Adenocarcinoma of the Esophagus and Gastroesophageal Junction

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The incidence of adenocarcinoma of the esophagus and gastroesophageal (GE) junction has risen dramatically in the United States and other Western countries over the last decades of the twentieth century. At midcentury, esophageal adenocarcinoma was a rare entity compared to squamous cell cancer of the esophagus, but adenocarcinomas now outnumber squamous cell carcinomas in many series. This increase has been particularly impressive in white men, in whom the incidence of adenocarcinoma of the esophagus has risen by more than 350 percent since the mid-1970s. The causes of this startling increase and its pattern are poorly understood although intense work on risk factors and etiology has yielded some insights.

The transitional nature of the anatomic GE junction has added further confusion to the understanding of this disease. Adenocarcinomas of the distal esophagus, GE junction, and gastric cardia have all increased in incidence, and many studies have grouped tumors at these locations together. Although there is a rationale for this grouping (increasing incidence rates in all locations, anatomic continuity, and similar pathologies), differences among these tumors exist as well (differing rates of increased incidence, proportion of cases involving Barrett’s metaplasia, possible differing patterns of nodal spread). Recently proposed classification schemes aim to further define the anatomic regions.

The specialized intestinal metaplasia that defines Barrett’s esophagus is recognized as a precursor lesion in most cases of esophageal adenocarcinoma and in many cases of adenocarcinoma at the GE junction. Barrett’s esophagus is a result of chronic gastroesophageal reflux disease (GERD), but only about 10 percent of patients with chronic GERD will develop Barrett’s changes. Predisposing factors to development of Barrett’s esophagus have yet to be defined, despite intense research. Molecular factors are beginning to be recognized. Asymptomatic Barrett’s esophagus occurs as well, complicating attempts at screening.

This chapter reviews the facts and controversies surrounding adenocarcinomas of the esophagus and GE junction, with particular attention to etiology, staging, and surgical therapy.

CLASSIFICATION

The classification of tumors, particularly at the GE junction, has been a problematic issue that has complicated the reporting of results. A consensus conference of the International Gastric Cancer Association (IGCA) and the International Society for Diseases of the Esophagus (ISDE) in 1998 defined and described adenocarcinomas of the GE junction as tumors that have their center within 5 cm proximally and distally of the anatomic cardia. Within this area, tumors are differentiated into the following three distinct entities (Figure 5–1):

Type I: Adenocarcinoma of the distal esophagus, usually arising from an area with specialized intestinal metaplasia of the esophagus...
(ie, Barrett’s esophagus); it may infiltrate the esophagogastric junction from above.

Type II: True carcinoma of the cardia, arising from the cardiac epithelium or short segments of intestinal metaplasia at the gastroesophageal junction; this entity is often referred to as “junctional carcinoma.”

Type III: Subcardial gastric carcinoma that infiltrates the esophagogastric junction and distal esophagus from below.4

This chapter focuses on adenocarcinomas of the distal esophagus and on type I and II tumors of the GE junction. For the purposes of this chapter, type III tumors are categorized as gastric tumors.

INCIDENCE AND EPIDEMIOLOGY

It was estimated that there would be 13,200 new cases of esophageal carcinoma diagnosed in the United States and 12,500 deaths due to esophageal cancer in the year 2001.8 These numbers represent all cancers of the esophagus (both squamous cell cancer and adenocarcinoma). Although squamous cell carcinoma was the predominant histology for most of the twentieth century, the incidence of adenocarcinoma has increased over the past several decades. In surgical series from the mid–twentieth century, adenocarcinomas represented a distinct minority, ranging from 1.3 to 10.0 percent of cases.9–11 Recent major surgical series have reported rates of adenocarcinoma incidence of between 59 and 70 percent.12–15 A single-institution study from the Johns Hopkins Tumor Registry reported sharp increases in cases of adenocarcinoma of the esophagus, beginning in 1978 and continuing to rise through 199416 (Figure 5–2). In 1994, the number of adenocarcinoma cases surpassed the number of squamous cell cancer cases for the first time since cases began to be recorded (in 1959).16

This rise has been confirmed by data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program showing adenocarcinoma cases exceeding squamous cell cancer cases in white males in 1990.3 Blot and colleagues, using SEER data, reported in 1991 that the occurrence of adenocarcinoma of the esophagus was increasing at a rate of 4 to 10 percent per year in the United States, faster than the rate of increase in any other cancer.1 During the period in question, squamous cell carcinoma trends were stable and the rates of adenocarcinoma of the distal stomach were decreasing.1 A report from the National Cancer Data Base (NCDB) looked at rates of esophageal cancer in 1988 and 1993.17 During this period, the rate of adenocarcinoma of the esophagus rose from 33.2 to 43.1 percent of all cases of esophageal cancer while the rate of squamous cell carcinoma fell from 66.2 to 56.0 percent of all cases.17 Similar trends have been observed in Denmark, Switzerland, Sweden, Norway, and the United Kingdom.6

Rates of adenocarcinoma of the GE junction and gastric cardia have also risen in a similar (though less steep) fashion. Data from the SEER program reveal that in white males, annual rates of adenocarcinoma of the gastric cardia rose from 2.1 cases per year per 100,000 population in 1974 to 1976 to 3.3 cases per year per 100,000 in 1992 to 1994.3 Rates rose in African American males also, from 1.0 cases per 100,000 in 1974 to 1976 to 1.9 per 100,000 in 1992 to 1994.3 A study of rates of gastric cardia cancer in Connecticut revealed even greater rates of increase in...
males, from 0.6 cases per 100,000 in 1955 to 1959 to 3.0 per 100,000 in 1985 to 1989, a fivefold increase. Similar rates of increase occurred in females, although with lower absolute numbers (from 0.1 cases per 100,000 in 1965 to 1969 to 0.6 per 100,000 in 1985 to 1989).

Pera and colleagues observed similar rates of increase in a population-based study in Olmsted County, Minnesota. Adenocarcinoma of the esophagus rose from 0.13 cases per 100,000 person-years in 1935 to 1971 to 0.74 cases per 100,000 person-years in 1974 to 1984 while adenocarcinoma of the GE junction rose from 0.25 cases per 100,000 person-years in 1935 to 1971 to 1.34 cases per 100,000 person-years in 1974 to 1984.

Overall rates of increase vary according to age, gender, and race, although increases are seen among all groups. Blot and colleagues showed a very high male-to-female ratio (~7.6:1) among white persons. In SEER data, the rising incidence of esophageal adenocarcinoma tended to affect all age groups whereas NCDB data showed the greatest rate of rise in older men. Multiple studies have revealed the greatest rate of rise to be among white males, with smaller but increasing rates in African Americans (males and females) and white females (Figure 5–3).

ETIOLOGY

The exact cause of this increased incidence is unclear. Table 5–1 lists factors identified in numerous reports to be associated with an increased or decreased risk of adenocarcinoma of the esophagus.

Barrett’s esophagus is the single most important factor for the development of adenocarcinoma of the esophagus and GE junction. Myriad studies have been conducted, and these studies place patients with Barrett’s esophagus at a 30 to 125 times increased risk of developing esophageal adenocarcinoma. The definition of Barrett’s esophagus has evolved over the last several decades, with wide variations over time and between investigators. For the purposes of this chapter, Barrett’s esophagus is defined as an acquired disorder of the distal esophagus, in which due to chronic GE reflux and resultant reflux esophagitis) squamous epithelium is eroded and replaced by columnar epithelium, either by metaplasia or by the extension of columnar epithelium from the stomach.

The controversies surrounding Barrett’s esophagus go back to Norman Barrett himself. Barrett, an influential British surgeon, wrote in 1950 that the “peptic” ulcers seen below the squamocolumnar junction were in a “pouch of stomach” drawn up into
the chest by scar. In 1953, Allison and Johnstone demonstrated that these ulcers actually occurred in a portion of the tubular foregut that had normal esophageal musculature, esophageal-type glands, and no peritoneal covering. In 1957, Barrett conceded that in some cases, columnar epithelium extended up into the esophagus, calling this “columnar-lined lower esophagus,” which has since been referred to as “Barrett’s esophagus.” Barrett, Allison, and others thought that the condition was congenital, but in 1959, Moersch recognized it as acquired. The association between columnar-lined esophagus and GERD was first shown in the landmark paper of Bremner in 1970, in an experimental model in dogs. The association between Barrett’s esophagus and adenocarcinoma of the esophagus has been recognized since the 1970s.

Other controversies of definition have existed as well, related to anatomy, cell pattern, extent, and etiology. Three types of columnar mucosa have been identified in the distal esophagus: the gastric-fundic type, which contains chief cells and parietal cells; the junctional type, which contains mucous cells without parietal cells; and the specialized type, which has intestinal characteristics. The specialized type, which is referred to as specialized intestinal metaplasia (SIM), is characterized by goblet cells, which stain with Alcian blue at a pH of 2.5. Of the three types of columnar mucosa, only SIM is known to be preneoplastic, with adenocarcinomas frequently being surrounded by SIM.

Anatomically, the exact GE junction is defined variously by anatomists, radiologists, endoscopists, and physiologists. There is no “gold standard” for precise localization of the GE junction, which makes characterizing the extent of columnar mucosa imprecise. Because of this, Barrett’s esophagus has been defined by some authors as a minimal length of columnar mucosa (most commonly 3 cm, with a range of from 2 to 5 cm), largely to avoid false-positives when studying the entity. At present, Barrett’s esophagus is referred to as “long-segment” Barrett’s esophagus (LSBE) when its length is ≥ 3 cm of columnar mucosa and as “short-segment” Barrett’s

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### Table 5-1. FACTORS ASSOCIATED WITH RISK OF ESOPHAGEAL ADENOCARCINOMA

<table>
<thead>
<tr>
<th>Association Factor</th>
<th>Odds Ratio</th>
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<tr>
<td>Barrett’s esophagus</td>
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<tr>
<td>GERD</td>
<td>7.7</td>
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<tr>
<td>Tobacco</td>
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<td>Obesity</td>
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<tr>
<td>Liquor consumption</td>
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</tr>
<tr>
<td>Colon cancer (men only)</td>
<td>—</td>
</tr>
<tr>
<td>Breast cancer (radiation only)</td>
<td>—</td>
</tr>
<tr>
<td>LES-relaxing drugs</td>
<td>—</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td></td>
</tr>
<tr>
<td><em>Helicobacter pylori</em> (cagA+ strains)</td>
<td>0.4</td>
</tr>
<tr>
<td>Wine consumption</td>
<td>0.6</td>
</tr>
<tr>
<td>High income</td>
<td>—</td>
</tr>
<tr>
<td>High education level</td>
<td>—</td>
</tr>
</tbody>
</table>

GERD = gastroesophageal reflux disease; LES = lower esophageal sphincter; NA = not available.
esophagus (SSBE) when it is < 3 cm in length. Dysplasia and cancer have been found to arise from both LSBE and SSBE. As well, there has been confusion between the cardiac region of the stomach, which is located distal to the GE junction and has oxyntic mucosa, and the cardia, which is located at and proximal to the GE junction in the distal esophagus and which may be lined with squamous mucosa or with junctional (cardiac) mucosa (only columnar cells and mucous cells). Specialized intestinal metaplasia has been documented in biopsy specimens of the cardia, and some investigators believe that it is the precursor for adenocarcinomas of the cardia.

