

REVIEW ARTICLE

MEDICAL PROGRESS

Esophageal Cancer

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ESOPHAGEAL CANCER IS ONE OF THE LEAST STUDIED AND DEADLIEST cancers worldwide. During the past three decades, important changes have occurred in the epidemiologic patterns associated with this disease. Recent advances in the diagnosis, staging, and treatment of this neoplastic condition have led to small but significant improvements in survival. These new observations serve as the focus of this review.

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INCIDENCE

Cancers arising from the esophagus, including the gastroesophageal junction, are relatively uncommon in the United States, with 13,900 new cases and 13,000 deaths anticipated in 2003.¹ The lifetime risk of this cancer is 0.8 percent for men and 0.3 percent for women.² The risk increases with age, with a mean age at diagnosis of 67 years.^{2,3} Esophageal cancer is the seventh leading cause of death from cancer among American men, particularly black men, who have a higher incidence of this disease (13 cases per 100,000 persons) than do men in other racial or ethnic groups.² Worldwide, esophageal cancer is the sixth leading cause of death from cancer.⁴

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PATHOLOGIC PROCESS

More than 90 percent of esophageal cancers are either squamous-cell carcinomas or adenocarcinomas.³ On rare occasions, other carcinomas, melanomas, leiomyosarcomas, carcinoids, and lymphomas may develop in the esophagus as well. Approximately three quarters of all adenocarcinomas are found in the distal esophagus, whereas squamous-cell carcinomas are more evenly distributed between the middle and lower third.^{3,5} The cervical esophagus is an uncommon site of disease.

The pathogenesis of esophageal cancer remains unclear. Data from studies in animals suggest that oxidative damage from factors such as smoking or gastroesophageal reflux, which cause inflammation, esophagitis, and increased cell turnover, may initiate the carcinogenic process.⁶ Once cancer develops, it may spread rapidly; 14 to 21 percent of submucosal cancers (T1 lesions) and 38 to 60 percent of cancers that invade muscle (T2 lesions) are associated with spread to lymph nodes.^{5,7} At the time of the diagnosis of esophageal cancer, more than 50 percent of patients have either unresectable tumors or radiographically visible metastases.

ETIOLOGIC FACTORS

Smoking is associated with an increased risk of both squamous-cell carcinoma and adenocarcinoma of the esophagus (Table 1).^{8,9} The ingestion of tobacco condensates is thought to bring tobacco carcinogens, particularly nitrosamines, in contact with the esophageal mucosa.¹⁰ The risk of esophageal cancer correlates directly with the quantity of cigarettes smoked per day and the duration of smoking.^{8,9}

Table 1. Risk Factors for Esophageal Cancer.*

Risk Factor	Squamous-Cell Carcinoma	Adeno-carcinoma
Tobacco use	+++	++
Alcohol use	+++	—
Barrett's esophagus	—	++++
Weekly reflux symptoms	—	+++
Obesity	—	++
Poverty	++	—
Achalasia	+++	—
Caustic injury to the esophagus	++++	—
Nonepidermolytic palmoplantar keratoderma (tylosis)	++++	—
Plummer–Vinson syndrome	++++	—
History of head and neck cancer	++++	—
History of breast cancer treated with radiotherapy	+++	+++
Frequent consumption of extremely hot beverages	+	—
Prior use of beta-blockers, anticholinergic agents, or aminophyllines	—	±

* A single plus sign indicates an increase in the risk by a factor of less than two, two plus signs an increase by a factor of two to four, three plus signs an increase by a factor of more than four to eight, and four plus signs an increase by a factor of more than eight. The plus–minus sign indicates that conflicting results have been reported, and the dashes indicate that there is no proven risk.

A history of radiotherapy to the mediastinum, such as for the treatment of breast cancer, lymphoma, and other neoplasms, also predisposes patients to both histologic types of esophageal cancer. Such cancers typically develop 10 or more years after exposure to radiation.¹¹

SQUAMOUS-CELL CARCINOMA

CHRONIC IRRITATION

Any factor that causes chronic irritation and inflammation of the esophageal mucosa appears to increase the incidence of squamous-cell carcinoma of the esophagus. Substantial alcohol intake, especially in combination with smoking, greatly increases the risk of squamous-cell carcinoma (but not adenocarcinoma),^{8,9} and may account for more than 90 percent of all cases of squamous-cell carcinoma of the esophagus in the developed world.⁹ The combination of smoking and alcohol abuse is associated with a similarly increased risk of head and neck cancer; indeed, clinically unsuspected squamous-

cell carcinoma of the esophagus is discovered incidentally in approximately 1 to 2 percent of patients with head and neck cancers.¹²

Other causes of chronic esophageal irritation include achalasia and esophageal diverticuli, in which food is retained and decomposed by bacteria, releasing various chemical irritants.^{13,14} In several countries, frequent consumption of extremely hot beverages appears to increase the incidence of squamous-cell carcinoma.^{15,16} Persons who have ingested lye or other caustic fluids should be monitored carefully for the development of this cancer.¹⁷

