Chapter 50
Esophageal Cancer

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Less than 15% of patients diagnosed with esophageal cancer are cured, with half of the patients presenting with unresectable or metastatic disease. This chapter will review the natural history and treatment of esophageal cancer, including risk factors, staging, results of current therapeutic approaches, and future treatment strategies.

Anatomy

The esophagus is a thin-walled, hollow tube approximately 25 cm in length. It is lined with stratified keratinized squamous epithelium, extending from the cricopharyngeus muscle at the level of the cricoid cartilage superiorly to the gastroesophageal junction inferiorly. The lower third (5 to 10 cm) of the esophagus may contain glandular elements. Replacement of the stratified squamous epithelium with columnar epithelium is referred to as Barrett's esophagus, often occurring in the lower third. The Z-line refers to the endoscopically visible junction of the squamous and glandular epithelium. The four esophageal wall layers consist of an innermost epithelial layer, followed by an inner circular muscle layer, an outer longitudinal muscle layer, and an adventitia. No serosa is present, facilitating extra esophageal spread of disease.

The esophagus is frequently divided into cervical and thoracic components. The cervical esophagus begins at the cricopharyngeus muscle (approximately the C7 level or 15 cm from the incisors) and extends to the thoracic inlet (approximately T3 level or 18 cm from the incisors, at the level of the suprasternal notch). The thoracic esophagus extends from approximately the level of T3 to T10 or T11 (108). Endoscopically, the gastroesophageal (GE) junction is often defined as the point where the first gastric fold is encountered, although this may be a "theoretical" landmark. The location of the GE junction can be accurately defined histologically as the squamocolumnar junction.

Useful landmarks in reference to endoscopy include the carina (approximately 25 cm from the incisors) and the gastroesophageal junction (approximately 40 cm from the incisors). The American Joint Committee on Cancer (AJCC) has divided the esophagus into four regions: cervical, upper thoracic, midthoracic, and lower thoracic (8) (Fig. 50.1).

Siewert et al. (117) characterized cancer of the gastroesophageal junction according to the location of the tumor. If the tumor center is located >1 cm above the gastroesophageal junction (Z-line), the tumor is classified as a type I adenocarcinoma of the distal esophagus. If the tumor center is located within 1 cm cephalad to 2 cm caudad to the gastroesophageal junction, it is classified as type II. If the tumor center is located >2 cm below the gastroesophageal junction, the tumor is classified as type III. However, locally advanced/bulky tumors can make it difficult to accurately distinguish where tumors originated in relationship to the GE junction.

Lymphatic Drainage

The esophagus has an extensive, longitudinal interconnecting system of lymphatics. Lymphatic channels in the mucosa and submucosa communicate with the lymphatic channels in the muscle layers throughout. Lymph can travel the entire length of the esophagus before draining into lymph nodes (108), and thus the entire esophagus is at potential risk for lymphatic involvement. Up to 8 cm or more of "normal" tissue can exist between gross tumor and micrometastases "skip areas" secondary to this extensive lymphatic network (141). Additionally, as many as 71% of frozen tissue sections scored as margin-negative by conventional histopathology show involvement by lymphatic micrometastases with immunohistochemistry (62). Lymphatics of the esophagus drain into nodes that usually follow arteries, including the inferior thyroid artery, the bronchial and esophageal arteries, and the left gastric artery (celiac axis) (115) (Fig. 50.2).

Epidemiology and Risk Factors

Esophageal carcinoma is an uncommon malignancy, accounting for approximately 1% of all malignancy and 6% of all gastrointestinal malignancies. In 2004, there will be an estimated 15,560 new patients diagnosed with esophageal cancer in the United States and 13,940 deaths. Most cases occur in males, at a rate of 3.5:1 relative to female (67).

In the United States, there has been a dramatic rise in the incidence of adenocarcinoma of the esophagus, particularly in Caucasian males. In 1987, adenocarcinoma was reported to represent 34% and 12% of esophageal cancers in Caucasian men and women, versus 3% and 1% for African American men and women, respectively (20). Over the past 20 years, there has been an increase in the incidence of adenocarcinoma at a rate of 5% to 10% per year. This is a more rapid increase than any other cancer (20). As of 1998, esophageal adenocarcinoma accounted for almost 55% of all diagnosed cases in Caucasian men. African American men are more frequently diagnosed with squamous cell carcinoma (35,103) (Fig. 50.3).