Estimates of the frequency of Barrett’s esophagus depend on whether length (ie, ≥ 3 cm) or histologic characteristics (ie, the presence of SIM) or a combination of the two is the defining characteristic. Commonly presented numbers indicate that Barrett’s esophagus is present in 0.45 to 2.2 percent of all patients undergoing upper endoscopy and in up to 10 to 12 percent of patients undergoing upper endoscopy for symptoms of reflux. In one study, SIM was found on biopsy of the GE junction in 18 percent of patients who underwent endoscopy in a general endoscopy unit. It has been hypothesized that many patients suffer reflux without typical symptoms and that columnar epithelium may be more acid resistant than normal squamous epithelium, and therefore less symptomatic, leading to a large number of patients with asymptomatic Barrett’s esophagus.

It is widely believed (and there is much evidence to support the concept) that Barrett’s esophagus is the result of prolonged GE reflux. Studies have documented a correlation between the degree of dysfunction of the lower esophageal sphincter, the amount of time that esophageal pH is < 4, and the poor esophageal clearance of acid with the extent of Barrett’s changes in the distal esophagus. Whereas previously it was thought that acid alone was the major injurious agent, there has been mounting evidence in the last decade that the presence of duodenal juice (principally bile) in the refluxate may lead to worsening of the injury, higher rates of Barrett’s esophagus, and complications of Barrett’s esophagus (ulcers, strictures, dysplasia, cancer). Patients with higher bilirubin exposure (determined by use of a Bilitec probe) have a greater prevalence of Barrett’s esophagus and its complications than patients without bilirubin in the refluxate. Fein and colleagues demonstrated that patients with dysplasia and Barrett’s esophagus had greater exposure to duodenal juice than did those with uncomplicated Barrett’s esophagus (p = .04), with the same overall acid exposure time. Stein and colleagues showed that there was an exponential increase in mean esophageal bile exposure time in those with erosive esophagitis and Barrett’s esophagus when compared to those with GERD without esophagitis (p < .01) and that pathologic bile exposure occurred in 54 percent of patients with Barrett’s esophagus and 78 percent of those with early adenocarcinomas in Barrett’s esophagus. The cause of SIM of the cardia is controversial; some investigators believe it to be reflux whereas others believe it is related to *Helicobacter pylori* infection and intestinal metaplasia of the stomach. These and similar data have led many to conclude that the combination of gastric and duodenal reflux may lead to the most severe esophageal mucosal damage and to Barrett’s esophagus and its complications. A possible sequence that has been proposed is shown in Figure 5-4.

The frequency with which Barrett’s esophagus degenerates into dysplasia and adenocarcinoma and

![Figure 5-4. Sequence in the development of esophageal adenocarcinoma.](image-url)
the frequency with which adenocarcinomas are found with surrounding Barrett’s esophagus have been examined in multiple series. In a study examining the prevalence of SIM in all patients undergoing upper endoscopy, Hirota and colleagues found that the overall prevalence of SIM was 13.2 percent (1.6% for LSBE, 6.0% for SSBE, and 5.6% for GE-junction SIM). Dysplasia or cancer was found in 31 percent of LSBE cases, 10 percent of SSBE cases, and 6.4 percent of GE-junction SIM cases ($p \leq .043$). Examining the question from the opposite angle (ie, what is the prevalence of Barrett’s esophagus in patients with adenocarcinomas of the distal esophagus and GE junction?), Clark and colleagues found that SIM was identified in histologic sections of resected specimens in 79 percent of esophageal adenocarcinomas, 42 percent of cardiac/GE-junction adenocarcinomas, and only 5 percent of subcardiac adenocarcinomas. Cameron and colleagues found Barrett’s esophagus in 100 percent of esophageal adenocarcinomas, 42 percent of GE-junction adenocarcinomas, and 0 percent of esophageal squamous cell cancers. Of note, both Clark and Cameron commented that in GE-junction adenocarcinomas, segments of Barrett’s esophagus/SIM tended to be short and had been missed on endoscopy in many cases. The incidence of adenocarcinoma in patients with known Barrett’s esophagus was examined by Drewitz and colleagues in 177 patients with Barrett’s esophagus observed for a mean of 4.8 years. Four adenocarcinomas developed during the study, for an incidence of 1 per 208 patient-years of follow-up. Other authors have stated that the annual incidence of adenocarcinoma in patients with Barrett’s esophagus ranges from 0.23 to 0.8 percent.

Factors other than Barrett’s esophagus are thought to play a role in the development of esophageal and GE-junction adenocarcinomas. The role of smoking in esophageal adenocarcinoma has been identified in several studies, although its impact in adenocarcinoma is less than in squamous cell carcinoma. In a landmark study, Gammon and colleagues examined risk factors for esophageal adenocarcinoma. A multicenter population-based case-control design was used. The risk of both esophageal and gastric adenocarcinomas was increased in current smokers, with an odds ratio (OR) of 2.4. A dose-response relation was demonstrated. Furthermore, no reduction in risk was observed until 30 years after smoking cessation. These results led to the conclusion that smoking is a major risk factor for esophageal and gastric cardiac adenocarcinomas and raised the possibility that the impact is at an early stage of carcinogenesis as no reduction was seen for many years after cessation. This may partly explain the rising incidence of these cancers, as rates of smoking increased steadily through the first two-thirds of the twentieth century.

These findings of a more than doubly increased risk are consistent with the results of six other case-control studies, which showed a statistically significant association between cigarette smoking and adenocarcinoma of the esophagus and gastric cardia. Zhang and colleagues reported that the odds ratio for risk of adenocarcinoma of the esophagus and gastric cardia was 2.36 if a patient’s smoking history was one of > 60 pack-years of smoking (contrasted with an odds ratio of 5.9 for esophageal squamous cell cancer in a patient with a history of > 40 pack-years). Although not as dominating a factor as in esophageal squamous cell cancer, tobacco use remains a reproducible, significant, and preventable risk factor for adenocarcinoma of the esophagus and gastric cardia.

Past data concerning the impact of body weight on esophageal adenocarcinoma have been weak and inconsistent. Several recent studies identified excess weight as a strong risk factor. In a multicenter population-based case-control study, Chow and colleagues showed that the OR for esophageal adenocarcinoma increased with increasing adult body mass index (BMI). The magnitude was greatest in the youngest patients. Increased BMI posed a less impressive but still greater risk for GE-junction adenocarcinoma. No association was seen between increased BMI and esophageal squamous cell carcinoma or noncardiac gastric cancer. On the basis of these findings, the authors concluded that the increasing prevalence of obesity in the United States might contribute to the upward trend in esophageal and esophagogastric adenocarcinomas. An even stronger and dose-dependent association emerged from a Swedish study by Lagergren and colleagues. In a population-based case-control study,
they demonstrated that among obese patients (BMI > 30 kg/m²), the OR for esophageal adenocarcinoma was 16.2 (compared to the leanest group [BMI < 22 kg/m²]) and that the OR was 4.3 for gastric cardia adenocarcinoma. No association was seen between BMI and esophageal squamous cell carcinoma. The mechanism of this increased risk is unclear. It has been proposed that increased BMI may lead to increased GERD and hiatal hernia, but one study found no association between GERD symptoms and BMI. In a case-control study, Zhang and colleagues found that a high intake of calories and fat was associated with an increased risk of adenocarcinoma of the esophagus, more suggestive of a dietary than a mechanical effect.

Special attention has been paid in recent years to the role of *Helicobacter pylori* in gastrointestinal-tract cancers. Whereas there is a positive association of atrophic gastritis and gastric cancers with cagA+ strains of *H. pylori*, there is a negative association for esophageal, GE-junction, and gastric cardia tumors. In a multicenter case-control study, Chow and colleagues demonstrated an inverse relation between *H. pylori* infection and esophageal cancer in the United States. The OR for cagA+ strains of *H. pylori* and esophageal adenocarcinoma was 0.4. In another study, the presence of cagA+ *H. pylori* appeared to be protective against the development of esophageal adenocarcinoma. The exact mechanism of the protective effect is unclear, but one theory states that there is decreased acid production in the presence of cagA+ *H. pylori* and therefore less acid reflux. Others have stated the opposite—that *H. pylori* infection is responsible for SIM of the cardia. Work is ongoing, but serious questions exist about the effects of widespread eradication of *H. pylori* on the rates of esophageal and GE-junction adenocarcinomas.

The role of alcohol consumption in the occurrence of esophageal and GE-junction adenocarcinomas is likely minimal, in direct contrast to the known impact of ethanol on the risk of squamous cell cancers of the esophagus. In the study of Gammon and colleagues, there was no association seen between consumption of beer or liquor and rates of esophageal and GE-junction adenocarcinoma (ORs of 0.8 for beer and 1.1 for liquor). Wine drinking was associated with a reduced risk of these cancers (OR = 0.6). Levi and colleagues demonstrated an OR of 1.8 for esophageal and GE-junction adenocarcinomas if more than 21 drinks per week were consumed (contrasted with an OR of 9.5 for esophageal squamous cell carcinoma, with the same level of intake).

The impact of various medications on the rate of esophageal and GE-junction adenocarcinomas has been examined as well. Two major categories of concern have been H₂ blockers and drugs that relax the lower esophageal sphincter (LES). Data from a case-control study conducted through the National Cancer Institute revealed no increased risk of adenocarcinoma of the esophagus and GE junction in users of H₂ blockers. Data on LES-relaxing drugs are conflicting at present. Theoretically, cancer risk would increase if LES pressure was reduced by drugs such as nitroglycerine, anticholinergics, β-adrenergic agonists, aminophyllines, benzodiazepines, and calcium channel blockers, secondary to increased reflux and development of Barrett’s changes. A study in the United States by Vaughn and colleagues found no increased risk with the use of calcium channel blockers (OR = 1.0) but found a positive increased risk with the long-term use of certain asthma medications. The OR was 2.5 for theophylline use and 1.7 for β adrenergic agonists. In a large Swedish case-control study, Lagergren and colleagues found an increased risk of adenocarcinoma of the esophagus in long-term (> 5 years) users of LES-relaxing drugs. (Calcium channel blockers were not examined in that study.) No consistent association was seen with these drugs and the incidence of adenocarcinoma of the gastric cardia or squamous cell cancer of the esophagus. The authors concluded that ~10 percent of esophageal adenocarcinomas in Sweden might be caused by the long-term use of drugs that promote LES relaxation.

In addition, interest has focused on whether the use of acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs) might reduce the risk of some gastrointestinal-tract malignancies as it has reduced the risk of colon cancers. A population-based case-control study demonstrated a decreased risk of esophageal adenocarcinoma, non-cardia gastric tumors, and squamous cell carcinoma of the esophagus with the use of ASA and NSAIDs. An OR of 0.37 was found for esophageal...
adenocarcinoma in current users of ASA. Further investigation is needed to confirm these results.

The role of GERD, independent of Barrett’s esophagus, has been examined. Reflux is thought to increase cancer risk by promoting cellular proliferation and by exposing esophageal epithelium to potentially genotoxic gastric and intestinal contents.\textsuperscript{57} Lagergren and colleagues demonstrated a dose-dependent relationship between the symptoms of GERD and the development of adenocarcinoma of the esophagus and GE junction.\textsuperscript{60} Patients with recurrent symptomatic reflux had an OR of 7.7 for esophageal adenocarcinoma and 2.0 for gastric cardia adenocarcinoma. More frequent, more severe, and longer-lasting symptoms were associated with an even higher risk. In another population-based case-control study, the risk of esophageal adenocarcinoma increased with the increasing frequency of GERD symptoms, with an OR of 5.5 among patients with daily symptoms.\textsuperscript{61} No further increased risk was seen with the use of H\textsubscript{2} blockers.