GENETIC PREDISPOSITION

Although familial clusters of esophageal cancer have been reported in several countries, nonepidermolytic palmoplantar keratoderma (tylosis), a rare autosomal dominant disorder defined by a genetic abnormality at chromosome 17q25, is the only recognized familial syndrome that predisposes patients to squamous-cell carcinoma of the esophagus.¹⁸ It is characterized by hyperkeratosis of the palms and soles, as well as by thickening of the oral mucosa, and in affected families, it confers up to a 95 percent risk of squamous-cell carcinoma of the esophagus by the age of 70 years.¹⁹

OTHER ASSOCIATIONS

Squamous-cell carcinoma (but not adenocarcinoma) is clearly linked to a low socioeconomic status.⁹ Deficiency syndromes associated with this cancer, such as the Plummer–Vinson syndrome, which is characterized by dysphagia, iron-deficiency anemia, and esophageal webs, are becoming increasingly rare in the developed world as overall nutrition improves.²⁰

ADENOCARCINOMA

GASTROESOPHAGEAL REFLUX DISEASE

Persons with recurring symptoms of reflux have an eightfold increase in the risk of esophageal adenocarcinoma.²¹ Other markers of gastroesophageal reflux disease, such as hiatal hernia, esophageal ulcer, and frequent use of antacids or histamine-H₂ blockers, are also associated with an increased risk but do not appear to be independent risk factors.²² Drugs that relax the gastroesophageal sphincter and increase reflux, such as anticholinergic agents, aminophyllines, and beta-blockers, may contribute to the development of up to 10 percent of these cancers (Table 1).^{23,24} It has been postulated that *Helicobacter*

Helicobacter pylori infection (particularly strains that are positive for the CagA protein) may reduce the risk of severe gastroesophageal reflux disease,^{25,26} thereby providing protection against the development of esophageal adenocarcinoma; this hypothesis remains unproven.^{27,28}

OBESITY

The increasing prevalence of obesity in the Western world is thought to add to the rising incidence of esophageal adenocarcinoma.^{8,24,29} It has been postulated that obesity increases intraabdominal pressure and gastroesophageal reflux, although one recent study provided contradictory results, and another found this hypothesis to be true only in women.^{30,31}

BARRETT'S ESOPHAGUS

Pathological Findings

Barrett's esophagus (characterized by abnormal "tongues" of salmon-colored mucosa extending proximally from the gastroesophageal junction into the normal pale esophageal mucosa) develops in approximately 5 to 8 percent of patients with gastroesophageal reflux disease.³² Barrett's esophagus may also occasionally occur in patients without symptoms of chronic reflux.³³ Microscopically, Barrett's esophagus is defined as the replacement of the normal stratified squamous epithelium of the distal esophagus with villiform, specialized columnar epithelium more typically seen in the stomach or intestine. Mutations may develop within this metaplastic tissue, eventually transforming the columnar epithelium into areas of dysplasia. The dysplasia is characterized by a distortion of the glandular architecture, crowding of cell nuclei, and hyperchromatism. Patients with Barrett's esophagus are at high risk for esophageal adenocarcinoma, with an annual rate of neoplastic transformation of approximately 0.5 percent.³⁴

Genetic Findings

The genetic and molecular changes underlying the development of Barrett's esophageal adenocarcinoma remain poorly understood. Genetic analysis of these cancers reveals frequent chromosomal losses (4q, 5q, 9p, and 18q), chromosomal gains (8q, 17q, and 20q), and occasional gene amplifications (7, 8, and 17q).³⁵⁻³⁷ Efforts to match specific chromosomal aberrations with particular genes have met with varying degrees of success. Genes (and their protein products) that may have a cen-

tral role in the development of this cancer include cyclooxygenase 2, Bcl-2, p53, p16, p27, cyclin D1, retinoblastoma protein, epidermal growth factor (and its receptor), erb-b2, E-cadherin, α -catenin, and β -catenin.³⁷⁻⁴⁴

Changing Histologic Findings

The overall incidence of esophageal cancer in the United States (4.8 cases per 100,000 persons) and the associated mortality rate (4.4 deaths per 100,000 persons) reflect increases of 15 to 20 percent over the past three decades,² during which time the histologic pattern of the disease has changed significantly. As recently as 1975, about 75 percent of cases of esophageal cancer diagnosed in the United States were squamous-cell carcinomas and the remaining 25 percent were adenocarcinomas. During the past 20 years, for as-yet-unexplained reasons, the incidence of squamous-cell carcinomas has decreased in both the black population and the white population (particularly among men), while the rate of adenocarcinoma has increased by 450 percent among white men and 50 percent among black men.^{2,45} Trends in smoking and obesity as well as changes in nutrition and the use of medications may account for some of these changes. Surveys conducted by the American College of Surgeons indicate that the relative incidence of squamous-cell carcinoma as compared with that of adenocarcinoma decreased from 2:1 in 1988 to 1.2:1 in 1994.^{3,46} Currently, there are probably more new cases of adenocarcinoma than of squamous-cell carcinoma in the United States and elsewhere.^{47,48}

