transmural)</td>
</tr>
<tr>
<td>T1</td>
<td>Regional lymph nodes (N)</td>
</tr>
<tr>
<td>T2</td>
<td>N0 No lymph node involvement</td>
</tr>
<tr>
<td>T3</td>
<td>N1 Less than 5 lymph nodes involved</td>
</tr>
<tr>
<td>T4</td>
<td>N2 More than 5 lymph nodes involved</td>
</tr>
<tr>
<td></td>
<td>Distant metastasis (M)</td>
</tr>
<tr>
<td>MX</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>MD</td>
<td>M1 Distant metastasis</td>
</tr>
</tbody>
</table>

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<td>Distant metastasis (M)</td>
</tr>
<tr>
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<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>MD</td>
<td>M1 Distant metastasis</td>
</tr>
</tbody>
</table>


In a second publication, using an expanded base of 408 resected patients, Ellis et al. [48] compared the 1988 AJCC staging criteria with the Skinner modified WNM system and showed evidence that a modified WNM staging system was more useful from a prognostic standpoint (Tables III, IV). Not only is the number of patients more evenly divided among the four stages in the modified Skinner system, but the comparison of the 5-year survival rates among stages is highly significant, with almost a 50% reduction in survival rates for each increasing stage. The major difference in the staging criteria of the proposed modification to the Skinner WNM system is the recognition that the number of nodes involved has a profound effect on prognosis. It is important to realize that Dr. Ellis has been a proponent of a limited resection and lymph node dissection. Thus, the data used to validate the modified staging system represent what the outcome would be for simple tumor removal. Consequently, the data serve as an excellent basis for comparison with the results of the more extensive en bloc resection or a preoperative chemotherapy program.

With improved staging, it is possible—with 80% accuracy—to identify patients who are potentially curable prior to surgical therapy by using endoscopic ultrasound to determine the depth of the wall penetration by the tumor and the presence of five or more lymph node metastasis [49]. A curative resection should be encouraged if endoscopic ultrasound indicates that the tumor does not penetrate through the esophageal wall and/or less than five enlarged lymph nodes are imaged. Recently, thorascopic and laparoscopic staging of esophageal cancer has been instituted. Preliminary results indicate that with its use, correct staging of esophageal carcinomas approaches 90% [50]. If these results persist, and the cost is not prohibitive, thoracoscopic and laparoscopic staging may become a valuable staging tool.
EXTENT OF RESECTION TO CURE DISEASE
CONFINED TO THE MUCOSA

The development of surveillance programs for the detection of early squamous cell carcinoma in endemic areas and for early adenocarcinoma in patients with Barrett’s esophagus has given rise to controversy over how to manage tumors confined to the mucosa. Some authors have endoscopically resected squamous carcinomas after using endoscopic ultrasound to determine that the depth of the tumor was limited to the mucosa [51]. Surprisingly, large areas of squamous mucosa can be resected without perforation or bleeding, leaving the smooth surface of the muscularis mucosa intact. Re-epithelization of the large artificially induced ulcer is usually complete in 3 weeks. To avoid missing a squamous cancer that has invaded deeper than expected, it is important to carefully examine the deep margins of the resected specimen and perform periodic endoscopic follow-up examinations with vital staining techniques. This technique is not applicable to multiple and widespread or circumferential squamous lesions for fear of developing a stricture on healing. In this situation, those acquainted with endoscopic resection would advocate an esophagectomy.

Although most experience with endoscopic mucosal resections has been with high-grade squamous cell dysplasia, a similar approach, i.e., endoscopic ablation, is being advocated to remove metaplastic areas of Barrett’s mucosa [52]. In this situation, not only must the abnormal mucosa be removed but reflux must be prevented in order to allow healing of the esophagus with squamous epithelium. Investigators have also applied mucosal ablation

TABLE III. Staging of Cancer of the Esophagus and Cardia: American Joint Committee on Cancer (AJCC) 1988*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Classification</th>
<th>No. of patients</th>
<th>5-year survival (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis N0 M0</td>
<td>16</td>
<td>100</td>
<td>NS</td>
</tr>
<tr>
<td>I</td>
<td>T1 N0 M0</td>
<td>22</td>
<td>78.9</td>
<td>0.0021</td>
</tr>
<tr>
<td>IIA</td>
<td>T2 N0 M0</td>
<td>80</td>
<td>37.9</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>T1 N1 M0</td>
<td>39</td>
<td>27.3</td>
<td>NS</td>
</tr>
<tr>
<td>III</td>
<td>T1 N1 M0</td>
<td>218</td>
<td>13.7</td>
<td>NS</td>
</tr>
<tr>
<td>IV</td>
<td>Any T Any N M1</td>
<td>33</td>
<td>0</td>
<td>0.0001</td>
</tr>
</tbody>
</table>


TABLE IV. Staging of Cancer of the Esophagus and Cardia: Modified Wall Node Metastases (WNM) Criteria*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Classification</th>
<th>No. of patients</th>
<th>Five-year survival (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>W0 N0 M0</td>
<td>38</td>
<td>88.2</td>
<td>0.0002</td>
</tr>
<tr>
<td>I</td>
<td>W0 N1 M0</td>
<td>59</td>
<td>50.3</td>
<td>0.0005</td>
</tr>
<tr>
<td>II</td>
<td>W1 N0 M0</td>
<td>95</td>
<td>22.5</td>
<td>0.02</td>
</tr>
<tr>
<td>III</td>
<td>W2 N0 M0</td>
<td>183</td>
<td>10.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>IV</td>
<td>Any W Any N M1</td>
<td>33</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

technology to areas of high-grade dysplasia and intramucosal carcinoma in Barrett’s mucosa [53–55]. Whether this methodology is appropriate for high-grade dysplasia or intramucosal cancer needs further study and discussion.