**DIAGNOSIS AND STAGING**

Most patients with esophageal cancer present with advanced-stage disease. Symptoms at presentation include dysphagia, weight loss, and bleeding. Precise histologic diagnosis and accurate tumor staging are prerequisites for the selection of the most suitable treatment, especially if the patient is being considered for clinical trials.\textsuperscript{62}

Clinical staging is determined by the extent of disease, which is established by a variety of diagnostic tests and imaging studies. Pathologic staging is determined by evaluating a surgical specimen after resection. The most recent American Joint Committee on Cancer (AJCC) staging system, based on the primary tumor (T)–nodal involvement (N)–distant metastasis (M) system, is shown in Table 5-2. The current staging system has been criticized, and revisions have been suggested. Because this staging system is largely based on retrospective data from Japan, it is most applicable to patients with squamous cell tumors of the upper and middle thirds of the esophagus. In particular, the classification of involved celiac lymph nodes as M1 disease has been questioned. A recent study evaluating survival with respect to lymph node involvement demonstrated that both lymph node location and number significantly influenced survival.\textsuperscript{12} A proposed staging system that reserves M1 status for visceral metastases and reclassifies extensive lymph node metastases as N2 reflects prognosis more accurately than the current AJCC system.\textsuperscript{12}

A general schema for the work-up of esophageal and GE-junction adenocarcinomas is shown in Figure 5–5. The diagnosis of esophageal cancer and the assessment of a tumor’s longitudinal extent are usually accomplished by endoscopy with biopsy, with

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**Table 5-2. AMERICAN JOINT COMMITTEE ON CANCER STAGING FOR ESOPHAGEAL CANCER**

| Tumor-Node-Metastasis Staging |  |
|------------------------------|  |
| Primary tumor (T)            |  |
| TX: Primary tumor cannot be assessed |  |
| T0: No evidence of primary tumor |  |
| Tis: Carcinoma in situ       |  |
| T1: Tumor invades lamina propria or submucosa |  |
| T2: Tumor invades muscularis propria |  |
| T3: Tumor invades adventitia  |  |
| T4: Tumor invades adjacent structures |  |
| Regional lymph nodes (N)     |  |
| NX: Regional lymph nodes cannot be assessed |  |
| N0: No regional lymph node metastasis |  |
| N1: Regional lymph node metastasis |  |
| Distant metastasis (M)       |  |
| General                      |  |
| MX: Distant metastasis cannot be assessed |  |
| M0: No distant metastasis    |  |
| M1: Distant metastasis       |  |
| Tumors of the lower thoracic esophagus |  |
| M1a: Metastasis in celiac lymph nodes |  |
| M1b: Other distant metastasis |  |
| Tumors of the mid thoracic esophagus |  |
| M1a: Not applicable          |  |
| M1b: Nonregional lymph nodes and/or other distant metastasis |  |
| Tumors of the upper thoracic esophagus |  |
| M1a: Metastasis in cervical lymph nodes |  |
| M1b: Other distant metastasis |  |

**Stage groupings**

0: Tis, N0, M0
I: T1, N0, M0
IIA: T2, N0, M0
IIB: T1, N1, M0
IIIA: T3, N1, M0
IVA: any T, any N, M1a
IVB: any T, any N, M1b

emphasis on both orthograde and retroflexed views of the GE junction. Barium studies (Figure 5–6) are useful in evaluating the morphology of the tumor and have a high sensitivity (~98%) for demonstrating esophageal tumors. A barium swallow provides essential information concerning gastric anatomy, the location and extent of the lesion, and whether there is pathology proximal or distal to the primary lesion. Though rarely the case with adenocarcinomas, bronchoscopy is recommended to rule out tracheal invasion when tumors lie at or above the carina.

Once the histologic diagnosis of esophageal cancer is established, staging of the extent of disease is done. Computed tomography (CT) of the chest and abdomen is considered the initial imaging study of choice for evaluating lymph node metastases, distant metastases, and extraesophageal tumor infiltration into mediastinal organs (Figure 5–7). Abdominal ultrasonography and magnetic resonance imaging (MRI) are occasionally useful in evaluating liver metastases. The use of positron emission tomography (PET) for staging patients with esophageal adenocarcinoma has recently been reported. In an early experience, Flamen and colleagues found that PET significantly improves the detection of stage IV disease, compared to the combination of CT and endoscopic ultrasonography (EUS). Patients in whom distant metastases are found are candidates for palliative treatment.

Much investigation has been done in the past decade into the role of EUS in the locoregional staging of esophageal cancer. It is the most accurate diagnostic modality for locoregional staging, providing detailed images of the mass and its relationship with the layers of the esophageal wall. Most studies of EUS have included both adenocarcinomas

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**Figure 5–5.** Algorithm for the work-up of esophageal adenocarcinoma patients. (CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography; UTS = ultrasonography.)
CANCER OF THE UPPER GASTROINTESTINAL TRACT

and squamous cell carcinomas. Overall, EUS is highly accurate in predicting T stage and multiple studies have found it to be superior to CT for T stage evaluation\(^70\) (Figure 5–8, A and B). The accuracy of EUS for T staging ranges from 76 to 89 percent whereas the accuracy of CT for T staging is between 43 and 59 percent.\(^70,71\) Endoscopic ultrasonography tends to overestimate T stage, particularly in T1 and T2 lesions (perhaps secondary to peritumoral inflammation). Accuracy rates for N staging with EUS range from 72 to 80 percent, compared to a CT range of 46 to 58 percent\(^70\) (see Figure 5–8, C and D). Results from several single-institution studies appear in Table 5–3. The recent study by Salminen and colleagues includes only patients with adenocarcinoma of the distal esophagus and GE junction; its results were similar to those of prior studies. The conclusion of many of these studies is that although EUS has distinct advantages in staging tumors and planning therapy, it has limitations as well, and that caution must be exercised when deciding resectability on the basis of EUS as it tends to err in the direction of up-staging tumors.\(^72\) A more direct approach to evaluating regional lymph node involvement is with EUS-guided fine-needle aspiration (FNA). Reports show that this technique of tissue sampling is safe and effective\(^70\) (Figure 5–9). Reed and colleagues recently reported an 88 percent confirmation of node positivity with EUS-guided FNA when EUS identified suspicious celiac lymph nodes.\(^73\) This improvement in staging may help guide treatment in patients with locally advanced esophageal adenocarcinomas.

Some of the limitations of EUS (eg, the inability of the probe to pass through near-obstructing tumors, and an inability to differentiate between intramucosal and intramural tumors) are now being overcome with microprobe EUS. These probes, which can be passed through the working ports of standard endoscopes, have been shown to be safe and accurate, with a particularly improved ability to determine depth of invasion. A study by Murata and colleagues focused on the ability of microprobes to determine the depth of invasion of superficial tumors and found an overall accuracy of 75 percent.
and an 84 percent accuracy for predicting tumor containment by the lamina propria. A more recent comparative study looked at 53 stenosing tumors, 58 percent of which were adenocarcinomas, and examined the tumors with both conventional EUS and microprobe EUS microprobe sonography (MPS). Accuracy for both T and N staging markedly improved with the MPS device (T stage, 87% vs 62%; N stage, 83% vs 70%).

There have been several recent reports looking at the role of laparoscopy and thoracoscopy in staging esophageal cancer patients. Both modalities are used to determine suitability for surgical resection. In one study of laparoscopy, contraindications to resection included evidence of hepatic metastases, peritoneal involvement, extensive lymph node involvement, direct invasion of the liver or colon, and poor tolerance of laparoscopy. Using these criteria, 42 percent of 244 patients were found to have contraindications to resection (38% had contraindications secondary to advanced local or metastatic disease and 4% had contraindications secondary to poor tolerance of laparoscopy). Laparoscopy was highly effective in detecting hepatic metastases and had sensitivity, specificity, and overall accuracy of 96 percent, 100 percent, and 98 percent, respectively.

In a study from Stein and colleagues, diagnostic laparoscopy with laparoscopic ultrasonography and

<table>
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<th>Study, Year</th>
<th>Ref. No.</th>
<th>n</th>
<th>% Not Traversable with Probe</th>
<th>T Stage Accuracy (%)</th>
<th>N Stage Accuracy (%)</th>
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<td>Peters, 1994</td>
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<td>19</td>
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<td>82</td>
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<tr>
<td>Salminen, 1999</td>
<td>72</td>
<td>32</td>
<td>19</td>
<td>66</td>
<td>72</td>
</tr>
</tbody>
</table>

NA = not available; n = sample size.
peritoneal lavage was found to be safe and to frequently provide therapeutically relevant new information in patients with locally advanced adenocarcinoma of the distal esophagus or cardia. Studies of thoracoscopy have shown it to be effective in intrathoracic tumor-node-metastasis (TNM) staging, allowing evaluation of direct mediastinal invasion and mediastinal nodal status. The overall accuracy of thoracoscopy and laparoscopy for detecting lymph node involvement was 94 percent.

**PROGNOSIS, NATURAL HISTORY, AND PATTERN OF TUMOR SPREAD**

The prognosis of esophageal adenocarcinoma is highly dependent on stage and is quite poor overall since most tumors are advanced at presentation. As reported by the AJCC, the 5-year survival rates for both esophageal adenocarcinoma and squamous cell cancer are 68 percent for stage I, 35 percent for stage II, 18 percent for stage III, and 5 percent for stage IV. Overall 10-year survival for all patients with esophageal cancer was 12.3 percent. For adenocarcinoma of the GE junction, Steup and colleagues reported an overall 5-year actuarial survival rate of 33 percent in surgically treated patients. The 5-year survivals were 100 percent for stage I, 68 percent for stage II, 37 percent for stage III, and 10 percent for stage IV. A recent report on radical surgery for esophageal and GE-junction adenocarcinoma demonstrated an overall 5-year survival of 35.3 percent in surgically treated patients. Obviously, these figures do not reflect those patients who were ineligible for surgery.

A variety of factors have proved to have prognostic significance in esophageal and GE-junction adenocarcinoma. These are summarized in Table 5–4 and include T stage, N stage, M stage, positive esophageal margin at resection, R0 (no residual disease at surgery) versus R1 (microscopic residual disease)/R2 (macroscopic residual disease) resection, and occurrence of postoperative complications. The number of diseased lymph nodes and the ratio of involved to removed lymph nodes have shown prognostic significance in some studies.