PREVENTION, SURVEILLANCE, AND SCREENING

Smoking cessation and moderation of alcohol intake are important steps in reducing the risk of squamous-cell carcinoma of the esophagus. The risk of this cancer decreases substantially a decade after smoking cessation.⁴⁹ In contrast, the risk of adenocarcinoma of the esophagus does not change appreciably, even 30 years after smoking cessation.⁵⁰ Substituting fresh fruits and vegetables for poorly preserved, high-salt foods contaminated with nitrosamine carcinogens or microbial and fungal toxins may reduce the risk of esophageal cancer by as much as half.⁵¹

The relatively low incidence of esophageal cancer, the absence of early symptoms, and the rarity of a hereditary form of the disease^{18,52,53} make pop-

ulation-based screening untenable except in certain high-risk areas⁵⁴ of the world. Patients who are found to have Barrett's esophagus, however, may be candidates for regular endoscopic surveillance, since the incidence of low-grade dysplasia, high-grade dysplasia, and cancer is approximately 4 percent, 1 percent, and 0.5 percent per year, respectively, among such patients.^{34,55-57} Some experts have recommended that endoscopy be performed every three to five years in patients who have Barrett's esophagus in the absence of epithelial dysplasia and more frequently if they are found to have low-grade dysplasia.⁵⁷

Treatment with proton-pump inhibitors improves the symptoms of gastroesophageal reflux disease and leads to complete healing of erosive esophagitis in most patients.^{58,59} Endoscopic ablation of the abnormal esophageal epithelium with the use of a laser or other methods, combined with proton-pump inhibitors, may cause a reversion to normal squamous mucosa in some patients with Barrett's esophagus.⁶⁰ Occasionally, intestinal neoplasia persists beneath the new squamous mucosa.⁶¹ Whether such a management strategy for Barrett's esophagus will actually reduce the risk of cancer is unknown.

The identification of high-grade dysplasia (i.e., carcinoma in situ) has been considered an indication for an esophagectomy, since occult invasive cancer has frequently been identified at the time of resection.⁶² Patients who are considered to be poor surgical candidates may undergo endoscopic mucosal ablation.⁶³⁻⁶⁵ Without treatment, invasive cancer reportedly develops within three years in up to half of patients with high-grade dysplasia.⁶⁶

DIAGNOSIS

CLINICAL PRESENTATION

Most patients with esophageal cancer (74 percent) have dysphagia, and 17 percent report odynophagia (pain on swallowing food and liquids) at the time of diagnosis.³ Weight loss is also common (occurring in 57 percent of patients) and is an independent indicator of a poor prognosis if there is a loss of more than 10 percent of body mass.⁶⁷ Although longstanding gastroesophageal reflux disease is not uncommon in this group of patients (diagnosed in 21 percent), 14 percent of Americans have identical symptoms,⁶⁸ and the vast majority of these people will never have esophageal cancer. Dyspnea, cough, hoarseness, and pain (retrosternal, back, or right

upper abdominal) occur less often but may reflect the presence of extensive, unresectable disease.

The physical examination is usually unremarkable. Lymphadenopathy, particularly in the left supraclavicular fossa (Virchow's node), hepatomegaly, and a pleural effusion are all common indicators of metastatic disease.

DIAGNOSTIC STUDIES

An esophagogram (i.e., a barium-swallow examination) (Fig. 1) is usually the initial diagnostic study