Several studies have shown that high-grade dysplasia and intramucosal tumors (invasive cancer limited by the muscular mucosa) are quite different in their biological behavior from submucosal tumors [56]. Vessel invasion and lymph node metastasis do not occur in severe dysplasia; they are uncommon in the intramucosal tumors but are the rule in submucosal tumors. As a consequence, the 5-year survival for severe dysplasia and intramucosal tumors differs significantly from that of submucosal tumors [29,57]. These findings indicate that intramucosal cancers (invasive cancer limited by the muscular mucosa) represent early malignant lesions of the esophagus. Consequently, it has been suggested that their surgical treatment may be amenable to endoscopic resection or ablation. We question this approach since somewhere between 0 and 30% of the patients with intramucosal carcinoma have one to two lymph node metastases. Such an approach would leave these nodes untreated.

A critical issue to be solved is whether an intramucosal tumor can be correctly discriminated from a submucosal tumor before surgery. The accuracy of using endoscopic ultrasound to determine the depth of tumors confined to the esophageal wall is questionable. In our experience, the differentiation of intramucosal from intramural tumors by endoscopic ultrasound was poor; only one of five intramucosal tumors was correctly classified, although all were correctly classified as being limited to the esophageal wall. The resolution of the present-day endoscopic ultrasonographic systems may not be sufficient to predictably differentiate the fine detail of tumor infiltration when it is limited to the esophageal wall [49]. Some have suggested that the endoscopic appearance of a mucosa lesion can be helpful in determining its depth. Obvious elevated or depressed lesions or ones that appear nodular usually have invaded down into the submucosa or deeper. Although these efforts are noble, it must be concluded that at present there is no dependable way of determining whether a tumor extends beyond the muscularis mucosa prior to its removal.

Of further concern is that up to 30% of patients with intramucosal tumors have lymph node metastases, although the number of involved nodes per patient is usually five or less [58]. Akiyama et al. [59,60] have reported that even though the number of involved nodes may be small, they can spread to distant nodal regions including cervical and abdominal nodes. Of concern is that this “jump metastasis” can occur in up to 10% of patients, i.e., nodes adjacent to the tumor can be free of disease while one or two distant nodes are involved. Consequently, early lymphatic spread of esophageal cancer is unique when compared to other cancers of the gastrointestinal tract. In other sites, lymph nodes close to the primary lesion are the first to be involved, with the subsequent involvement of more distant nodes in a stepwise manner.

Even though the number of involved nodes in patients with intramural tumors may be small, and the pattern of nodal metastasis is unpredictable, there appears to be some relationship between the location of the primary tumor in the esophagus and the anatomical site of lymph node metastasis. Upper esophageal cancers commonly involve cervical and mediastinal nodes, lower esophageal cancers, mediastinal and abdominal nodes. Middle esophageal cancers commonly involve cervical, mediastinal, and abdominal nodes. Consequently, if an extensive lymphadenectomy is done for intramucosal tumors, it should include the neck and mediastinum for upper esophageal cancers, and the mediastinum and abdomen for lower esophageal cancers. Cancers of the middle esophagus need the most extensive lymphadenectomy, i.e., of the cervical, mediastinum, and abdominal lymph nodes.

Since it is difficult to determine preoperatively the depth to which a tumor has penetrated the esophageal wall—and we know that tumors which invade through the muscularis mucosa into the submucosa have a 60% or more incidence of lymph node metastasis, and further, that the distance from the epithelium to the muscularis mucosa is only 1–2 mm less than to the submucosa—conservative surgeons familiar with esophageal carcinoma elect to perform an en bloc esophagectomy for the treatment of intramucosal tumors. This also holds true for patients with Barrett’s esophagus and high-grade dysplasia since 50% of these patients will harbor an unknown intramucosal tumor. In both situations, we perform a mediastinal and abdominal lymph node dissection as well, but the proximal stomach is not resected because the possibility of extensive submucosal spread is minimal. Gastrointestinal continuity is reestablished by pulling the stomach up into the neck and performing an esophagogastrectomy.

In summary, it appears that intramucosal cancer, i.e., tumors limited by the muscularis mucosa, may not be completely resected or ablated by endoscopic surgery, particularly if there is unrecognized penetration of the tumor into the submucosa. Further, there is a small but consistent prevalence of lymph node metastasis in these patients. At present, it is undecided whether a transhiatal esophagectomy without lymphadenectomy or an en bloc esophagectomy with systematic lymphadenectomy should be done for these patients. Most surgeons agree that when a tumor penetrates the submucosa, tumor cells can spread intramurally several centimeters from the primary site and metastasize to the regional lymph nodes. In view of the difficulty to differentiate between intramucosal and submucosal tumors, and that these are the most curable tumors, it is our policy that patients in whom an intramucosal tumor is suspected should have a total removal of their thoracic esophagus.
with a systematic lymph node dissection [61–65]. This opinion, however, is far from universally accepted and many surgeons would perform a transhiatal esophagectomy without a systematic lymphadenectomy.

**EXTENT OF RESECTION TO CURE DISEASE BEYOND THE MUCOSA**

Some have advocated that the current treatment strategies for carcinoma of the esophagus that extends beyond the mucosa, i.e., the muscularis mucosa, limit the role of surgery to removing the primary tumor, with the belief that this is sufficient for early tumors and in the hope that adjuvant therapy will increase cure rates of more advanced tumors by destroying systemic and unresected regional disease. This approach emphasizes the concept of biologic determinism, i.e., that the outcome of treatment in esophageal cancer is determined at the time of diagnosis, and that surgical therapy aimed at removing more than the primary tumor is not helpful. This approach regards lymph node metastases, regardless of the number involved, simply as markers of systemic disease, and deems the systematic removal of involved regional lymph nodes not to be beneficial. This concept is based on the belief that the removal of the primary tumor by transhiatal esophagectomy results in the same survival rate as would a more extensive en bloc resection.