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**Table 5–4. FACTORS INFLUENCING PROGNOSIS OF ADENOCARCINOMA OF THE ESOPHAGUS AND GASTROESOPHAGEAL JUNCTION**

<table>
<thead>
<tr>
<th>By Univariate Analysis</th>
<th>By Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>T stage</td>
<td>T stage</td>
</tr>
<tr>
<td>N stage</td>
<td>N stage</td>
</tr>
<tr>
<td>M stage</td>
<td>M stage</td>
</tr>
<tr>
<td>Number of disease nodes</td>
<td>R0 resection</td>
</tr>
<tr>
<td>Positive esophageal margin</td>
<td>Ratio of positive to removed nodes</td>
</tr>
<tr>
<td>Occurrence of postoperative complications</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Siewert et al., Steup et al., Thomas et al., Nigro et al.
Lymph node status appears to be the single most important factor for prognosis in esophageal adenocarcinoma. Figure 5–10 summarizes a number of these studies. In a report from Lerut, node-negative patients had a 5-year survival of 63 percent, compared with 12 percent for node-positive patients. Holscher and colleagues reported that in patients undergoing R0 resection for distal esophageal tumors, pN0 patients had a 63 percent 5-year survival compared to a 27.5 percent 5-year survival for pN1 patients (p < .02). Steup and colleagues, in a study of adenocarcinoma at the GE junction, found that the 5-year survival rate for node-negative patients was 72 percent, versus 16 percent for node-positive patients (p < .005). A study looking at the absolute number of positive lymph nodes in patients with GE-junction adenocarcinomas showed that patients with four or fewer involved lymph nodes had a statistically significant survival advantage compared to patients with more than four metastatic nodes (p < .05). In patients with transmural distal esophageal adenocarcinomas, Nigro and colleagues demonstrated that patients with more than four involved nodes had a worse prognosis than those with no positive nodes or one to four positive nodes.

Patterns of lymph node spread from the esophagus and esophageal cancer have been studied extensively. Siewert states that the embryologic development of the distal esophagus from the primitive intestinal loop dictates that lymph flow is primarily directed toward the large lymphatic collection area around the celiac axis. Tanabe used an injection of radiolabeled colloid into the esophageal wall to examine patterns of lymph flow (Figure 5–11). Injection into the midesophagus resulted in flow both up into the superior mediastinum and cervical nodes and down into the abdomen. Injection into the wall of the lower esophagus showed that the main direction of flow was down, into the abdomen. Reports of surgery for esophageal adenocarcinoma have documented the pattern of positive nodes in various nodal basins (Figure 5–12). A summary of these results is presented in Table 5–5. The percentage of positive nodes varies across these studies largely because of the different percentages of T stages included. A general pattern can be identified, with the highest rate of involved nodes being in the lower paraesophageal, paracardial (cardia of the GE junction), and parahiatal level and with lower rates of involvement of the splenic, hepatoduodenal, superior mediastinal, and cervical nodes.

The depth of invasion of the primary tumor is prognostically significant and correlates with nodal positivity. In the study by Holscher and colleagues, patients with pT1 tumors had a significantly better 5-year survival rate (83%) compared with those with pT2 tumors (36.8%) (p = .001), and the 5-year survival rate of the pT4 cases (7%) was significantly less than that for pT3 cases (27.5%) (p < .05). In that study, pT1 tumors had a low rate of nodal positivity.
Figure 5–11. Pattern of lymph flow from the esophagus. A, Flow from the midesophagus is both cephalad and caudad. B, Flow from the distal esophagus is principally caudad. (Adapted from Tanabe G, Baba M, Kuroshima K, et al. [Clinical evaluation of the esophageal lymph flow system based on RI uptake of dissected regional lymph nodes following lymphoscintigraphy]. Nippon Geka Gakkai Zasshi 1986;87:315–23.)

Figure 5–12. Lymph node distribution in esophageal cancer. Lymph node location code: 1 = lower paratracheal; 2 = subcarinal; 3 = paraesophageal; 4 = parahiatal; 5 = splenic hilum; 6 = splenic artery; 7 = greater curve; 8 = lesser curve; 9 = left gastric; 10 = hepatic; 11 = suprapyloric; 12 = portal; 13 = right gastric; 14 = retropancreatic. (Adapted from Nigro JJ, DeMeester SR, Hagen JA, et al. Node status in transmural esophageal adenocarcinoma and outcome after en bloc esophagectomy. J Thorac Cardiovasc Surg 1999;117:960–8.)
Adenocarcinoma of the Esophagus and Gastroesophageal Junction

(13.2%), significantly different from pT2 tumors (77%), pT3 tumors (83%), and pT4 tumors (96%) \( (p < .001) \). In a study from the University of Southern California (USC) by Clark and colleagues using the wall node metastasis (WNM) system, positive nodes occurred in 33 percent (2 of 6) of intramucosal tumors, 67 percent (6 of 9) of intramural tumors, and 89 percent (25 of 28) of transmural tumors \( (p < .01) \).

Three-field lymph node dissection (abdominal, mediastinal, and cervical) has been proposed by some surgeons who favor radical en bloc resections. When patients with esophageal adenocarcinoma have undergone three-field dissections, positive cervical nodes have been identified. In a study of three-field lymphadenectomies in 30 patients, half of whom had adenocarcinoma, Altorki found that 27 percent of the adenocarcinoma patients had occult cervical node metastases, irrespective of T status. In no patient with adenocarcinoma were the cervical nodes the only involved nodal basin. It has been suggested by Siewert that drainage of lymph into the cervical nodes occurs only when the aboral route is blocked by previous nodal metastases.

**MOLECULAR-BIOLOGIC ASPECTS**

In recent years, a variety of molecular studies have been carried out to increase understanding of the metaplasia-dysplasia-carcinoma sequence and to attempt to identify early markers of malignant transformation. The molecular and genetic abnormalities identified include deoxyribonucleic acid (DNA) content, growth factors, oncogenes, tumor-suppressor genes, adhesion molecules, microsatellite instability, and specific genetic anomalies. Of interest, several molecular factors that have been found to be important in some cancers (such as the \( Ras \) oncogene, the retinoblastoma (Rb) gene, and \( bcl-2 \)) have been found to play no definitive role in esophageal adenocarcinoma as yet.

**Phenotypic Abnormalities**

On the phenotypic level, increased expression or changes in patterns of expression in a number of molecular factors have been identified. Many studies have used immunohistochemical staining of spe-
specific antigens. A nuclear antigen that is expressed in proliferating cells (G1, S, G2, and M phases) but not in resting cells (G0 phase) is Ki-67. Hong and colleagues examined Ki-67 patterns in various degrees of dysplasia and adenocarcinoma. The pattern of Ki-67 nuclear staining correlated with the histologic findings, with increased size of the proliferative zone and spread of proliferation through the entire thickness of the epithelium in high-grade dysplasia and cancer ($p < .001$). Other studies have confirmed these results. It has been suggested that the Ki-67 staining pattern may represent an additional parameter for differentiating patients with dysplasia from those without dysplasia.

The overexpression of certain growth factors has been noted. Studies of epidermal growth factor receptor (EGFR) and transforming growth factor-α (TGF-α) show a steady increase from nonmetaplastic through adenocarcinoma tissues. One hundred percent of Barrett’s adenocarcinomas were positive for TGF-α, and 64 percent were positive for EGFR; EGFR expression correlated with poorer survival on univariate analysis. Data on the overexpression of c-erb B2 in Barrett’s dysplasia and adenocarcinoma are conflicting. While several studies have shown no change or a decreased expression of c-erb B2 in esophageal adenocarcinomas, other studies have demonstrated overexpression of c-erb B2. Hardwick and colleagues reported no immunostaining for nondysplastic columnar-lined esophagus whereas 26 percent (8 of 31) of adenocarcinomas stained positive for c-erb B2. They concluded that overexpression of c-erb B2 is a relatively late event in some Barrett’s adenocarcinomas. Flejou and colleagues found that 11 percent (7 of 66) of Barrett’s adenocarcinomas overexpressed c-erb B2 and that this correlated with a poorer prognosis.

Abnormally decreased expression of adhesion molecules has been documented in cases of esophageal adenocarcinoma. This altered expression is thought to lead to decreased cell-cell interaction, possibly increasing the propensity for metastases. Washington and colleagues studied specimens of Barrett’s esophagus (with and without dysplasia) and esophageal adenocarcinomas and found that abnormally decreased expression of β-catenin, α-catenin, and E-cadherin was significantly associated with higher degrees of dysplasia. Fourteen of 16 cases (87.5%) of high-grade dysplasia and 7 of 7 cases (100%) of intramucosal carcinoma showed abnormal expression of β-catenin, compared with 3 of 6 cases (50%) that were indefinite for dysplasia and 11 of 17 cases (65%) with low-grade dysplasia ($p = .022$). This alteration in adhesion molecules appears to occur relatively early in the dysplasia-carcinoma sequence.

Abnormalities in Deoxyribonucleic Acid Content

In Barrett’s epithelium, a sequence of DNA content changes has been identified along the metaplasia-dysplasia-carcinoma sequence, with an increased S phase in metaplasia, an increased tetraploid (4N) fraction in low-grade dysplasia, and aneuploidy in high-grade dysplasia and carcinoma. In a prospective cohort study, Reid and colleagues observed 62 patients with Barrett’s esophagus. Of 13 patients with aneuploidy or increased tetraploidy (4N) on initial flow cytometry, 9 developed high-grade dysplasia or cancer during follow-up (mean = 34 months). None of the 49 patients without these abnormalities progressed ($p < .0001$). This suggests that neoplastic progression in Barrett’s esophagus may occur in patients who have an acquired genomic instability that generates abnormal clones of cells. It has been suggested that flow cytometry for aneuploidy may help identify those patients who warrant more frequent endoscopic surveillance. In addition to aneuploidy, other cytogenetic abnormalities principally related to chromosome loss have been noted. Frequent losses of chromosomes 4, 18, 21, and Y have been noted. Few data exist, however, as to the sequence or timing of these losses.

Specific Genetic Abnormalities

Several specific gene alterations in Barrett’s esophagus and adenocarcinoma have been identified by single-strand confirmation polymorphism (SSCP), sequence analysis, immunohistochemistry, and other techniques. Of these, abnormalities in p53 at the gene and protein level have been most extensively studied.

The gene for p53 resides on the short arm of chromosome 17 (17p). Mutations in the p53 gene
are the most common mutations found in human cancers to date; approximately one-half of all human cancers contain a p53 mutation. The normal p53 protein has important regulatory functions related to the cell cycle and acts as a tumor suppressor. It has been referred to as the “guardian of the genome” because of its role in G1-S checkpoint regulation, DNA repair, and induction of apoptosis when repair is not possible. Loss of normal p53, therefore, leads to cell-cycle abnormalities, lack of DNA repair, and avoidance of apoptosis. Loss of normal p53 also results in increased angiogenesis, possibly due to a lack of thrombospondins.7

Data concerning p53 in the metaplasia-dysplasia-carcinoma sequence are many, although questions have arisen as to the reliability of some methods of detecting abnormal p53. Immunohistochemical detection of abnormal p53 is possible because mutated p53 accumulates in the cell nucleus; this has been the technique most commonly used. However, it is not specific because (1) normal p53 can be detected at times in the nucleus and (2) not all p53 mutations lead to an excess accumulation of protein. The most sensitive method is sequencing of DNA.7