The outcome for patients with esophageal carcinoma is bleak. In the 1990s, the 5-year survival rate for esophageal cancer was approximately 11%, with a median survival rate of approximately 9 months. Collectively, little difference in outcomes between histologic types has been observed (106).

Globally, the incidence of esophageal carcinoma varies widely. This malignancy is seen in high frequency in northern China, Iran, and Russia, near the Caspian Sea. Incidence rates can be as high as 100+ per 100,000 persons (70,85,109,145). Although the reasons for the geographic discrepancy are unknown, some reports have linked the arid climate and alkaline soil with these high-risk areas, as well as the ingestion of nitrosamines and inversely to the consumption of riboflavin, nicotinic acid, magnesium, and zinc (28,86). High-risk clusters have also been observed in South Africa, northern France, Hong Kong, and Brazil.

In North America and Western Europe, alcohol and tobacco use are the major risk factors for squamous cell carcinoma, accounting for 80% to 90% of cases (113). Reports have described the relative risk of esophageal cancer by the amount of alcohol

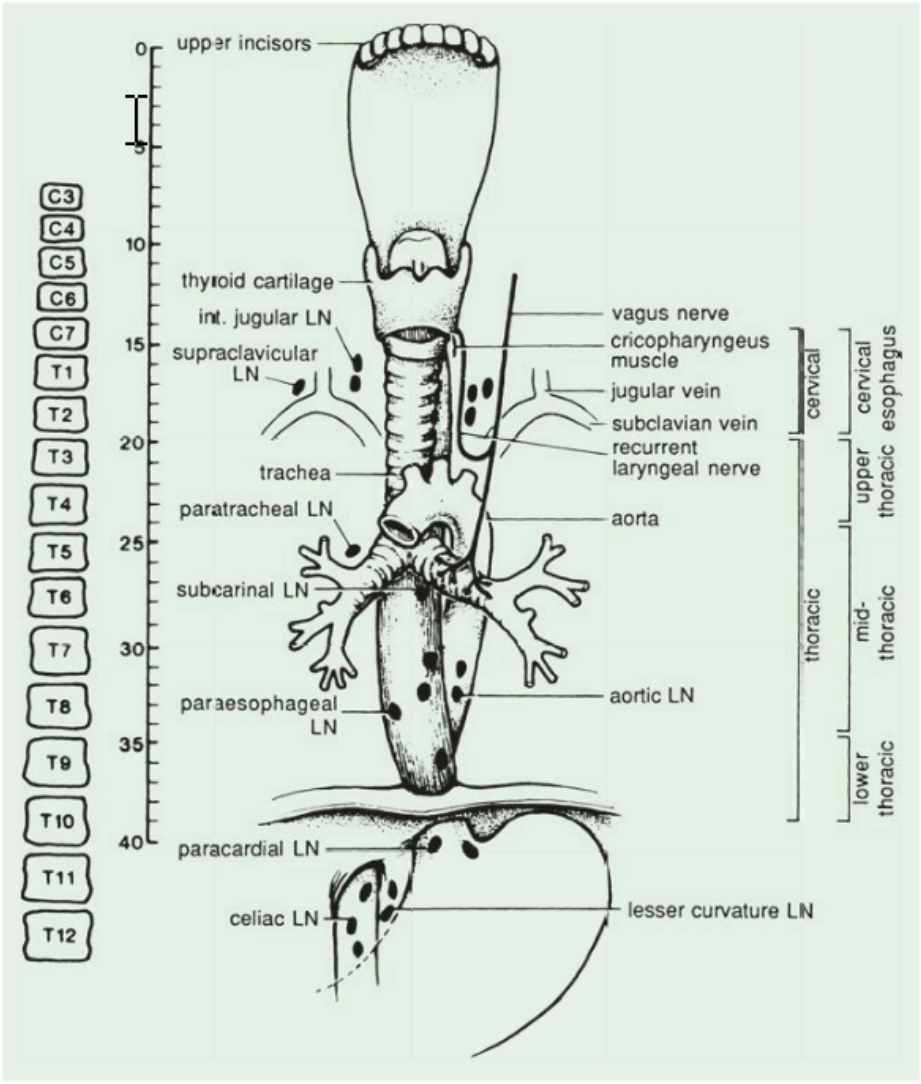


FIGURE 50.1. Anatomy of the esophagus. Note the lengths of the various segments of the esophagus from the upper central incisors and the two classification schemes for subdividing the esophagus. LN, lymph node

and tobacco consumed, including a relative risk of 155:1 when consuming >30 g per day of tobacco along with 121 g per day of alcohol (21).