The concept of an extended en bloc resection for carcinoma of the esophagus began with a report by Logan in 1963 [66]. He was the first surgeon to apply the traditional concepts of surgical oncology to esophageal cancer. Logan described an en bloc resection for carcinoma arising in the distal one third of the esophagus and the gastric cardia. The 5-year survival rate of 16% was better than any of the other reports up to that time, but the 21% mortality rate associated with the procedure hindered widespread acceptance of the operation. Skinner [64] and Akiyama et al. [62] subsequently modified the procedure, reduced the mortality to 11% and 5.2%, respectively, and increased the 5-year survival rates to 18% and 42%, respectively. Subsequent modifications regarding the selection of patients and the extent of gastric and esophageal resection have led to further reductions in mortality rates, while preserving the improved survival [59,61].

To perform an adequate en bloc resection requires three incisions made in the following order: 1) a right posterolateral thoracotomy for en bloc dissection of the esophagus and mediastinum, closure of the thoracotomy, repositioning of the patient in the recumbent position; 2) an upper abdominal midline incision for an en bloc dissection of the stomach; and 3) a left neck incision for mobilization and division of the cervical esophagus. Some surgeons add an inverted T sternotomy above the articulation of the third rib in order to dissect out the superior mediastinal nodes along the left recurrent laryngeal nerve. The dissected specimen is removed transhiatal from the thorax. For tumors of the mid and upper third of the thoracic esophagus, gastrointestinal continuity is reestablished using a gastric pull-up with a cervical esophagogastric anastomosis. For tumors of the lower third of the esophagus and cardia, we prefer to add a proximal gastric resection along with the resection of the thoracic esophagus in order to obtain adequate distance below the tumor to accommodate submucosal spread of the tumor within the gastric margins of the resection. Gastrointestinal continuity is reestablished utilizing an interposed colon based on the left colic artery and inferior mesenteric vein, and placed isoperistaltically between the cervical esophagus and distal stomach [61].

The concept of a transhiatal esophagectomy was introduced in 1933 when Turner [67] first successfully utilized this approach in a patient with esophageal cancer. This technique was reintroduced by Akiyama [68] in 1981 and was popularized in the United States by Orringer [69] following his report of a large series of patients in 1984. As it is applied today, this procedure involves separation of the esophagus from the adjacent mediastinal structures through an abdominal and left neck incision, largely by blunt dissection. Gastrointestinal continuity is reestablished by bringing the stomach up through the posterior mediastinal tunnel with an anastomosis to the cervical esophagus in the neck.

In the transhiatal procedure there is no specific attempt made to remove lymph node-bearing tissue in the posterior mediastinum. In contrast, the en bloc esophagectomy removes the tumor covered on all surfaces with a layer of normal tissue, and the long length of foregut above and below the lesion is resected to incorporate submucosal spread of the tumor. To be consistent, this means that for patients with a tumor in the lower third of the thoracic esophagus or cardia, the proximal two thirds of the stomach should also be resected. Appropriate cervical, mediastinal, and abdominal lymph node dissections are included using an en bloc technique to remove potentially involved regional lymph nodes. Arguments to support the more extensive esophagectomy, gastrectomy, and lymph node dissection are listed in Table V.

We have advocated a selective approach to patients with cancer of the esophagus in regard to the extent of the resection. Deciding between a curative en bloc esophagectomy or a palliative, transhiatal esophagectomy is based on the location of the tumor, the patient’s age and physiological fitness, and the extent of disease on endoscopic ultrasound and intraoperative staging (Fig. 2) [70]. En bloc esophagectomy is an option for patients who are physically fit, whose tumor is located below the carina and clinically assumed to be limited to the esophageal wall and/or have less than five nodes involved. If patients are physically unfit, a palliative transhiatal esophagectomy is done. In-
traoperative staging is done because inaccuracies with existing clinical staging methodology still exist. Staging is based on the observation that patients with a tumor that penetrates the esophageal wall and metastasizes to five or more regional lymph nodes have advanced disease with poor prognosis, and in whom an extended resection would not be appropriate. The surgical approach required is one that allows intraoperative switching from a curative en bloc to a palliative resection. A curative en bloc dissection is abandoned and a palliative transhiatal esophagogastrectomy is done if intraoperative findings reveal cavitary spread of the tumor, extension of the tumor through the mediastinal pleura, multiple gross lymph node metastases, or microscopic evidence of lymph node involvement at the margins of an en bloc resection, i.e., low paratracheal, porta hepatis, subpancreatic, or periaortic lymph nodes.

To investigate the relationship between the type of resection performed and the survival rate in patients with esophageal cancer, we reviewed our experience with en bloc and transhiatal esophagectomy for carcinoma arising in the esophagus below the level of the carina including the gastric cardia in the patients whose tumor is clinically assumed to be limited to the wall and/or have less than five nodes involved [61]. Overall, survival was significantly better in patients having en bloc resection (41%) than in patients having transhiatal resections (14%, \( P < 0.001 \)). Utilizing the WNM system of postoperative histological staging, patients were grouped in those with limited disease, defined as intramural tumors associated with less than five involved nodes. Survival was significantly better following en bloc resection, compared to transhiatal resection (75% vs. 20%, \( P < 0.01 \)). When all patients with intramural tumors, regardless of lymph node status, were evaluated, survival was significantly better following en bloc resection \( (P < 0.05) \). This was so even though the incidence of less than five lymph nodes involved was the same in both groups. Conversely, when all patients with involvement of less than five lymph nodes, regardless of the depth of tumor penetration, were evaluated, survival was significantly better following en bloc resection \( (P < 0.005) \). This was so even though the incidence of transmural tumor penetration was
the same in both groups. It appears on the basis of these studies that en bloc esophagectomy is most beneficial to patients with tumors limited to the esophageal wall and/or less than five lymph nodes involved.