Studies show that a loss of p53 function plays a role in the transition of Barrett’s metaplasia to dysplasia and cancer. This conclusion was first published in 1991 by Casson and colleagues, who identified p53 gene mutations in specific codons in both Barrett’s epithelium and adenocarcinomas.101 Since then, many investigators have confirmed abnormal p53, by immunohistochemical techniques and by SSCP/sequencing. The frequency of p53 mutation in high-grade dysplasia and adenocarcinoma ranges from 45 to 88 percent in various studies.7,102–105 The question of exactly when the p53 mutation occurs in the metaplasia-dysplasia-carcinoma sequence has been investigated. Data indicate that mutation of p53 is found only occasionally in metaplastic and low-grade dysplastic tissues. It has been hypothesized that mutation of p53 is an event in the progression to carcinoma in Barrett’s metaplasia, possibly following increased S phase and 4N fractions but preceding aneuploidy, thereby acting as a switch from low- to high-grade dysplasia106 (Figure 5–13). Gimenez and colleagues demonstrated a statistically significant increase in positive staining for p53 and abnormal cytometric data (increasing aneuploidy) throughout the metaplasia-dysplasia-carcinoma sequence, with a marked increase in p53 mutation in tissues with low- and high-grade dysplasia and with increased aneuploidy in high-grade dysplasia and adenocarcinoma.107 Mutations are generally found in exons 5 to 8, and the majority are CpG transitions.108,109 It has been suggested that p53 (along with other antibodies) could be helpful in the distinction between low-grade and high-grade dysplasia.110 Ribeiro and colleagues showed a positive correlation between p53 point mutations and pTNM stage (p = .03) as well as between p53 mutations and residual disease in the resected specimen, following neoadjuvant chemoradiotherapy (p = .01).105 Further, both overall survival (p = .0038) and disease-free survival (p = .0004) were significantly lower for patients with p53 mutations than for those without mutations105 (Figure 5–14). Other studies also have suggested an association between p53 overexpression and reduced overall survival.111,112

Other tumor-suppressor genes have been investigated, and these may play a role in the development of esophageal adenocarcinoma. These include p16 (chromosome 9q), APC (5q), and DCC/DPC (18q).100,113–117 Many of the studies of these genes have used the microsatellite analysis technique to identify sites of allelic loss or loss of heterozygosity (LOH). Studies of APC have shown that loss of APC occurs as a late event, after loss of p53, as opposed to its early loss in the colon cancer sequence.114

<table>
<thead>
<tr>
<th></th>
<th>Barrett’s alone</th>
<th>LGD</th>
<th>HGD</th>
<th>Adenoca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal p53</td>
<td>5.3%</td>
<td>20%</td>
<td>65.6%</td>
<td>64.7%</td>
</tr>
<tr>
<td>By IHC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 5–13. Protein p53 in Barrett’s esophagus. (Adenoca = adenocarcinoma; IHC = immunohistochemistry; HGD = high-grade dysplasia; LGD = low-grade dysplasia.) (Data from Ireland AP, Clark GW, DeMeester TR. Barrett’s esophagus. The significance of p53 in clinical practice. Ann Surg 1997;225:17–30.)
concerning LOH at 18q and 9q are variable; some investigators identify an early loss of chromosomal material, even in diploid cell populations\textsuperscript{115,116} whereas others find these abnormalities only as a late event.\textsuperscript{113,117} Attempts to further define the order of specific gene loss in the metaplasia-dysplasia-carcinoma sequence are ongoing. Figure 5–15 summarizes some of the proposed molecular and genetic changes in the malignant progression to esophageal adenocarcinoma.

**TREATMENT**

**Barrett’s Esophagous without Dysplasia or with Low-grade Dysplasia**

There are several components in the “treatment” of Barrett’s esophagus without dysplasia or with low-grade dysplasia. These include attempts to (1) treat its symptoms, (2) cause its regression, (3) prevent its progression, and (4) detect progression if it occurs. The components of a possible treatment plan for Barrett’s include a surveillance program, medical therapy, and surgical therapy. While all of these play a part in the successful management of Barrett’s esophagus, the exact role of each continues to evolve.

Many studies have shown that relief of symptomatic reflux can be achieved with both medical and surgical therapy although the significance of symptomatic relief has been questioned. Barrett’s esophagus is often asymptomatic or minimally symptomatic, and reflux of gastric and duodenal contents can persist even in the face of improved symptoms. The possibility that the columnar-lined esophagus may have decreased pain sensitivity has been raised as well.\textsuperscript{118} Treatment with proton pump inhibitors and H\textsubscript{2} blockers can lead to the complete eradication of symptoms, while esophageal pH remains abnormal. For this reason, some have recommended 24-hour pH monitoring to titrate drug doses.\textsuperscript{119} Also, proton pump and H\textsubscript{2} blocker therapy has no effect on bile reflux and may place esophageal pH into a range in which bile is more damaging to the mucosa.\textsuperscript{28} Prokinetic agents may assist in decreasing the bile reflux.

Both laparoscopic and open anti-reflux procedures are very effective in resolving symptoms, and abolishing both bile and acid reflux into the esophagus.\textsuperscript{37,120} Patti and colleagues showed that laparoscopic Nissen fundoplication led to resolution of heartburn in 95 percent of patients, of regurgitation in 93 percent of patients, and of cough in 100 percent of patients.\textsuperscript{120} A randomized study by the Department of Veterans Affairs assigned patients to either medical or surgical therapy for “complicated” GERD; both were effective for relief of symptoms and improved endoscopic signs of GERD, but in the initial report, surgical therapy was statistically significantly more effective ($p < .003$).\textsuperscript{121} However, a recently published follow-up report stated

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Figure 5–14. The influence of p53 status on survival in esophageal cancer patients. Overall (\textit{A}) and disease-free (\textit{B}) survival curves for patients with (\textit{broken line}) and without (\textit{solid line}) p53 mutations. (Reproduced with permission from Ribeiro U Jr, Finkelstein SD, Safatle-Ribeiro AV, et al. p53 sequence analysis predicts treatment response and outcome of patients with esophageal carcinoma. Cancer 1998;83:7–18.)
that at a median follow-up of ~7 years, the majority of patients in both groups were taking anti-reflux medications regularly and that there was no difference in the frequency of treatment for esophageal stricture between the two groups. Furthermore, there was no significant difference between groups in the incidence of esophageal cancer (~0.4% per year in patients with Barrett's esophagus at baseline, ~0.07% per year in those without Barrett's esophagus). Finally, survival at 140 months was significantly lower in the surgical group in comparison with the medical group. These findings at follow-up call into question the role of anti-reflux surgery in the era of proton pump inhibitor therapy, as well as the role of routine surveillance, given the extremely low incidence of adenocarcinoma in this high-risk population.

The next issue is the effect medical or surgical therapy has on the regression of Barrett's esophagus or on the prevention of progression. Data suggest that neither acid-suppression therapy nor anti-reflux surgery results in the predictable disappearance or regression of Barrett's esophagus. Malesci and colleagues found that 60 mg/d of omeprazole consistently improved gastric pH and decreased the amount of time that esophageal pH was < 4.0 over a 1-year period and that this resulted in a partial but significant regression in the length of Barrett's epithelium. However, investigators at the University of Arizona in Tucson found that both \text{H}_2 \text{ blocker therapy and proton pump inhibitor therapy} led to an improvement in symptoms but to no consistent reduction in the extent of Barrett's epithelium. Of 64 patients who underwent anti-reflux procedures at USC, 35 patients were unchanged, 12 had complete regressions (all had SSBE initially), 12 had partial length regressions, and 5 had progressions in length or degree of dysplasia. In a randomized study of medical versus surgical therapy for Barrett's esophagus, Ortiz and colleagues found that the length of Barrett's esophagus decreased more often after surgical therapy (25% vs 7%) and increased more commonly with medical therapy (40% vs 9%). Progression to low-grade dysplasia occurred in several patients on medical therapy and progression to high-grade dysplasia occurred in one patient on medical therapy and in one surgical patient after failed fundoplication. In a prospective study of treatment of Barrett's esophagus in the United Kingdom, Attwood and colleagues found that surgical therapy was statistically significantly superior to medical therapy for both the control of symptoms and the prevention of complications of Barrett's esophagus. However, progression to adenocarcinoma has been documented in the setting of both medical and surgical therapy. Therefore, surveillance is required regardless of the type of therapy undertaken.

The rationale for surveillance in Barrett's esophagus is clear: there is a documented 30 to 125 times increased risk of adenocarcinoma in people with Barrett's esophagus compared to the general population, and the disease is often fatal if discovered at an advanced stage. If a patient with Barrett's esophagus has a reasonable life expectancy and is a candidate for therapy, surveillance is mandatory since neither medical nor surgical therapy reliably protects against malignant degeneration. Though there are no con-
trolled trials, surveillance has been shown in several reports to increase survival. Peters and colleagues demonstrated that endoscopically surveyed patients had better outcomes postoperatively than nonsurveyed patients, principally secondary to earlier-stage tumors.128 Similarly, Streitz and colleagues found that endoscopically surveyed patients had tumors detected at an earlier stage and that this led to improved long-term survival,129 as was also the case in the report of Thomas and colleagues.83 Current published recommendations for surveillance are for “traditional” (ie, >3 cm in length) Barrett’s esophagus since adequate data on SSBE do not yet exist. The surveillance intervals suggested are based on the time to progression from metaplasia to dysplasia and cancer in a number of reports and are by no means absolute. Surveillance endoscopy should be accompanied by systematic biopsy (ie, four-quadrant biopsies done along at least every 2 cm of Barrett’s mucosa, with additional specific biopsies of any abnormal [eroded, ulcerated, nodular, strictured] mucosa). The current surveillance guidelines are summarized in Table 5–6. As discussed earlier, many different markers (DNA content, specific gene abnormalities, proliferative indices, etc.) have been investigated to assist in the discrimination of surveillance biopsy specimens, but none (besides histopathologic confirmation of dysplasia) have been proven to conclusively predict progression to adenocarcinoma.

A relatively recent development in terms of treatment for Barrett’s metaplasia is endoscopic mucosal ablation. The concept is to ablate the abnormal epithelium and allow squamous mucosa to re-epithelialize the area, thus obviating the cancer risk. This has been proposed for Barrett’s metaplasia and low-grade dysplasia as well as for high-grade dysplasia and intramucosal adenocarcinomas in high-risk patients. Various methods have been attempted, including chemical, thermal, and ultrasonic techniques. Common to all approaches is acid reflux suppression during healing, to optimize squamous regrowth. Early results with all modalities are promising although complications and recurrence are already recognized pitfalls.