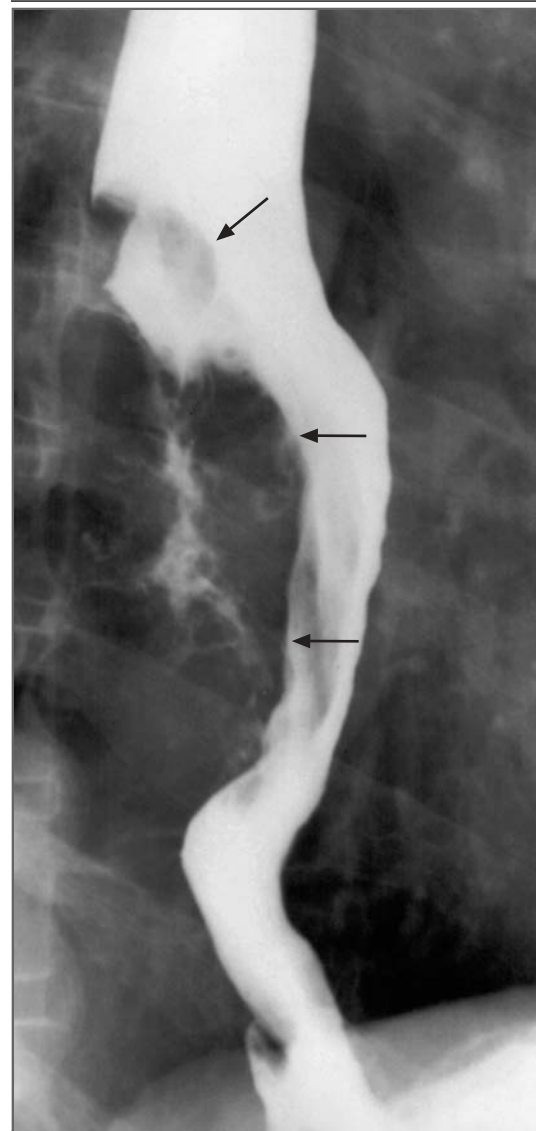


Figure 1. Esophagogram Showing a Malignant Esophageal Stricture (Arrows).

Courtesy of John Braver, M.D.

obtained and typically shows a stricture or ulceration of the esophagus. Upper endoscopy (Fig. 2A) reveals a friable, ulcerated mass. A computed tomographic (CT) scan of the chest, abdomen, and pelvis with intravenous contrast medium should be obtained to detect metastatic disease.

Patients with esophageal cancer that is thought to be restricted to the esophagus may benefit from further evaluation with the use of endoscopic ultrasonography (Fig. 2B). This technique can be used to predict the depth of tumor invasion (the tumor stage) in 80 to 90 percent of patients and the extent of lymph-node involvement by metastatic disease (the node stage) in 70 to 80 percent of patients.⁶⁹ The ability to detect regional lymph-node involvement may be further enhanced by the use of endoscopic, ultrasonographically guided fine-needle aspiration, which has an accuracy of more than 90 percent at many centers.⁷⁰ Endoscopic ultrasonography is useful for determining the correct stage (prognosis) and accurately identifying superficial lesions, which are best treated with surgery alone.

Positron-emission tomography (PET) with fludeoxyglucose F 18 is increasingly being used to identify disease that has spread to regional lymph nodes or to sites that are undetectable by CT or endoscopic ultrasonography (Fig. 3). Recent studies have suggested that PET scanning with fludeoxyglucose F 18 can detect metastatic disease in 15 percent of patients who were thought on the basis of conventional diagnostic techniques to have localized esophageal cancer.^{71,72} Although thoracoscopic or laparoscopic staging is highly accurate (more than 90 percent),⁷³ these procedures are invasive and have been replaced at many institutions by PET scanning with fludeoxyglucose F 18. In contrast, standard tumor markers, such as carcinoembryonic antigen, cancer antigen (CA) 19-9, and CA 125, have a low sensitivity and specificity in esophageal cancer and are therefore thought to be of little value for screening, detecting recurrences, or predicting the response to therapy or the likelihood of survival.⁷⁴

STAGING AND PROGNOSIS

Esophageal cancer is classified according to the 2002 American Joint Committee on Cancer tumor-node-metastasis (TNM) classification system (Table 2), which takes into account the characteristics of the primary tumor, regional nodal metastases, and distant metastases.⁷⁵ Overall, more than 50 percent of patients have unresectable or metastatic disease at the time of presentation. Among patients

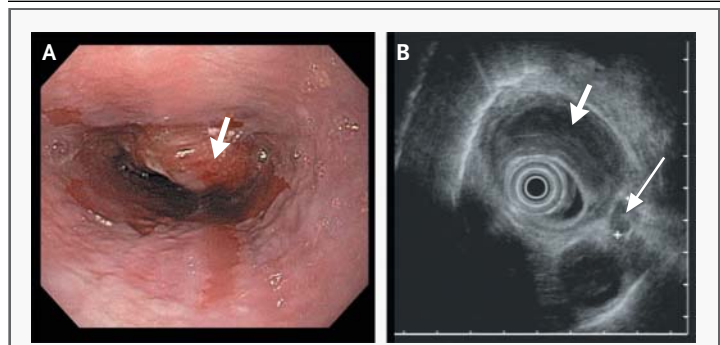


Figure 2. Endoscopic Image (Panel A) and Endoscopic Ultrasonogram (Panel B) Showing a Transmural Adenocarcinoma of the Esophagus Associated with Barrett's Esophagus (Short Arrows), with Lymph-Node Metastases (Long Arrow). Courtesy of John Saltzman, M.D.

who are undergoing primary surgery, 13 to 20 percent have stage I disease, 14 to 27 percent stage IIA disease, 7 to 16 percent stage IIB disease, and 40 to 54 percent stage III disease.^{5,7,79} The stage at presentation appears to be relatively similar for adenocarcinomas and squamous-cell carcinomas.⁵