For tumors located in the mid- or upper-thoracic esophagus (which are mainly squamous cell carcinoma), a three-field lymphadenectomy has been recommended. In this situation, gastrointestinal continuity is reestablished with a gastric pull-up. Recently, Akiyama et al. [59] have published results following three-field lymphadenectomies for patients with squamous cell carcinoma who were classified as having R₀ or R₁ resection. Patients with intraepithelial cancer and tumors limited by the muscularis mucosa were excluded. The 5-year survival was 51% and confirms that patients with disease that extends beyond the muscularis mucosa can be cured by an en bloc resection that includes a three-field lymphadenectomy. Dr. Ellis’ results with similar staged patients, but a limited standard resection, were 22%.

There are four possible explanations why transhiatal esophagectomy, or for that matter, a standard transthoracic esophagectomy, fails to achieve the results obtained with en bloc esophagectomy in patients with tumors in the distal esophagus or cardia and disease that extends beyond the mucosa. First, there is the potential dissemination of tumor cells during the dissection of the thoracic esophagus. Second, in an effort to preserve a lengthy stomach with sufficient blood supply to perform a cervical anastomosis, an inadequate distal tumor margin is created. Third, with the gastric pull-up, there is a transfer of unrecognized perigastric metastatic nodes into the thorax. Fourth, there is a probability that the limited or blunt thoracic dissection leaves residual nodal disease in the mediastinum. (This may be so, particularly in patients who are histologically free of lymphatic metastasis but, on histochemical studies, have evidence of microlymphatic metastasis.) An en bloc esophagectomy effectively eliminates all of these potential causes of recurrence.

In summary, as the understanding of the pathology of esophageal cancer improves and experience with its resection increases, evidence is accumulating to indicate that for patients with an intramural tumor in the distal third of the esophagus or cardia, the best chance for cure is an en bloc esophagectomy and a cervical lymph node dissection with gastrointestinal continuity reestablished with a colon interposition. For patients with a similar tumor in the middle or upper third of the esophagus, the best chance for cure is an en bloc esophagectomy and a cervical lymph node dissection with gastrointestinal continuity reestablished with a gastric pull-up. Table VI is a summary of the extent of resection for tumors extending various depths into the esophageal wall.

### ROLE OF ADJUVANT CHEMOTHERAPY

The proposal to use adjuvant chemotherapy in the treatment of esophageal cancer began when it became evident that most patients develop postoperative systemic metastasis without local recurrence. This observation led to the hypothesis that undetected systemic micrometastases were present at the time of diagnosis, and if effective systemic therapy was added to local regional therapy, survival should improve.

Recently, this hypothesis has been supported by the observation of epithelial tumor cells in the bone marrow in 37% of patients with esophageal cancer who were resected for cure. These patients had a greater prevalence of relapse at 9 months after surgery compared to those patients

### TABLE VI. Recommended Surgical Therapy for Esophageal Carcinoma

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Confined areas of high grade dysplasia (intraepidermal cancer)</td>
<td>Endoscopic mucosal resection (at present only applicable to squamous carcinoma).</td>
</tr>
<tr>
<td>2. Widespread or circumferential area of high-grade dysplasia (intraepidermal cancer)</td>
<td>Esophagectomy without thoractotomy.</td>
</tr>
<tr>
<td>3. Tumor invading through the baseline membrane but not through the muscularis mucosa (intramucosal tumors)</td>
<td>? Esophagectomy without thoractotomy or en bloc resection with node dissection; reconstruction with a gastric pull-up.</td>
</tr>
<tr>
<td>4. Tumor deeper than muscularis mucosa but not through the esophageal wall (intramural tumors)</td>
<td>En bloc esophagectomy with appropriate systematic lymphadenectomy of the cervical, upper mediastinal (above tracheal bifurcation), lower mediastinal (below tracheal bifurcation) and abdominal nodes. (For upper and middle third cancers mediastinal dissection must include the node along the left recurrent nerve. For lower third esophageal and cardia cancers, omit cervical and upper mediastinal node dissection but include proximal stomach in the resection. For upper third esophageal cancers, omit abdominal lymph node dissection). Reconstruction with gastric pull-up for middle and upper third tumors, and with colon interposition for lower third and cardia tumors.</td>
</tr>
<tr>
<td>5. Tumor extending through the muscularis propria (transmural tumors)</td>
<td>Same as for intramural tumors unless five or more lymph nodes are assumed to be involved, in which case a palliative transhiatal esophagectomy is done.</td>
</tr>
</tbody>
</table>
without such cells [71]. Such studies emphasize that hematomogenous dissemination of viable malignant cells occurs early in the disease and that systemic chemotherapy may be helpful if the cells are sensitive to the agent. On the other hand, if the cells are resistant, systemic chemotherapy may be a hindrance because of its immunosuppressive properties. Unfortunately, current technology is not able to test tumor cell sensitivity to chemotherapeutic drugs, and the choice of drugs must rest solely on their clinical effectiveness against grossly similar tumors.