Thermal ablation, by multipolar electrocoagulation or laser (argon, neodymium:yttrium-aluminum-garnet [Nd:YAG], neodymium:potassium titany/phosphate [KTP]), has been used with some success. In an early report from Berenson and colleagues, argon laser was used to ablate metaplastic tissue, with repeat endoscopy/ablation/biopsies every 2 to 5 weeks.130 This resulted in the partial or complete disappearance of columnar tissue and the re-epithelialization with squamous mucosa in 38 of 40 locations treated in 10 patients.130 Such results are complicated, however, by frequent relapse at 1 year (47%) despite proton pump inhibitor therapy and by the presence of residual Barrett’s glands under new squamous epithelium.130,131 In addition, the development of invasive adenocarcinoma under new squamous mucosa has been documented.132

Photodynamic therapy (PDT) uses a systemic photosensitizer (such as sodium porfimer [Photofrin] or 5-aminolevulinic acid [5-ALA]) and the intraesophageal application of light to chemically ablate abnormal mucosa.133 Initially used to treat severe dysplasia, this technique has been applied to metaplastic and low-grade dysplastic mucosa as well. Early studies that used Photofrin reported a high incidence of stricture formation (40 to 58%). Sensitivity to sunlight for several weeks after administration of Photofrin was a frequently reported side effect although this is avoided with newer agents such as 5-ALA. In a recent prospective randomized controlled trial, investigators in the United Kingdom randomized 18 patients to 5-ALA administration followed by laser endoscopy and 18 patients to placebo administration followed by laser endoscopy. A response was obtained in terms of decreased area (a median decrease in area of 30%) in 16 (89%) of 18 treated patients and the disappearance of low-grade dysplasia in 18 (100%) of 18 patients in the treated group. This compares favorably to a 10 percent decrease in area in 2 of 18 control patients (a

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**Table 5–6. RECOMMENDED SURVEILLANCE INTERVALS FOR BARRETT’S ESOPHAGUS**

<table>
<thead>
<tr>
<th>Dysplasia</th>
<th>Follow-Up Endoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>After 2 negative, every 2–3 years</td>
</tr>
<tr>
<td>Low grade</td>
<td>Every 6 months × 2, then every year</td>
</tr>
<tr>
<td>High grade</td>
<td>Immediate re-endoscopy and biopsy; expert confirmation; resection for surgical candidates</td>
</tr>
</tbody>
</table>

Adapted with permission from Sampliner RE. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett’s esophagus. The Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol 1998;93:1028–32.
median decrease in area of 0%) and the disappearance of dysplasia in 33 percent of the control group ($p < .001$). No side effects were seen, and the effects of treatment were maintained for up to 24 months. The investigators concluded that 5-ALA–induced PDT can provide safe and effective ablation of low-grade dysplastic epithelium.

The use of ultrasonic energy to ablate columnar mucosa has also been investigated. The Cavitron ultrasonic surgical aspirator can be used to ablate only the epithelium superficial to the muscularis mucosa. An advantage of this method is that tissue can be aspirated for cytologic studies, not destroyed as in the above techniques. At present, the use of this method has been reported only in animal models; all cases demonstrated complete squamous re-epithelialization and no stricture formation.

### Barrett’s Esophagus with High-Grade Dysplasia

The treatment of Barrett’s esophagus with high-grade dysplasia is controversial for several reasons. First, the diagnosis itself is difficult. Interobserver variation between pathologists is high, and confirmation of high-grade dysplasia by an experienced pathologist is prerequisite for any definitive therapy. Second, although high-grade dysplasia is a recognized premalignant condition, the timetable for the development of invasive adenocarcinoma is highly variable, and the natural history is less than completely understood. Sampliner and colleagues reported that 21 of 61 patients with high-grade dysplasia developed invasive adenocarcinoma over 0.2 to 4.5 years. In a prospective study by Hameeteman and colleagues, adenocarcinoma following low-grade and high-grade dysplasia developed in 1.5 to 4 years. Others have observed patients with high-grade dysplasia for up to 44 months without seeing the development of cancer. This has prompted a call for less aggressive intervention until invasive cancer is documented. Third, when invasive adenocarcinoma occurs, it can be fatal, prompting others to call for early aggressive therapy. The current options for treating high-grade dysplasia include esophagectomy, surveillance endoscopy with biopsy, and endoscopic mucosal ablation techniques.

The standard therapy for high-grade dysplasia in patients with acceptable operative risk is esophagectomy. Proponents of this approach base their argument on the fact that occult adenocarcinomas are found in 36 to 55 percent of esophagectomies for preoperatively diagnosed high-grade dysplasia. These are often (but not always) early-stage tumors, with an improved survival rate as compared to more advanced disease. In a report from Heitmiller and colleagues, 30 patients underwent esophagectomy for high-grade dysplasia, and 13 (43%) of these patients had invasive adenocarcinoma (8 patients with AJCC stage I, 2 patients with stage II, and 3 patients with stage III) (Figure 5–16).

![Figure 5–16. Pathologic findings at surgery for high-grade dysplasia.](image-url)
meta-analysis of the published results of 119 patients undergoing esophagectomy for high-grade dysplasia, Ferguson and Naunheim reported an operative mortality rate of 2.6 percent, a 47 percent incidence of invasive adenocarcinoma, and an 82 percent 5-year survival rate for patients with invasive carcinoma. Based on these results, many believe that esophagectomy for high-grade dysplasia is safe, effective, and necessary.

The surgical approach to esophagectomy may vary. Most surgeons accept a transhiatal esophagectomy with a gastric pull-up; others have done more radical resections, believing that the removal of lymph nodes has an impact on survival; still others have advocated vagal-sparing esophagectomy, with colon interposition for improved quality of life. No randomized studies exist to compare the outcomes of these various approaches.

Some argue that a procedure with the morbidity and mortality of esophagectomy should be done only for histologically proven invasive cancer. These investigators advocate surveillance endoscopy with systematic biopsy (following a specific protocol with four-quadrant biopsy specimens taken every 2 cm of metaplasia) as proper treatment for high-grade dysplasia. Levine and colleagues found that analysis of endoscopic biopsy specimens was accurate in detecting high-grade dysplasia and differentiating it from early adenocarcinoma in 50 patients studied, 28 of whom underwent surgery and 22 of whom had continued surveillance and biopsy. Furthermore, operative mortality was 14 percent (1 in 7) in patients with high-grade dysplasia only on final pathology whereas no patient in the observation group died from missed esophageal adenocarcinoma. A recent report from this group at the University of Washington revealed that a four-quadrant 1-cm biopsy protocol most consistently detects early cancers arising in high-grade dysplasia. (Intervals between endoscopies are individualized.) Critics of this approach claim that cancer will be missed during surveillance and will be advanced beyond the curable stage, leading to higher mortality, and that such intensive surveillance protocols are untenable in the nonuniversity setting.

Studies of endoscopic ablation for high-grade dysplasia have proliferated in recent years. Photodynamic therapy is the principal approach that has been used. Several studies have documented the eradication of high-grade dysplasia in the majority of patients treated, with squamous regeneration in the setting of acid suppression with a proton pump inhibitor. Some of these studies have been troubled by the occurrence of subsquamous islands of nondysplastic Barrett’s epithelium and, in one case, a subsquamous adenocarcinoma. In the PDT study by Overholt and colleagues, esophageal stricture occurred at a rate of 34 percent with Photofrin, but this has not been reported with 5-ALA. Endoscopic mucosal resection has been used and is addressed below. At present, the results of PDT are promising, but examination of the results of long-term follow-up is necessary before PDT can replace surgery as the standard therapy for high-grade dysplasia.

TREATMENT OF ADENOCARCINOMA OF THE ESOPHAGUS AND GASTROESOPHAGEAL JUNCTION

Esophageal Resection

Resection of the esophagus for treatment of esophageal cancer was first successfully performed in the early part of the twentieth century and became standard practice in the decades that followed. Torek used a transthoracic approach in 1913, and Denk described the concept of a transhiatal esophagectomy the same year. In 1933, Turner refined this “blunt” transhiatal technique. The first series of esophagectomy with immediate esophagogastrectomy was published by Ohsawa in 1933 and first reported in the United States by Adams and Phemister in 1938. Significant milestones in esophageal surgery since then include the description by Ivor Lewis of a combined right thoracotomy and laparotomy for esophagectomy in 1946 and Orringer’s re-introduction of Turner’s “esophagectomy without thoracotomy” in 1978.

At present, esophagectomy represents the only known potentially curative treatment for esophageal cancer, and it is the best palliative method as well. Surgery remains the primary treatment modality in the absence of known metastatic disease or medical
Adenocarcinoma of the Esophagus and Gastroesophageal Junction

Contraindications to surgery. The primary goal of treatment is a prolonged disease-free state, with relief of dysphagia. Outcomes vary with stage, and esophageal wall penetration and lymph node involvement rank as the major prognostic factors in almost all studies. Although survival rates vary between different studies, an approximate 20 percent overall 5-year survival rate is reported in the majority of series.

The choice of operation for adenocarcinoma of the esophagus and GE junction depends on several factors, which were summarized in a 1988 report by Mathisen. These include surgeon preference, tumor location, body habitus, prior operations, overall medical condition of the patient, choice of esophageal substitute, and history of prior radiation therapy.15 Much has been written and much controversy generated about the choice of surgical approach for esophageal cancer. The various approaches are listed in Table 5–7. Each of the major approaches, with their principal strengths and weaknesses, are summarized below, in Table 5–8, and in Figure 5–17, followed by what comparative data exist to assess the various techniques.

### Transhiatal Esophagectomy

Originally described by Denk in 1913 and Turner in 1933, “esophagectomy without thoracotomy” was reintroduced and popularized by Orringer, beginning with his 1978 publication. Orringer described undertaking the procedure in 22 patients with esophageal cancer but not with a curative intent. Since that time, the procedure and its results have been reported by Orringer and others as a choice in the armamentarium of potentially curative procedures for esophageal cancer. The purported advantages are as follows:

1. Cervical anastomotic leak is less devastating as it is rarely associated with mediastinitis.
2. Thoracotomy is avoided, leading to less pulmonary morbidity.
3. The procedure can be curative, with a reported survival equivalent to transthoracic or en bloc radical resection.

Opponents of this technique argue that complete lymphadenectomy is compromised with transhiatal esophagectomy and is a necessary component for resection of esophageal carcinoma, primarily for staging and possibly for cure.

Results of transhiatal esophagectomy have been reported widely although most extensively by Orringer. Mortality rates range from 4 to 7 percent, with a trend toward decreased mortality in the past decade. Common complications include pulmonary compromise (atelectasis, pneumonia, etc.) and anastomotic leak, with complications such as delayed gastric emptying, bleeding, gastric tube necrosis, recurrent laryngeal nerve paralysis, chy-
lo thorax, tracheal laceration, and pneumothorax occurring less frequently.\textsuperscript{157,165} Late complications include dumping syndrome, regurgitation, and dysphagia, often secondary to anastomotic stricture.\textsuperscript{157,165} Anastomotic strictures occur often in the setting of a prior cervical anastomotic leak and can be a major long-term problem. That pattern of complications led Orringer to explore techniques that would minimize

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{esophagectomy_diagrams.png}
\caption{Surgical approaches to esophagectomy. A, Transhiatal esophagectomy. B, Ivor Lewis esophagectomy. C, Left thoracotomy/thoracoabdominal approach. D, Laparoscopy assisted transhiatal esophagectomy.}
\end{figure}
the chances of anastomotic leak.\footnote{166} Using the side-to-side stapled technique, Orringer was able to decrease the leak rate from the 10 to 15 percent range, as seen in over 1,000 hand-sewn anastomoses, to 2.7 percent.\footnote{166} The survival rate for patients after transhiatal esophagectomy has been reported as in the range of 23 to 40 percent at 5 years.\footnote{87,157}

**Ivor Lewis Esophagectomy**

The combined right thoractomy and laparotomy for resection of esophageal cancer was first presented in 1946 by Ivor Lewis in the Hunterian Lecture to the Royal College of Surgeons.\footnote{153} Originally described as a two-stage procedure, the one-stage variation has been used routinely since that time and is described by many as the procedure of choice for lesions of the middle third of the esophagus.\footnote{167,168} The anastomosis can also be done in the neck, using a three-incision technique initially described in 1985 by McKeown, who used a right cervical incision.\footnote{169} Advantages of the combined abdominal and thoracic approach include direct visualization of the midportion of the esophagus and exposure for complete regional (thoracic) lymph node dissection, including the periesophageal, subcarinal, and upper mediastinal nodes. Disadvantages include the physiologic insult of combined chest and abdominal incisions and the risk of mediastinal anastomotic leaks, which historically have a high fatality rate.