The overall survival rate at five years is poor but has increased from 4 percent in the 1970s to 14 percent currently.² After complete surgical removal of the tumor, the five-year survival rate exceeds 95 percent for stage 0 disease, and is 50 to 80 percent for stage I disease, 30 to 40 percent for stage IIA disease, 10 to 30 percent for stage IIB disease, and 10 to 15 percent for stage III disease.⁷⁶⁻⁷⁸ Patients with metastatic (stage IV) disease who are treated with palliative chemotherapy have a median survival of less than one year.⁸⁰ In addition to the TNM stage, multivariate analyses suggest that a weight loss of more than 10 percent of body mass, dysphagia, large tumors, advanced age, and lymphatic micrometastases (identified by immunohistochemical analysis) are independent predictors of a poor prognosis.^{67,81-84}

MANAGEMENT OF ADVANCED (STAGE IV) DISEASE

Both squamous-cell carcinoma and adenocarcinoma of the esophagus are responsive to chemotherapy. Shrinkage of the tumor by at least 50 percent may occur in 15 to 30 percent of patients who are treated with fluorouracil, a taxane (paclitaxel or docetaxel), or irinotecan.^{80,85} Similar responses have been reported in 35 to 55 percent of patients

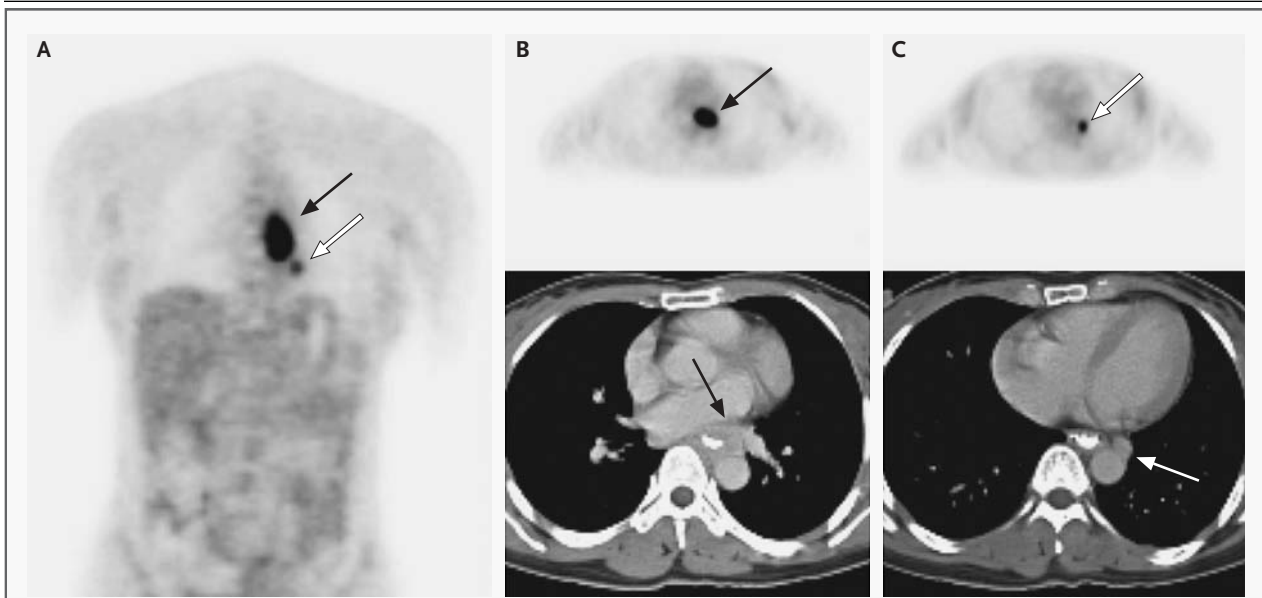


Figure 3. Cancer of the Distal Esophagus (Panels A and B) with Metastasis to a Paraesophageal Lymph Node (Panels A and C). Panel A shows a coronal section of a positron-emission tomographic (PET) study with fludeoxyglucose F 18. A cancer of the distal esophagus is present (black arrow) with metastasis to a paraesophageal lymph node (white arrow). Panels B and C show corresponding axial sections of the PET scan (top two images) and a CT scan (bottom two images); the cancer in the distal esophagus is indicated by the black arrows in Panel B, and the metastatic paraesophageal lymph node by the white arrows in Panel C. Courtesy of Annick D. Van den Abbeele, M.D.

who receive cisplatin in combination with these agents.⁸⁶⁻⁹¹ Although chemotherapy can palliate symptoms in many patients, the response to chemotherapy typically lasts no longer than a few months, and survival is short, rarely exceeding one year. Although combination-chemotherapy regimens tend to result in a higher likelihood of tumor reduction than can be achieved with single-drug regimens, the therapeutic benefit of more intensive treatment must be balanced against its greater potential for toxic effects. Treatment with single drugs or combination-chemotherapy regimens appears to result in similar outcomes for adenocarcinomas and squamous-cell carcinomas, with the squamous-cell subtype being perhaps slightly more responsive.⁸⁰