The decision to use preoperative rather than postoperative chemotherapy was based on the ineffectiveness of chemotherapeutic agents when used after surgery, and on animal studies suggesting that agents given before surgery were more effective. The claim that patients who received chemotherapy before resection were less likely to develop resistance to the drugs was in reality only opinion and unsupported by data. Similarly, the claim that drug delivery is enhanced because blood flow is more robust before the patients undergo surgical dissection is also flawed in that if enough blood reaches the operative site to heal the wound or anastomosis, the flow also should be sufficient to deliver chemotherapeutic drugs. An agreed-upon benefit that can be attributed to preoperative chemotherapy in esophageal carcinoma is its ability, if effective, to facilitate surgical resection, particularly squamous cell tumors above the level of the carina. Reducing the size of the tumor may provide a safer margin between the tumor and the trachea and allow an anastomosis to a tumor-free cervical esophagus just below the criopharyngeus. The involved margin at this level usually requires a laryngectomy to prevent subsequent local recurrence.

**Does Preoperative Chemotherapy Improve Survival?**

Three randomized prospective studies with squamous cell carcinoma have shown no survival benefit with preoperative chemotherapy, i.e., neoadjuvant therapy, over surgery alone (Table VII) [72–74]. Similar studies for adenocarcinoma have not been done. For squamous cell tumors, a complete response to chemotherapy occurred only in 6% of patients. Some proponents of neoadjuvant therapy have emphasized the benefits by focusing only on patients who responded to treatment, leaving nonresponders out of the equation. This is inappropriate because the success of surgery could be similarly inflated by focusing only on those in whom all tumor could be completely removed and by comparing their survival to those in whom tumor was left behind, i.e., R0 and R1 vs. R2 resections—survival for the former group is statistically better. Other proponents have pointed to the increase in the “disease-free” interval of patients who received neoadjuvant therapy as a justification for its use. This cannot be assumed to be irrefutable in that the intensity and frequency of the hunt for recurrent disease can vary depending on the investigator’s prejudices, or patients who have an increased disease-free interval may develop metastasis in organs that are less likely to be scrutinized. Further, an increase in the disease-free interval without an increase in survival requires that the interval between recurrent disease and death is accelerated. This suggests that a more aggressive clone of tumor cells were selected out by the chemotherapy.

With the exception of the potential to improve resectability of tumors located above the carina, the benefits cited by those in favor of preoperative chemotherapy are questionable. Investigators have allowed their quest for prolonged survival to assume secondary importance as they have become more intrigued with the opportunity neoadjuvant therapy provides for an in vivo assessment of the tumoricidal effectiveness of a drug or combination of drugs. Studies on survival take up to 5 years to complete, whereas studies on tumor chemosensitivity can be completed within 3 months by evaluating the resected specimens. In summary, preoperative chemotherapy alone can potentially downstage the tumor, particularly squamous cell carcinoma. It also can potentially eliminate or delay the appearance of metastasis. However, there is no evidence that it can prolong survival of patients with resectable carcinoma of the esophagus. Most failures are due to distant metastatic disease, underscoring the need for improved systemic therapy. Further, postoperative septic and respiratory complications are more common in patients receiving chemotherapy.

**Does Preoperative Chemoradiotherapy Improve Survival?**

Preoperative chemoradiotherapy using the drug combinations of platinum with 5-fluorouracil (5-FU) has been reported by several investigators to be beneficial in both adenocarcinoma and squamous cell esophageal carci-

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**TABLE VII. Esophageal Carcinoma: Randomized Preoperative Chemotherapy Vs. Surgery Alone**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>n = C/S</th>
<th>Cell type</th>
<th>Regimen</th>
<th>CR (%)</th>
<th>Survival C vs. S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth et al. [72]</td>
<td>1988</td>
<td>19/20</td>
<td>Squamous</td>
<td>P, V, B</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Nygaard et al. [73]</td>
<td>1992</td>
<td>50/41</td>
<td>Squamous</td>
<td>P, B</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Schlag [74]</td>
<td>1992</td>
<td>21/24</td>
<td>Squamous</td>
<td>P, 5-FU</td>
<td>5</td>
<td>NS</td>
</tr>
</tbody>
</table>

*P = cisplatin; C = preoperative chemotherapy; V = vindesine; S = surgery only; B = bleomycin; CR = complete response to chemotherapy; 5-FU = 5-fluorouracil.
Esophageal Carcinoma: Current Controversies

Esophageal Carcinoma— but particularly for squamous cell—by increasing the number of complete pathological responses of the primary tumor prior to resection. There have been only five randomized prospective studies, three with squamous cell and one with both squamous cell and adenocarcinoma and one with only adenocarcinoma (Table VIII) [73, 75–77]. All but one have shown no survival benefit with preoperative chemoradiotherapy over surgery alone. Most authors report that the treatment is accompanied by substantial morbidity and mortality. Despite this, many have been encouraged by the observation that some patients who had a complete response have remained free of recurrence at 3 years.

The study reported by Walsh [92] and associates represents the one positive outcome and deserves special comment. Several concerns have arisen about this trial. First, before the results are accepted as gospel, it must be kept in mind that three other studies have not shown any benefit to this approach and the report of this study is only an interim analysis at 3 years. Things could change with further follow up. If one more death occurs in the multimodal group, the p-value would go from 0.01 to 0.03, and with two deaths to > 0.05 [93]. Second, the number of early stage tumors was low in the surgery group and hence a worse survival than what is generally reported following resection. In contrast, nothing is known about the initial stage of the multimodal therapy group. The number in each arm is small and there could be a stage bias. Third, there is no clear account of the kind of surgical resection performed, i.e., R₀, R₁, or R₂. Fourth, withdrawals from the protocol may have resulted in a selection that favored the outcome of multimodal therapy in that 10 patients were withdrawn from that arm compared to only one from the surgical arm. Five of the 10 withdrawals from the multimodal therapy arm completed a full course of chemotherapy. Fifth, 51 patients (45%) of the original 113 evaluated were excluded from randomization which questions if the studied population is an accurate representation of the disease as seen in the clinics.