Many series of esophagectomies via the Ivor Lewis approach have been reported; these were recently summarized (in comparison to transhiatal esophagectomy) by Rindani and colleagues.\footnote{164} Mortality rates range from < 2.0\% to 9.5 percent.\footnote{164} Over the last decades, these rates have dropped significantly with improvements in intraoperative and postoperative care. Complications include anastomotic leak, atelectasis/pneumonia, cardiovascular complications, wound infections, and chylothorax. While anastomotic leak in the thorax previously had an associated mortality rate of nearly 50 to 60 percent, the rate has now decreased due to improved intensive care practices and the wide application of parenteral or enteral nutritional supplementation. Late complications include anastomotic stricture, dysphagia, dumping syndrome, and reflux. Five-year survival rates for patients after Ivor Lewis esophagectomy for adenocarcinoma range from 8\% to 26 percent.\footnote{164,170}

**Left Thoracotomy or Left Thoracoabdominal Approach**

The left transthoracic approach to the lower esophagus is performed via a left lateral thoracotomy or a left thoracoabdominal approach. Historically, this has been an approach to tumors in the lower third of the esophagus and in the gastric cardia. Advantages include excellent exposure to the lower third of the esophagus and the fact that the patient does not need to be repositioned intraoperatively.\footnote{171} The disadvantages are that (1) the heart and aorta limit the proximal extent of the esophageal dissection and make intrathoracic anastomosis difficult, (2) the gastric drainage procedure and the Kocher maneuver can be difficult to perform via a left thoracotomy, and (3) postoperative reflux esophagitis occurs in many patients.

**Radical En Bloc Esophagectomy**

First proposed by Logan in 1963\footnote{172} in an attempt to apply accepted oncologic resection techniques to carcinoma of the esophagus and cardia, the radical en bloc esophagectomy has been championed by Skinner and associates\footnote{173,174} as well as by DeMeester\footnote{175} and Akiyama.\footnote{176} The objective of this approach is a more extensive removal of tissues adjacent to the esophagus in order to resect all nodal metastases. This approach adheres to Halsted's view that cancer progresses in an orderly fashion to the lymph nodes prior to becoming a systemic disease. Originally stated to be indicated for patients with limited (stage I to IIB) disease (by preoperative assessment), a recent paper from Altorki and Skinner supports it as the procedure of choice in stage III disease as well.\footnote{174} Supporters claim (1) that a more complete cancer resection decreases the likelihood of local recurrence and improves long-term survival without substantial morbidity or mortality, (2) that the technique allows better and more accurate staging, and (3) that prolonged survival and even cure may occasionally be possible after extended lymphadenectomy with positive nodes. Detractors state that “radical” esophagectomy has no
clear survival advantage over any other approach and that considerable postoperative complications are associated with this approach. To date, no randomized trials exist comparing this radical approach to any other surgical approach.

The overall principles of the approach include proximal and distal margins of at least 10 cm whenever possible, with total excision of adjacent tissues with the arterial and venous supply and lymphatic drainage. For tumors of the lower third of the esophagus or at the GE junction, the spleen, a large portion of stomach, and a rim of diaphragm are routinely removed. In the chest, the azygous vein, thoracic duct, and a portion of pericardium and pleura are taken en bloc. Either the remaining stomach or a colon interposition can be used to restore gastrointestinal continuity. A cervical anastomosis and possibly a cervical lymph node dissection may be included in the procedure. An extensive mediastinal and abdominal lymph node dissection is an important aspect of the radical resection.

Mortality rates for the radical operation range from 2.4 to 11.0 percent in institutions that commonly perform the procedure. Complications occur in ~50 percent of cases and include respiratory and cardiac problems, anastomotic leak, chylothorax, and ischemia or necrosis of the esophageal substitute.

Three-Field Lymphadenectomy

The three-field lymphadenectomy approach, which stresses the dissection of lymph nodes in the abdomen, mediastinum, and cervical region, is a variation of the radical esophagectomy. This technique was pioneered at several Japanese centers after recurrence was noted in cervical lymph nodes in 30 to 40 percent of patients in which abdominal and mediastinal lymph nodes had been dissected. Interesting data as to the pattern of lymph node spread have been generated, including the fact that metastases to the cervical nodes occurred in 20 percent of tumors of the lower third of the esophagus. Those who support this technique state that survival is improved after three-field resection, compared to survival after two-field resection. Detractors point out that all of the survival data are derived from non-controlled retrospective series; that the worth of lymphadenectomy, especially distant lymph node excision, has never been proven; and that greater morbidity (particularly secondary to paralysis of the recurrent laryngeal nerve) is common with this more extensive procedure.

Total Gastrectomy for Tumors at the Gastroesophageal Junction

Recently, Siewert and colleagues reported on surgery in 1,002 patients with GE-junction tumors. For type II and type III tumors, an extended total gastrectomy was recommended, with transhiatal resection for distal esophageal tumors only. The extended total gastrectomy is done via a midline laparotomy only, and an extensive lymph node dissection similar to that suggested for gastric cancer is performed. An esophagojejunostomy is done to restore gastrointestinal continuity.

Choice of Esophageal Substitute

With resection of the esophagus, a substitute must be fashioned to traverse the mediastinum. In the early part of the twentieth century, this was sometimes accomplished with rubber tubing (either externally or subcutaneously). At present, there are typically two choices for esophageal substitute: the stomach or the colon. Both have advantages and disadvantages.

The stomach is now considered the preferred substitute following esophageal resection. The stomach has the advantage that gastrointestinal continuity is restored with a single anastomosis. Given the potential morbidity and mortality of an anastomotic leak, this is a serious consideration. Further, the gastric mobilization is technically easier than the colonic mobilization, and the blood supply of the gastric remnant is more consistent and reliable than that of the colon. However, the stomach may not be available or appropriate in the setting of prior gastric surgery or severe ulcer disease. Additional disadvantages include the fact that reflux esophagitis and stricture formation occur with gastric substitutes, especially with an intrathoracic anastomosis.

The colon is an excellent esophageal substitute when needed. Either the right or left colon can be used although the left is better suited to the intrathoracic transposition. This can be done via either a
substernal or posterior mediastinal route. The advantages include the colon's availability in cases in which the stomach cannot be used and the ability to place the substitute in an isoperistaltic orientation to minimize reflux. The disadvantages include the fact that the colon can become elongated and redundant, leading to obstructive symptoms, and that this procedure is more difficult technically and requires a total of three anastomoses (esophagocolic, cologasttric, and colocolonic).

**Laparoscopic Esophagectomy**

As laparoscopic and thoracoscopic techniques and instrumentation have improved, the ability to do more complex procedures has increased. Laparoscopic and thoracoscopic approaches to esophagectomy for cancer and high-grade dysplasia have been reported. A variety of approaches have been used, including endoscopic Ivor Lewis esophagectomy,\textsuperscript{178} combined laparoscopic and thoracoscopic techniques,\textsuperscript{179,180} completely laparoscopic transhiatal esophagectomy,\textsuperscript{179,181,182} and hand-assisted laparoscopic transhiatal esophagectomy.\textsuperscript{183} Overall, feasibility has been demonstrated. The potential advantages include lower morbidity and mortality and better patient tolerance of the procedure (shorter recovery times, etc.). Survival results are pending.

**Endoscopic Techniques for Early Esophageal Adenocarcinoma**

Endoscopic resection techniques have been attempted in patients with early-stage esophageal adenocarcinoma, as they have for patients with high-grade dysplasia. Indications include small (< 2 cm), superficial (intramelithelial or microinvasive, not into submucosa), and early (N0) tumors in high-surgical-risk patients and in those refusing surgery. Endoscopic ultrasonography staging is essential, with the high-frequency (20 MHz) probe preferred. Treatment options include resection or destruction of the tumor. Resection is done by endoscopic mucosal resection (EMR) (Figure 5–18), which provides tissue for

![Figure 5–18. Endoscopic mucosal resection (EMR) of intramucosal adenocarcinoma. A. Patch of intramucosal adenocarcinoma in Barrett's esophagus at 25 cm from incisors. B. HFUS (20 MHz), showing no invasive disease. C. Periphery of lesion is marked for resection with BICAP. D. Site after EMR with strip biopsy technique. At a 2-year follow-up, there was no recurrence at the site with Barrett's epithelium only. (Courtesy of I. Waxman, MD.)](image)
pathologic evaluation; this is done by piecemeal excision, using a plastic overtube and snare electrosca
tery. Early results from Japan demonstrated the effective removal of superficial cancers, with a 6.8 per
cent rate of major complications (hemorrhage, perforation, and stenosis), a 3 to 7 percent local recur-
rence rate, and a 5-year survival rate of 80 percent.185

Tumor destruction is accomplished by either Nd:YAG laser or PDT. These are easier to perform than EMR, but no pathologic specimen is obtained. The experience for both modalities in early cancer is limited, but reports demonstrate the effective ablation of cancer in 73 percent of cases with Nd:YAG laser and in 87 percent of cases using PDT. Overall, these procedures must be viewed as experimental, given the inaccuracies of preoperative staging modalities in differentiating mucosal from submucosal tumors.

**Results of Surgery**

Mortality rates following esophageal resection in recent series range from 2 to 10 percent; the accept-
able 30-day mortality is approximately 5 percent.13,15,157 Overall, this does not vary greatly among the surgical techniques used.164 Frequently seen complications of esophageal resections (for all patholo-
gies) with the transhiatal and Ivor Lewis approaches are summarized and compared in Table 5–9. Pul-
monary complications are the most frequent. Anastomotic leak is also a commonly reported complica-
tion, with rates varying from 0 to 15 percent.157 In the summary report of Rindani and colleagues, anas-
tomotic leaks occurred more frequently in the transhiatal group (16%) than in the transthoracic group
(10%). Similarly, the rate of recurrent laryngeal nerve injury was slightly higher with the transhiatal approach (11.2%) than with the transthoracic approach (4.8%).164 Postoperative mortality (ie, 30-
day mortality) was higher in the transthoracic group (9.5%) than in the transhiatal group (6.3%).164

Survival after esophagectomy for adenocarci-
noma of the esophagus and gastroesophageal junction is dependent on stage, as discussed above.
Table 5–10 presents a summary of complications and survival in a number of series looking exclusi-
avely at adenocarcinoma of the esophagus and GE junction. Five-year survival rates range from 13 to 34 percent.63,81,83,84,129,188,189

The issue of whether one surgical approach is superior to another has been debated in the literature for decades. No randomized trials exist comparing one technique with another for adenocarcinoma of the esophagus and GE junction. Two prospective ran-
domized trials in squamous cell carcinoma of the esophagus have shown no differences in morbidity, 30-day mortality, or long-term survival between transhiatal and transthoracic techniques.158,159 Many retro-
spective series have been reported of single-institution experiences with transhiatal and transthoracic esophagectomy, usually for a mixture of histologies. These have shown no differences between the tran-
shiatal and transthoracic approaches with respect to operative mortality or overall survival.160–162 The summarized results of comparative trials published by Rindani and colleagues confirm the similarity in overall survival, with a 5-year survival of 24 percent for transhiatal esophagectomy and 26 percent for Ivor Lewis esophagectomy.164 Reports of improved sur-
vival with radical extended en bloc resections have involved highly selected patients and are impossible to interpret. All the existing data point to the conclusion that one technique is not superior to another oncologically and that the surgical approach is to be individualized according to patient factors (location and extent of tumor, body habitus, prior surgery, medical condition) and surgeon factors (preference, expe-
rience). As stated by Pairolero of the Mayo Clinic, “[t]he operation for cancer of the esophagus is local
therapy. The debate about which operation is better should be laid to rest once and for all as we try to achieve better control of this malignancy.”15