MANAGEMENT OF LOCALIZED ESOPHAGEAL CANCER

SURGERY

Localized esophageal cancer is most commonly resected with the use of either a right transthoracic or a transhiatal approach. The right transthoracic approach combines a laparotomy and right-sided

thoracotomy, leading to an esophagogastric anastomosis either in the upper chest (the Ivor-Lewis technique) or in the neck (the three-field technique). The transhiatal approach uses a laparotomy with blunt dissection of the thoracic esophagus and places the anastomosis in the neck. Although a transthoracic resection permits better visualization of the tumor and a more thorough dissection of adjacent lymphatics, the thoracotomy increases the risk of cardiopulmonary complications and, if the Ivor-Lewis technique is used, places the patient at risk for an anastomotic leak into the chest. Although neither retrospective trials⁹² nor prospective trials^{79,93} have demonstrated any significant differences in survival or operative mortality between these two types of surgery, the results of one trial suggest that the transhiatal approach has a lower rate of perioperative complications (mainly fewer pulmonary complications and a lower incidence of chylous leakage).⁷⁹

Until relatively recently, there was concern that the morbidity and mortality associated with primary resection of an esophageal carcinoma could outweigh the likelihood of a long-term benefit. This

concern has been addressed through the development of improved surgical techniques and better postoperative care. Recent multiinstitutional randomized trials have documented resectability rates of 54 to 69 percent, operative mortality rates of 4 to 10 percent, and rates of perioperative complications (primarily cardiopulmonary complications, infections, and anastomotic leaks) of 26 to 41 percent.^{47,94,95} Patients undergoing surgery as the sole treatment had a median survival ranging from 13 to 19 months; 2-year survival rates ranged from 35 to 42 percent, and 5-year survival rates from 15 to 24 percent.

RADIOTHERAPY

The use of primary radiotherapy as an alternative to surgery was initially evaluated in patients with squamous-cell carcinomas of the esophagus whose general medical condition made them poor operative candidates. A review of uncontrolled series of such patients treated with primary radiotherapy (total dose, 5000 to 6800 cGy) suggested the same likelihood of survival for five years as that projected at the time for surgery.⁹⁶ The most important advantage of primary radiotherapy is the avoidance of perioperative morbidity and mortality. However, primary radiotherapy is probably not as effective a palliative maneuver as surgery in providing reliable and prolonged relief from dysphagia and odynophagia and appears to be associated with a higher probability of such catastrophic local and regional complications as esophagotracheal fistulas.

COMBINATION THERAPY

Given the disappointing results of surgery or radiotherapy alone and the demonstrated activity of chemotherapy in patients with advanced disease, strategies that combine these three treatment approaches have been investigated as a means of enhancing local control and improving survival among patients with localized esophageal cancer.

PREOPERATIVE RADIOTHERAPY

At least five randomized trials, involving 100 or more patients, have compared preoperative radiotherapy with immediate surgery.⁹⁷ The total dose of radiation in these studies has ranged from 2000 to 4000 cGy. Most of the patients in these trials had squamous-cell carcinomas. None of the studies demonstrated a survival advantage with the use of preoperative radiotherapy.

Table 2. Five-Year Survival Rates for Esophageal Carcinoma, According to the Tumor–Node–Metastasis Classification.*

Stage	Tumor	Node	Metastasis	5-Yr Survival %
0	Tis	N0	M0	>95
I	T1	N0	M0	50–80
IIA	T2-3	N0	M0	30–40
IIB	T1-2	N1	M0	10–30
III	T3	N1	M0	10–15
	T4	Any N	M0	
IVA	Any T	Any N	M1a	<5
IVB	Any T	Any N	M1b	<1

* Data are from Greene et al.,⁷⁵ Pera et al.,⁷⁶ Headrick et al.,⁷⁷ and Reed.⁷⁸ The primary tumor (T) is classified as follows: Tis, carcinoma in situ; T1, invasion of lamina propria or submucosa; T2, invasion of muscularis propria; T3, invasion of adventitia; and T4, invasion of adjacent structures. Regional lymph-node metastases (N) are classified as follows: N0, no regional lymph-node metastases; and N1, regional lymph-node metastases. Distant metastases (M) are classified as follows: M0, no distant metastases; M1a, metastasis to cervical nodes in the case of cancer of the upper thoracic esophagus and metastasis to celiac nodes in the case of cancer of the lower thoracic esophagus; and M1b, other distant metastases.