Caution must be exercised in emphasizing the effects of chemoradiotherapy with this approach, because the addition of preoperative radiation therapy to chemotherapy elevates the complete response rate and inflates the benefit of chemotherapy. With chemoradiation, the complete response rates for adenocarcinoma range from 17–24% (Table IX) [78]. When radiation was removed, the complete response fell to 0–5%, which suggests that the effects of chemotherapy are negligible. If radiotherapy is the factor responsible for improved response rate, surgery alone could do the job as well since numerous studies in the past have shown that the combination of surgery and radiation does not provide any beneficial survival advantage.

**The Ultimate Question Regarding Chemotherapy**

Most medical and radiation oncologists, dismayed by the high local recurrence and distant failure rates after transhiatal or standard transthoracic esophagectomy, have called into question the relevance of surgery in the treatment of esophageal cancer. In their minds, it has become a medical disease despite sound evidence to the contrary. Surgeons who perform a more extended en bloc resection and lymphadenectomy for cure of appropriately staged disease have shown gratifyingly low local recurrence rates in long-term survivors.

The ultimate question is this: Should a patient with carcinoma of the esophagus go through three cycles of chemotherapy on the 5% chance that they may get a complete response in the primary tumor and on the little evidence that such a response will control systemic disease? Prudence would encourage going directly to surgery and avoiding the morbidity associated with preoperative chemotherapy, particularly chemoradiation therapy. Some studies have shown that the rates of infection, anastomotic breakdown, incidence of adult respiratory distress syndrome, and the long-term use of a respirator were greater in patients receiving adjuvant therapy as compared with those receiving surgery alone [74].

Most treatment failures in patients with adjuvant therapy are due to distant disease. This underscores the negative answer to the original hypothesis and the need to understand that systemic therapy requires further improvement before it can be unconditionally recommended to patients. Rather than calling into question the relevance of surgery, oncologists need to answer the question, “Is chemotherapy with the newer agents, given at the time of systemic recurrence, effective in prolonging survival?” [79] Perhaps the newer agents are more effective at this stage if patients have not received chemotherapy before. In summary, current data

<table>
<thead>
<tr>
<th><strong>TABLE VIII. Esophageal Carcinoma: Randomized Preoperative Chemoradiotherapy Vs. Surgery Alone</strong>*</th>
<th><strong>Ref.</strong></th>
<th><strong>Year</strong></th>
<th><strong>n = C/S</strong></th>
<th><strong>Cell type</strong></th>
<th><strong>Regimen</strong></th>
<th><strong>Survival C vs. S</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nygaard et al. [73]</td>
<td>1992</td>
<td>47/41</td>
<td>Squamous</td>
<td>P, B, 35 Gy</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Le Prise et al. [75]</td>
<td>1994</td>
<td>41/45</td>
<td>Squamous</td>
<td>P, 5-FU, 20 Gy</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Apinop et al. [76]</td>
<td>1994</td>
<td>35/34</td>
<td>Squamous</td>
<td>P, 5-FU, 40 Gy</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Urba et al. [77]</td>
<td>1995</td>
<td>50/50</td>
<td>Squamous + adenocarcinoma</td>
<td>P, 5-FU, 45 Gy</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Walsh [92]</td>
<td>1996</td>
<td>48/54</td>
<td>Adenocarcinoma</td>
<td>P, 5-FU, 40 Gy</td>
<td>p=0.01</td>
<td></td>
</tr>
</tbody>
</table>

*P = cisplatin; C = preoperative chemotherapy; 5-FU = 5-fluorouracil; S = surgery only; B = bleomycin; V = vinblastine.
advanced esophageal carcinoma has lost quality of life due to this definition, an individual who is diagnosed with an interpersonal relationships, and anxiety level. According to factors, some of the most important being health, attitude, an alized state of peace derived from a balance of multiple A workable definition is that quality of life is a conceptu nal approach and measurable outcome to palliative therapy. the goal of the operation, is still a chance possibility. relief of symptoms with less surgery, and cure, while no longer the goal of surgery is palliation. This approach provides rate a curative en bloc resection, or is over the age of 75, the patient has insufficient cardiopulmonary reserve to tol erate a curative en bloc resection, or is over the age of 75, the goal of surgery is palliation. This approach provides relief of symptoms with less surgery, and cure, while no longer the goal of the operation, is still a chance possibility. “Quality of life” must be defined if there is to be a ratio nal approach and measurable outcome to palliative therapy. A workable definition is that quality of life is a conceptu alized state of peace derived from a balance of multiple factors, some of the most important being health, attitude, interpersonal relationships, and anxiety level. According to this definition, an individual who is diagnosed with an advanced esophageal carcinoma has lost quality of life due to an imbalance of at least three factors: health, due to the symptoms he or she is experiencing; attitude, due to the de pression he or she is feeling; and anxiety, due to the presence of a life-threatening tumor. A palliative removal of the tumor can improve a patient’s quality of life by alleviating symp toms and relieving anxiety. Palliative surgery is also likely to contribute to an improved attitude by restoring hope. Prior to a palliative resection, the surgeon must be sure that the patient’s symptoms can be palliated. Symptoms which call for palliation are dysphagia, anorexia, nausea, vomiting, pain, and bleeding. Of these, anorexia and the pain of invasion are the most difficult, if not impossible, to palliate by a surgical resection; however, dysphagia, nau sea from obstruction, ulcer pain, and bleeding are readily palliated. Because survival is usually about 14 months in patients with locally advanced disease and 6 months in those with distant organ metastasis, a palliation resection should not be performed in a patient with systemic disease. Dysphagia is the most common symptom requiring palliation, and its relief is of utmost importance to the quality of the patient’s remaining survival time. Table X is a functional classification of the degrees of dysphagia. Grade III or higher is an indication for a palliative procedure. Figure 3 shows the correlation between the grade of dysphagia and the Linear Analogue Self-Assessment test (LASA) which assesses a patient’s physical and psychological well-being and symptom control, including dysphagia [81]. As shown, there is a significant negative correlation between dysphagia grade and quality of life as measured by the LASA.