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**Table 5–9. MORBIDITY AND MORTALITY AFTER ESOPHAGECTOMY**

<table>
<thead>
<tr>
<th>Mortality and Morbidity</th>
<th>Transhiatal (%)</th>
<th>Ivor Lewis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day mortality</td>
<td>6.3</td>
<td>9.5</td>
</tr>
<tr>
<td>Respiratory complications</td>
<td>24.0</td>
<td>25.0</td>
</tr>
</tbody>
</table>
| Cardiovascular complica-
| tions                  | 12.4           | 10.5          |
| Wound infection         | 8.8            | 6.2           |
| Chylothorax             | 2.1            | 3.4           |
| Anastomotic leak        | 16.0           | 10.0          |
| Anastomotic stricture   | 28.0           | 16.0          |
| Recurrent laryngeal nerve injury | 11.2 | 4.8 |

MULTIMODALITY THERAPIES FOR ADENOCARCINOMA OF ESOPHAGUS AND GASTROESOPHAGEAL JUNCTION

Given the overall poor prognosis obtained with surgery alone, especially for advanced-stage tumors, other strategies have been used to improve survival in patients with adenocarcinoma of the esophagus and GE junction. These strategies include neoadjuvant chemoradiotherapy, neoadjuvant chemotherapy, and chemoradiotherapy alone as primary treatment. Many of these studies combined patients with adenocarcinoma and squamous cell histologies; few examined adenocarcinoma exclusively. The rationales, results, and conclusions of these approaches will be reviewed briefly.

Neoadjuvant Chemoradiotherapy Followed by Surgery

The theoretical foundations of neoadjuvant chemoradiotherapy include the following:

1. Local control will be better than chemoradiotherapy alone because residual disease is removed.
2. Regional control will be better because the chemoradiotherapy will eradicate disease that might remain at the margins of resection.
3. Distant control will improve after early exposure to chemotherapy, eliminating occult micrometastatic disease.

Important components in planning for neoadjuvant chemoradiation include accurate staging, drug choice, and method of administration.

Neoadjuvant chemoradiation for esophageal cancer has been studied in numerous phase II trials and in several phase III trials. Upon examination of the phase II trials, several principles emerge. Responses were seen with many regimens, and pathologic complete responses occurred in ~24 to 40 percent of cases. These protocols used 5-fluorouracil (5-FU) and cisplatin, with and without additional agents that include vinblastine, etoposide, and interferon-α (IFN-α). Radiation was given concurrently, with doses ranging from 40 to 45 Gy. Improvement in survival has been seen in comparison to historical controls. Further, in patients with pathologic complete responses, survival was improved when compared to those with residual disease at surgery. An exemplary phase II study was that carried out at Johns Hopkins Hospital by Forastiere and colleagues. In a study of 50 patients, 33 had adenocarcinoma of the esophagus. All were staged by preoperative CT and contrast esophagography. Neoadjuvant treatment included cisplatin, 5-FU, and 44 Gy of radiation. Two deaths occurred preoperatively, and there was a 94 percent operability rate and a 90 percent resectability rate. No operative mortality occurred. The pathologic complete response rate was 40 percent. Median survival was 31 months, and the 2-year survival was 58 percent, which compared favorably with institutional controls. Survival analysis by histologic type showed no difference between squamous cancers and adenocarcinoma. Survival by pathologic response did show a significant difference: the 2-year survival with pathologic complete response (CR) was 78 percent (median survival, 58 months) compared with a 2-
year survival of 46 percent with positive pathology (median survival, 22.4 months).  

Two prospective randomized trials of neoadjuvant chemoradiotherapy have included patients with adenocarcinoma, and the results were conflicting. The often cited study by Walsh and colleagues included only patients with adenocarcinoma; these patients were randomized to surgery alone or to preoperative treatment with 5-FU, cisplatin, and 40 Gy of radiation. The pathologic complete-response (pCR) rate was 25 percent. Median survival in the multimodality-treated group was 16 months as compared to 11 months in the surgery-alone group \( (p = .01) \) (Figure 5–19, A). Three-year survival was 32 percent in the multimodality group and 6 percent in the surgery-alone group \( (p = .01) \). This study has been criticized for inadequate prerandomization staging methods, for including both esophageal and cardia adenocarcinoma, and for including patients with early-stage disease. Also, the 6 percent 3-year survival rate with surgery alone is well below that of most historical controls.

A much anticipated study from a group at the University of Michigan was published recently. This study was based on the promising results of a phase II trial at that institution. In the pilot study, half (21) of the 43 patients had adenocarcinoma. The median survival of patients treated with intensive cisplatin, fluorouracil, and vinblastine concurrently administered with 45 Gy of radiation was 29 months, compared to a 12-month median survival in historical institutional controls. Histologic complete responders had a 70-month median survival. Based on these results, a prospective randomized trial was designed comparing transhiatal esophagectomy to treatment with cisplatin, 5-FU, vinblastine, and radiation (45 Gy) followed by transhiatal esophagectomy. The study included 100 patients with esophageal cancer, 75 of whom had adenocarcinoma. The results showed no significant difference in survival between the two arms at a median follow-up of 8.2 years. Median survival was 17.6 months in the surgery-alone arm and 16.9 months in the combined-therapy arm. Three-year survival was 16 percent with surgery alone and 30 percent for combination therapy, but this was not statistically significant \( (p = .15) \) (see Figure 5–19, B). The study has been criticized for including patients with positive celiac nodes and for being inadequately powered to detect small yet potentially clinically significant differences in outcome. At present, neoadjuvant chemoradiotherapy remains an experimental approach, to be pursued in the clinical trial setting. Large randomized trials will be necessary to show a benefit if one exists. New agents, including paclitaxel, are under investigation in phase II studies but have yet to be tested widely.

**Neoadjuvant Chemotherapy Followed by Surgery**

Preoperative chemotherapy alone, without concurrent radiation, has been investigated extensively. Two advantages are that the intact primary can be used to determine sensitivity to a specific chemotherapy regimen and that chemotherapy is introduced early to act against microscopic distant disease. The combination of 5-FU and cisplatin produces an objective response rate (> 50% tumor shrinkage) in approximately 50 percent of patients in several phase II studies. However, complete responses occur in only 5 percent.

Several small randomized trials have investigated these regimens versus surgery alone, primarily for squamous cell carcinoma of the esophagus. Response rates of ~50 percent and no benefit for survival were found common to all three trials. A larger intergroup trial was reported in 1998. In this prospective trial, 440 patients with either squamous cell carcinoma or adenocarcinoma were randomized to surgery alone or to preoperative chemotherapy with cisplatin and 5-FU followed by surgery. No differences were found in median survival (14.9 months vs 16.1 months) or 2-year survival (35% vs 37%). No differences were found between squamous cell carcinoma and adenocarcinoma responses, and there was no increase in operative morbidity in patients who received preoperative chemotherapy. In summary, neoadjuvant chemotherapy can lead to response rates of ~50 percent, but complete responses are rare, and no survival advantage has been identified to date.

**Chemoradiotherapy without Surgery for Locally Advanced Disease**

Interest in nonsurgical approaches to potentially resectable esophageal cancer developed in the 1980s...
in response to poor 5-year survival rates in some surgical series and high surgical mortality rates that sometimes exceeded the percentage of 5-year survivors. These studies generally combined external beam radiation with multiagent chemotherapy in order to target distant disease and to enhance radiation effects locoregionally. Higher doses of radiation were used than in the neoadjuvant setting. Several phase II trials (mostly involving patients with squamous cell cancer) supported feasibility and effect. This prompted a multicenter intergroup phase III study. Initially restricted to patients with squamous cell cancer, patients with adenocarcinomas were added after the 1st year of the trial, and these ultimately made up 15 percent of the overall study population of 192 patients. This study, most recently reported by Cooper in 1999, included patients with locally advanced esophageal cancer (T1–3, N0–1, M0) who were treated with 50 Gy of radiation concurrent with cisplatin and 5-FU, with additional postradiation chemotherapy, versus patients treated with 64 Gy of radiation alone. An additional group of patients received combination therapy after the period of randomization; this group is reported separately in the final analysis. The results demonstrated a survival benefit of combined-modality treatment greater than that of radiation alone, with 5-year survivals of 26 percent and 0 percent and median survivals of 14.1 months and 9.3 months ($p < .001$), respectively. No statistical difference was seen in relation to histologic type. Of note, local disease persisted in 26 percent of the combined-modality group, and locoregional failures alone occurred in an additional ~16 percent, accounting for the majority of treatment failures (Table 5–11). Results from trials examining the worth of preoperative chemoradiotherapy confirm that the vast majority of patients have residual disease following induction chemoradiotherapy. These data strongly suggest that definitive chemoradiotherapy should not be used to treat potentially resectable disease but should be reserved for patients with T4 disease or with medical risks that preclude surgery.

### Treatment for Metastatic Adenocarcinoma of the Esophagus and Gastroesophageal Junction

Many patients with adenocarcinoma of the esophagus and GE junction have inoperable disease at the time of diagnosis (70 to 80% in the Western Hemisphere), contributing to the grim prognosis for esophageal adenocarcinoma. Numerous options exist for palliative treatment of these patients,
including chemotherapy, radiation, and local endoscopic therapies. Effective chemotherapy regimens exist for metastatic esophagogastric carcinoma. A recent study of therapy with the combination of epirubicin, cisplatin, and fluorouracil (ECF) reported overall response rates of 61 percent (11% CR) and acceptable toxicity.205 A randomized trial comparing the ECF regimen with the standard combination of 5-FU, doxorubicin (Adriamycin), and methotrexate (FAMTX) for patients with advanced esophagogastric cancer showed improved response and survival for ECF, with additional benefits in quality of life and cost-effectiveness. Patients receiving ECF had an overall response rate of 45 percent, versus 21 percent for patients receiving FAMTX ($p = .0002$).206 The median survival was 8.9 months with ECF and 5.7 months with FAMTX ($p = .0009$), and the 1-year survival was 36 percent with ECF, versus 21 percent with FAMTX.206

Local palliative options exist as well, with the goal of improving quality of life by improving swallowing ability. Options include palliative surgery, esophageal dilatation, esophageal stenting, PDT, Nd:YAG laser excision, endoesophageal BICAP cauterization, local injection therapies, and brachytherapy.207 Radiochemotherapy has been attempted for metastatic disease, with some success.208,209 Treatment decisions for patients with advanced disease should be individualized, with a clear understanding of the goals of therapy.

**CONCLUSION**

Exploring the biologic basis of adenocarcinoma of the esophagus and GE junction will be central to expanding and improving the therapeutic options necessary to alter the natural history of this disease. The urgency for defining effective treatment is more pronounced when it is apparent that the incidence of esophageal adenocarcinoma continues to increase at an alarming rate. Properly designed clinical trials will be crucial to confirm the promise of novel therapeutic agents and approaches developed in the laboratory. Focusing on active prevention and targeting known premalignant conditions will likely constitute a high-yield endeavor.

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