PREOPERATIVE CHEMOTHERAPY

The value of preoperative chemotherapy (consisting of cisplatin and fluorouracil) has been assessed in two large multiinstitutional trials, and the outcomes are conflicting. A randomized study involving 440 North American patients showed no benefit, with 35 percent of patients in the chemotherapy-plus-surgery group alive after two years as compared with 37 percent of patients in the surgery-alone group.⁹⁵ A seemingly similar study involving 802 British patients suggested that a comparable treatment program increased the survival rate at two years from 34 percent after surgery alone to 43 percent after preoperative chemotherapy.⁴⁷

It is difficult to reconcile the differences in survival benefits between these two trials. Although the British study included almost twice as many patients, it did not require preoperative CT staging or stipulate the surgical technique. The North American study required CT staging, prescribed the operative technique, and used a longer and more intensive course of chemotherapy, delaying definitive

surgery. In any case, if preoperative chemotherapy consisting of cisplatin and fluorouracil is beneficial for esophageal cancer, such a benefit is small.

PREOPERATIVE CHEMOTHERAPY AND RADIOOTHERAPY

At least eight randomized trials have been conducted to address the potential benefit of preoperative chemotherapy plus radiotherapy in patients with esophageal cancer (Table 3).^{48,83,94,98-102} Only two studies enrolled sufficient numbers of patients to provide statistically meaningful results, and neither reported an advantage of preoperative chemotherapy and radiotherapy.^{48,94}

A sole randomized trial at one institution, reported by Walsh et al., showed a benefit of chemotherapy and radiotherapy in 113 patients with adenocarcinoma of the esophagus who either underwent immediate surgery or received preoperative cisplatin and fluorouracil combined with 4000 cGy of radiation.¹⁰¹ After a relatively short follow-up (1.5 years), the authors reported that estimates of 3-year survival favored preoperative chemotherapy and radiotherapy. Definitive interpretation of the results is clouded, however, by the small number of patients, the brief duration of follow-up, and the unusually poor outcome among the patients assigned to undergo immediate surgery (a 6 percent proba-

Table 3. Randomized Trials Comparing Preoperative Chemotherapy and Radiotherapy with Surgery Alone in Patients with Localized Esophageal Cancer.*

Study, Year, and Group	No. of Patients	Histologic Diagnosis	Chemotherapy	Total Dose of Radiotherapy cGy	Median Survival mo	3-Yr Survival %
Nygaard et al., ⁹⁸ 1992		Squamous-cell carcinoma				
Surgery alone	41				NA	9
Preoperative chemotherapy and radiotherapy	47		Cisplatin, bleomycin†	3500†	NA	17
Le Prise et al., ⁹⁹ 1994		Squamous-cell carcinoma				
Surgery alone	41				10	14
Preoperative chemotherapy and radiotherapy	45		Cisplatin, fluorouracil†	2000†	10	19
Apinop et al., ¹⁰⁰ 1994		Squamous-cell carcinoma				
Surgery alone	34				7	20
Preoperative chemotherapy and radiotherapy	35		Cisplatin, fluorouracil	4000	10	26
Walsh et al., ¹⁰¹ 1996		Adenocarcinoma				
Surgery alone	55				11	6‡
Preoperative chemotherapy and radiotherapy	58		Cisplatin, fluorouracil	4000	16	32
Bosset et al., ⁹⁴ 1997		Squamous-cell carcinoma				
Surgery alone	139				19	37
Preoperative chemotherapy and radiotherapy	143		Cisplatin	3700	19	39
Law et al., ¹⁰² 1998		Squamous-cell carcinoma				
Surgery alone	30				27	NA
Preoperative chemotherapy and radiotherapy	30		Cisplatin, fluorouracil	4000	26	NA
Urba et al., ⁸³ 2001		Squamous-cell carcinoma (25%) and adenocarcinoma (75%)				
Surgery alone	50				18	16
Preoperative chemotherapy and radiotherapy	50		Cisplatin, vinblastine, fluorouracil	4500	17	30
Burmeister et al., ⁴⁸ 2002		Squamous-cell carcinoma (39%) and adenocarcinoma (61%)				
Surgery alone	128				22	NA
Preoperative chemotherapy and radiotherapy	128		Cisplatin, fluorouracil	3500	19	NA

* NA denotes not available.

† Therapy was sequential.

‡ P=0.01 for the difference in survival between the groups. There were no significant differences between groups in any of the other studies.

bility of survival at three years), which is far inferior to the 26 percent estimate of survival at three years among 629 patients who were randomly assigned to undergo surgery alone in multiinstitutional randomized trials.^{47,95} In addition, preoperative CT scans were not required, which in such a small trial, may have resulted in a prognostic imbalance between the two cohorts, accounting in large part for the differences in outcome.