In high-risk populations, diets of corn, wheat, millet, scant amounts of fruits, vegetables, and animal products are associated with increases in squamous cell carcinoma (136). Patients with Plummer-Vinson (Paterson-Kelly) syndrome, a condition characterized by iron deficiency anemia and low riboflavin levels, are at an increased risk for oral cavity, hypopharyngeal, and esophageal cancer. Additionally, dietary intake of nitrosamines, nitrosamides, and *N*-nitroso compounds has been implicated in esophageal carcinoma. Examples of nitrate-rich foods include pickled vegetables, alcoholic beverages, cured meats, and fish (82,90).

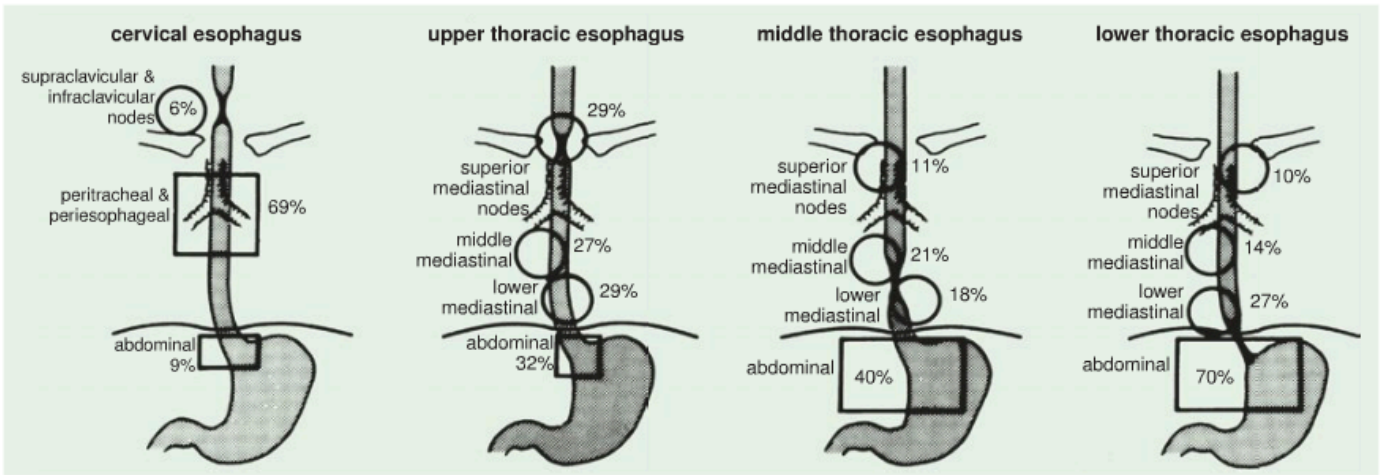


FIGURE 50.2. Positive lymph node distribution according to the location of the primary tumor. (Modified from Akiyama H, Tsurumaru M, Kawamura T, et al. Principles of surgical treatment for carcinoma of the esophagus: analysis of lymph node involvement. Circles represent potential sites of lymph node involvement while squares represent the dominant site of lymphatic spread. *Ann Surg* 1981;194:438; and Dormans E. Das Oesophaguscarcinoma: Ergebnisse der unter Mitarbeit von 39 pathologischen Instituten Deutschlands Durchgefuhrten Erhebung uber das Oesophaguscarcinomon [1925–1933]. *Z Krebforsch* 1939;49:86, with permission.)