Simple resection of the tumor provides the best palliation of dysphagia, improves the quality of life, and gives hope, although small, for a cure. In addition, it also pre-

**TABLE IX. Results of Neoadjuvant Therapy in Adenocarcinoma of the Esophagus**

<table>
<thead>
<tr>
<th>Institution</th>
<th>Year</th>
<th>No. of patients</th>
<th>Regimen</th>
<th>CR (%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.D. Anderson</td>
<td>1990</td>
<td>35</td>
<td>P, E, 5-FU</td>
<td>3</td>
<td>42% at 3 years</td>
</tr>
<tr>
<td>SLMC</td>
<td>1992</td>
<td>18</td>
<td>P, 5-FU, RT</td>
<td>17</td>
<td>40% at 3 years</td>
</tr>
<tr>
<td>Vanderbilt</td>
<td>1993</td>
<td>39</td>
<td>P, E, 5-FU, RT</td>
<td>19</td>
<td>47% at 4 years</td>
</tr>
<tr>
<td>Michigan</td>
<td>1993</td>
<td>21</td>
<td>P, VBL, 5-FU, RT</td>
<td>24</td>
<td>34% at 5 years</td>
</tr>
<tr>
<td>MGH</td>
<td>1994</td>
<td>16</td>
<td>P, 5-FU</td>
<td>0</td>
<td>42% at 4 years</td>
</tr>
<tr>
<td>MGH</td>
<td>1994</td>
<td>22</td>
<td>EAP</td>
<td>5</td>
<td>58% at 2 years</td>
</tr>
</tbody>
</table>


would support giving chemoradiotherapy preoperatively to reduce tumor size in a young person with surgically incurable squamous cell carcinoma above the carina, and giving chemotherapy as salvage therapy for patients who have not had previous chemotherapy and who developed recurrent systemic disease after surgical resection.

**PALLIATION OF ESOPHAGEAL CANCER**

Prior to curative surgical therapy, the surgeon must con firm that the patient is able to withstand the planned operation. It is futile to perform an operation aimed at increasing the long-term survival for a patient whose physiological life expectancy is short. Similarly, the patient’s age is a factor. The majority of deaths over the age of 75 are due to cancer, stroke, or heart disease. Since humans must die, reducing the number of cancer deaths will only increase the mortality from heart disease or stroke, and will not affect life expectancy at birth. This concept is referred to as the theory of competing risks, which states: “In a developed society where the exponentials describing the cumulative rates with age for the more common causes of death have similar intercepts, the elimination of one cause of death does not significantly affect life expectancy” [80]. In other words, curing an octogenarian of cancer will not affect life expectancy at birth. This concept is re ferred to the theory of competing risks, which states: “In a developed society where the exponentials describing the cumulative rates with age for the more common causes of death have similar intercepts, the elimination of one cause of death does not significantly affect life expectancy.” [80]. In other words, curing an octogenarian of cancer will not affect life expectancy at birth. This concept is referred to the theory of competing risks, which states: “In a developed society where the exponentials describing the cumulative rates with age for the more common causes of death have similar intercepts, the elimination of one cause of death does not significantly affect life expectancy.” [80].

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Figure 3 shows the correlation between the grade of dysphagia and the Linear Analogue Self-Assessment test (LASA) which assesses a patient’s physical and psychological well-being and symptom control, including dysphagia [81]. As shown, there is a significant negative correlation between dysphagia grade and quality of life as measured by the LASA.

Simple resection of the tumor provides the best palliation of dysphagia, improves the quality of life, and gives hope, although small, for a cure. In addition, it also pre-

**TABLE X. Functional Grades of Dysphagia**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Able to eat a normal diet</td>
</tr>
<tr>
<td>I</td>
<td>Able to eat solid food</td>
</tr>
<tr>
<td>II</td>
<td>Able to eat semisolids only</td>
</tr>
<tr>
<td>III</td>
<td>Able to swallow liquids only</td>
</tr>
<tr>
<td>IV</td>
<td>Complete obstruction</td>
</tr>
</tbody>
</table>
Esophageal Carcinoma: Current Controversies

Due to the short life expectancy of 6 months, a palliative surgical resection is not a viable option for patients with distant organ metastasis. Thus, the presence of a malignant pleural effusion, distant organ metastasis, a malignant fistula to the airway, or a primary tumor that extends into adjacent organs, discourages a palliative resection and encourages other means of palliating the dysphagia. Figure 4 is an algorithm of the factors to be considered in deciding if a patient should undergo an en bloc esophagectomy or a palliative resection and, if neither, one of the nonoperative methods of palliation.

External beam radiation therapy is an important method of nonoperative palliation and provides relief of dysphagia to approximately 80% of patients, and one half of them remain free of dysphagia until the time of death [83]. Usually, the higher the dose, the better the palliation. The disadvantages are the average time of 4–6 weeks to treatment effect and the 30–50% incidence of complications such as severe esophagitis, stenosis, and fistula formation [84]. Further, radiation therapy is usually not an effective means of palliation when the esophageal lumen is completely occluded.

Endoluminal brachytherapy is a form of radiation therapy that directly attacks the intraluminal tumor causing the dysphagia while shortening the treatment time. Doses up to 20 Gy can be given in three fractions with 90% improvement in dysphagia lasting an average of 5 months. This is accomplished at the expense of moderate to severe self-limiting esophagitis in 50% of patients [85].