Despite the fact that five^{83,94,98-100} of the six randomized trials assessing the value of preoperative chemotherapy and radiotherapy reported thus far have failed to demonstrate any survival benefit, the positive results of the sixth study, by Walsh and colleagues,¹⁰¹ described above, appear to have influenced thoracic surgeons and oncologists (at least in North America) substantially. An attempt in the United States to perform a trial with adequate statistical power, comparing preoperative cisplatin and fluorouracil combined with 5040 cGy of radiotherapy with immediate surgery in 620 patients, was closed prematurely after fewer than 75 patients had been registered within 2.5 years. However, this apparent acceptance of preoperative chemotherapy and radiotherapy has recently been challenged by preliminary data from a randomized trial in Australia involving 256 patients.⁴⁸ This trial also failed to demonstrate any survival advantage with the use of preoperative treatment.⁴⁸ Consequently, despite the widespread use of preoperative chemotherapy and radiotherapy, there remains no proof of principle that this strategy is effective in patients with esophageal cancer.

POSTOPERATIVE TREATMENT

Postoperative chemotherapy and concurrent radiotherapy are frequently offered to patients whose tumor cells extend to the surgical margin (as a result of incomplete resection). There is no documented evidence that postoperative chemotherapy or radiotherapy is beneficial in the absence of residual disease.¹⁰³⁻¹⁰⁵

NONSURGICAL CHEMOTHERAPY AND RADIOTHERAPY

Whereas radiotherapy alone rarely cures esophageal cancer,⁹⁶ the combination of radiotherapy and concurrent chemotherapy with cisplatin and fluorouracil has led to long-term survival in approximately 25 percent of patients — an outcome similar to that associated with surgery alone or even surgery after preoperative therapy.¹⁰⁶⁻¹⁰⁸ In a trial

involving 123 patients with squamous-cell carcinoma or adenocarcinoma of the esophagus, 61 patients were randomly assigned to receive cisplatin and fluorouracil combined with 5000 cGy of radiation, and 62 were treated with 6400 cGy of radiation alone. After five years of follow-up, the overall survival rate was 26 percent in the combined-therapy group, as compared with 0 percent in the group given radiotherapy alone. Attempts to enhance this beneficial effect by increasing the radiation dose to 6480 cGy have proved unsuccessful.¹⁰⁹

CONTROL OF SYMPTOMS

DYSPHAGIA AND OBSTRUCTION

Surgery offers the most immediate and best long-term palliation for dysphagia in patients with localized esophageal cancer.¹¹⁰ Patients who undergo surgery require esophageal stenting or dilation after the completion of therapy less frequently than do those treated with chemotherapy and radiotherapy. For patients with unresectable disease, cisplatin-based chemotherapy appears to be as effective as radiotherapy for the palliation of dysphagia and may also be effective for the treatment of disease at distant sites.^{88,111,112} Improvement or resolution of dysphagia can be expected in 70 to 90 percent of patients after two to six weeks of chemotherapy.^{88,113}

Patients with dysphagia may have prompt palliation of symptoms after balloon dilation, placement of a coated, expandable metal stent, laser ablation, or photodynamic therapy.¹¹⁴⁻¹¹⁶ The results of small, randomized trials comparing stenting, laser ablation, and photodynamic therapy suggest that stenting offers similar degrees of relief from dysphagia and at lower cost, but that the stent may cause severe acid reflux if extended beyond the gastroesophageal junction.¹¹⁴⁻¹¹⁶

ESOPHAGEAL-AIRWAY FISTULA

The development of an esophageal-airway fistula is a life-threatening complication of esophageal cancer. Initial symptoms most often include a cough (in 56 percent of patients), aspiration (in 37 percent), and fever (in 25 percent), frequently culminating in pneumonia.¹¹⁷ More than half such fistulas involve the trachea; alternatively, a connection with the left or right main bronchus may be formed. Historically, patients with esophageal-airway fistulas have been treated with radiotherapy or esophageal bypass.¹¹⁷ The development of coated, expandable metal stents has revolutionized the care of this prob-

lem. Nearly all malignant fistulas can be sealed successfully with these stents, substantially improving the patients' quality of life.¹¹⁸

THE FUTURE

Esophageal cancer is a relatively uncommon malignant condition with a low likelihood of cure. To decrease the incidence of this cancer, we must determine the cause of the rapid increase in the proportion of cases involving adenocarcinoma and Barrett's esophagus. More precise, data-driven recommendations regarding the value of endoscopic surveillance in patients with Barrett's esophagus are

also needed. Clinical trials evaluating the use of preoperative chemotherapy or preoperative chemotherapy and radiotherapy have focused on chemotherapy with fluorouracil and cisplatin and have frequently had design flaws or have been statistically underpowered, failing to provide convincing evidence of a benefit. Alternative forms of systemic treatment that incorporate a taxane, irinotecan, or a targeted form of treatment (e.g., an antagonist of the epidermal growth factor receptor or a cyclooxygenase-2 inhibitor) merit exploration. A series of carefully designed controlled, randomized trials will most likely be required to address these important issues.

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