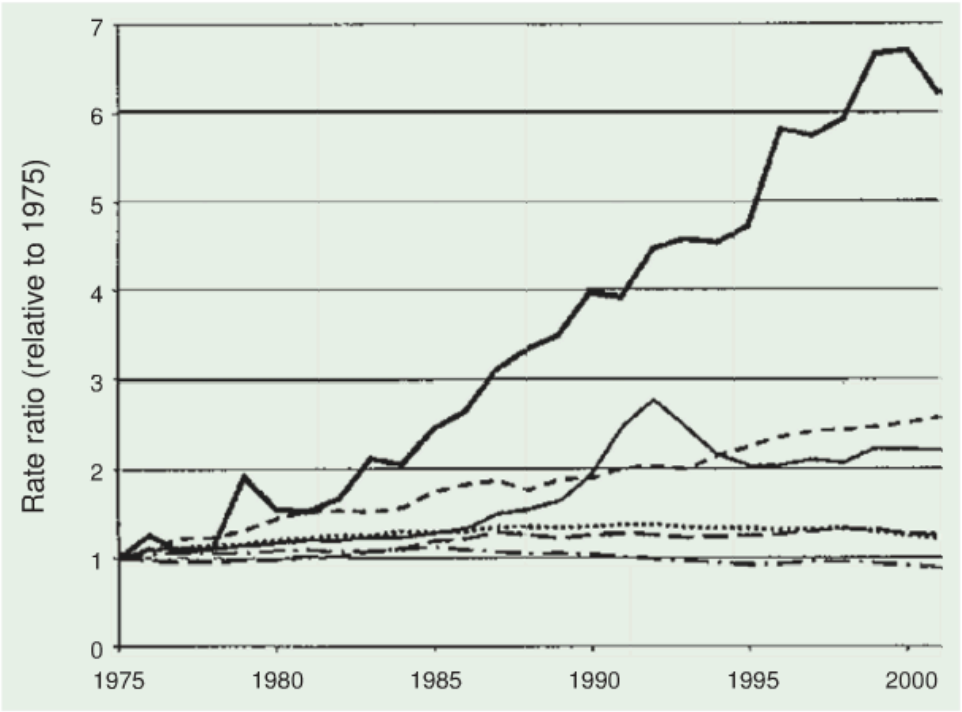


FIGURE 50.3. Relative change in incidence of esophageal adenocarcinoma and other malignancies (1975–2001). Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program with age-adjustment using the 2000 U.S. standard population. Base line was the average incidence between 1973 and 1975. solid black line, esophageal adenocarcinoma; short dashed line, melanoma; line, prostate cancer; dashed line, breast cancer; dotted line, lung cancer; dashed and dotted line, colorectal cancer

Other risk factors associated with esophageal carcinoma include achalasia, caustic burns (especially lye corrosion), and tylosis. Achalasia of long duration (25 years) is associated with a 5% incidence of squamous cell carcinoma (10,61). Patients with tylosis (hyperkeratosis of the palms and soles and papilloma of the esophagus) have a reported 38% risk in developing esophageal cancer at a mean age of 45 years (57). Additionally, carcinoma of the esophagus occurs in 2% to 4% of patients with head and neck cancer.

Risk factors leading to the development of adenocarcinoma of the esophagus are not as well understood. Most esophageal adenocarcinomas tend to arise from the metaplastic columnar-lined epithelium known as Barrett's esophagus (122). Severe and long-standing gastroesophageal reflux disease (GERD) has clearly been shown to be a significant risk factor for Barrett's esophagus, which may lead to adenocarcinoma. It has been estimated that patients with long-standing severe reflux have a 44-fold risk of developing adenocarcinoma (74). In addition, smokers have a two- to threefold greater risk for developing esophageal adenocarcinoma versus nonsmokers (37,150). The relative risk of esophageal adenocarcinoma persists to three decades following smoking cessation, in contrast to a significant decline in similar patients with squamous cell carcinoma (58). Obesity has also been linked to a three- to fourfold risk of adenocarcinoma, possibly due to an increased risk of reflux (25). It has been estimated that a middle-aged patient with Barrett's esophagus has a 10% to 15% risk of developing esophageal adenocarcinoma during his or her lifetime (34).

Differences between tumor types as classified by Siewert include higher male to female ratios, increased incidence of hiatal hernia, GERD and Barrett's esophagus for type I tumors compared to types II and III, and more differentiated tumors observed in types I and II versus III (117).

Although many risk factors are associated with esophageal carcinoma, few studies have demonstrated a causal relationship leading to pathogenesis. Motesano et al. (94) reported possible genetic abnormalities involved in the genesis of esophageal cancer. In addition, possible differences in mechanisms of pathogenesis for squamous cell carcinoma and adenocarcinoma were described. Genetic abnormalities in squamous cell carcinoma include p53 mutations and multiple allelic losses at 3p and 9q, with amplification of cyclin D1 and epidermal growth factor receptor (EGFR). These mutations lead to cell hyperplasia, low- and high-grade dysplasia, and ultimately, squamous cell carcinoma. In contrast, genetic abnormalities in adenocarcinoma include overexpression of p53, multiple allelic losses at 17p, 5q, and 13q, and amplification and overexpression of EGFR and human epidermal growth factor receptor 2 (HER-2). These abnormalities may be involved in the stepwise development of Barrett's esophagus, dysplasia, and, ultimately, adenocarcinoma. These differences suggest that squamous cell carcinoma and adenocarcinoma have different pathogeneses and therefore different etiologies. These mechanisms remain ill-defined.