Fig. 3. Scatter diagram of relation between dysphagia grade and Linear Analogue Self-Assessment (LASA) in 38 patients with esophagogastric carcinoma. Eighty-six paired scores obtained at various times through the patients’ survival have been plotted. The negative correlation shown is highly significant (P < 0.0001) with Spearman coefficients of −0.49 and −0.43, respectively. From Loizou LA, Grigg D, Atkinson M, et al: A prospective comparison of laser therapy and intubation in endoscopic palliation for malignant dysphagia. Gastroenterology 1991;100 (5 Pt 1):1307. [40]. With permission.

Fig. 4. Algorithm for the evaluation of esophageal cancer patients to select the proper therapy: curative en bloc resection, palliative transhiatal resection, or nonoperative palliation.
Brachytherapy can be combined with external beam radiation therapy to increase the local effect, but at the risk of developing the late complication of esophageal ulcers and strictures in up to 30% of the patients.

Chemoradiation is rarely used for palliation because of its 50–60% rate of severe and life-threatening acute toxicity, its lengthy treatment to effect time, and its treatment mortality of 2%. The reported 75% improvement in dysphagia is not sufficient to outweigh these risks. It is best reserved for the good-risk patient with locally advanced disease who refuses surgical palliation. Patients with distal esophageal tumors seem to do better than those with upper and middle lesions [86].

Dilatation can afford relief of dysphagia in up to 70% of patients, if they can be dilated. The procedure has a 15% failure rate due to the inability to pass a guide wire through an obstructing tumor and a complication rate of 2–10%. The disadvantage is that the average benefit from dilatation lasts 12 days. Its most important use is the initial step in several alternative nonoperative palliative techniques.

Peroral intubation with a prosthesis is the most popular worldwide method for palliating advanced esophageal cancer [87,88]. The advantages are simplicity, short hospitalization, and immediate improvement in swallowing. The procedure is most useful for malignant esophago-bronchotracheal fistula; for which it has become the treatment of choice. Contraindication is a tumor within 3 cm of the cricopharyngeus. Intubation at this level causes persistent pharyngeal discomfort. Side effects are reflux and potential aspiration when the prosthesis traverses the gastro-esophageal junction. Early complications include perforation (6%), hemorrhage (3.5%), aspiration pneumonia (0–2%), and dislocation (15%). Late complications are obstruction (9.5%) from tumor overgrowth, food impaction, or angulation with impingement of the opening against the esophageal or gastric wall, dislocation (8%), and pressure necrosis (3%). The mortality rate after perforation is 25–50%. The overall complication rate is 20–60%; and the overall hospital mortality rate is 8%. Although virtually every patient who is successfully intubated improves in swallowing, only 10–50% can eat solids, and the remaining patients are restricted to a semisolid diet.

Expandable metallic stents have been introduced in an effort to improve the ease of insertion and to lessen the complication of the standard prosthesis. The stent is compressed and restrained on a delivery device, and after positioning,

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Fig. 5. Suggested global algorithm for the management of carcinoma of the esophagus. Modified from the unpublished guidelines prepared by DeMeester TR, Kimmey MB, Kozarek RA, et al. for the 95th Annual American Gastroenterological Association’s Clinical Practice Section symposium on esophageal cancer; 1994 May 15–18; New Orleans, Louisiana.
expands according to a variety of techniques. This provides for more proper placement, fewer complications, and greater ease of insertion. Problems associated with metallic stents are tumor ingrowth and inflammation with reduction or obstruction of the lumen. As a consequence, newer metallic stents are coated with silicone. Their greatest disadvantage is the cost.

Lasers have been used to destroy luminal protrusions of an esophageal tumor as a means of nonoperative palliation [87,89]. Initial dilatation and retrograde treatment is favored to allow more efficient therapy. For totally obstructing tumors that cannot be dilated safely, an antegrade approach is utilized. Tumors that are relatively short (<6 cm), nonangulated, exophytic, noncircumferential, and in the mid or distal esophagus are most amenable to laser ablation. Tumors near the upper sphincter can be treated, but less successfully. Angulated tumors are not suitable for treatment, and circumferential tumors are more vulnerable to posttreatment strictures. The technical success of laser therapy ranges from 90 to 100%, but this must be distinguished from functional success which averages from 75 to 80%. About 50% of patients treated maintain luminal patency until death. Retreatment is required by many patients at 4- to 6-week intervals. Major complications are perforation (3%), fistula formation (2.3%), and hemorrhage (1.4%). The advantage of laser therapy is its high success rate and few complications. Dysphagia is palliated immediately and treatment can be repeated indefinitely. Its disadvantages are its dependency on expensive equipment, skilled support personnel and the need for retreatment. With some success to decrease the time interval between laser sessions, external radiation therapy and brachytherapy have been added to laser therapy.

There have been few studies comparing the various nonoperative palliative modalities because tumor characteristics and patient condition vary so greatly in advanced disease that firm conclusions are difficult. In one of the rare randomized trials, palliation of obstructing nonresectable squamous cell carcinoma of the mid or distal esophagus was similar whether a stent, a stent plus radiation, or endoscopic laser therapy with radiation was used [82,90]. With either technique, quality of survival is dependent on restoring the ability to swallow. Mean survival is about 4 months, and adding radiation therapy significantly increases time in treatment. For tumors crossing the cardia, a stent appears to work better; for tumors of the proximal esophagus, laser therapy is probably better.

CONCLUSIONS

A global management scheme that incorporates choices in areas of controversies is shown in Figure 5 [91].

REFERENCES

26. Iftikhar SY, James PD, Steele RJ, et al: Length of Barrett’s oesopa-