Natural History and Patterns of Spread

Squamous cell carcinoma is characterized by extensive local growth and proclivity to lymph node metastases (55). Because the esophagus has no covering serosa, direct invasion of contiguous structures occurs early (100). Lesions in the upper esophagus can impinge on or invade the recurrent laryngeal nerves, carotid arteries, and trachea. If extraesophageal extension occurs in the mediastinum, tracheoesophageal or bronchoesophageal fistula may occur. Tumors in the lower third of the esophagus can invade the aorta or pericardium, resulting in mediastinitis, massive hemorrhage, or empyema (64).

For T1 lesions, the reported incidence of nodal spread is 14% to 21%; for T2 lesions, this rises to 38% to 60% (31,117). The location of involved lymph nodes is influenced by the origin of the primary tumor. Lymph node metastases are found in approximately 70% of patients at autopsy (5,19,39) (see Fig. 50.2). In patients with cervical lesions, lymph node metastases to the abdominal lymph nodes are rare. Distant hematogenous metastasis can occur at almost any site (9) (Table 50.1).

For lower esophageal and gastroesophageal junctional adenocarcinomas, approximately 70% of patients will have nodal metastases at presentation. This is influenced by tumoral depth of penetration, with nearly all T3-4 lesions exhibiting metastases in surgical series (Fig. 50.4). In patients with lower esophageal cancer, involvement of both mediastinal and abdominal lymph nodes is common (40) (Fig. 50.5). The incidence of abdominal nodal involvement increases as one proceeds distally in the esophagus to the gastroesophageal junction. For patients with tumors arising from the gastroesophageal junction, mediastinal involvement is less common. Nodal metastases

Table 50.1 DISTRIBUTION OF METASTASES BY ANATOMIC SITE

Site	No. of Patients	Percentage
Lymph nodes	58	73
Lung	41	52
Liver	37	47
Adrenals	16	20
Diaphragm	15	19
Bronchus	13	17
Pleura	13	17
Stomach	12	15
Bone	11	14
Kidneys	10	13
Trachea	10	13
Pericardium	9	11
Pancreas	9	11

From Anderson LL, Lad TE. Autopsy findings in squamous-cell carcinoma of the esophagus. *Cancer* 1982;50:1587–1590, with permission.

above the level of the carina are rare in lower esophageal and junctional tumors (93). Additionally, histologic analyses of lower esophagus and gastroesophageal junction adenocarcinoma specimens suggest that many patients without nodal involvement on conventional histopathology actually have involvement when assessed by immunohistochemistry (116).

The primary direction for lymphatic flow for the lower esophagus is toward the abdomen. According to the classification by Siewert, nodal metastases are often seen in the mediastinum and abdomen for type I tumors, whereas type III tumors metastasize almost exclusively inferiorly, toward the celiac axis. Type II tumors are intermediate, preferentially spreading inferiorly and less frequently into the mediastinum. The primary value in the Siewert classification is to the guidance of appropriate type surgery (i.e., type I tumors are generally treated with esophagectomy and mediastinal lymph node resection, with types II and III approached through the abdomen) (117).

Patterns of Failure

Aisner et al. (4) and LePrise et al. (81) reviewed the patterns of failure in esophageal cancer after radical irradiation, radical surgery, or a combination of both (Table 50.2). These data suggest that high rates of local recurrence occur when either radiation therapy or surgery alone are used. In a series at the Hospital of the University of Pennsylvania and Fox Chase Cancer Center of patients with adenocarcinoma of the esophagus and gastroesophageal junction treated with surgery alone, the local-regional recurrence rate was 77% (143). In contemporary randomized trials, local failure rates with surgery alone range from 32% to 45% (63,69,77,133). Data from recent randomized trials of esophageal cancer using "definitive" chemoradiation therapy suggest local failure is a major cause of overall failure, with approximately 50% of patients failing locally (Table 50.3). In many trials patterns of failure are reported as first site of recurrence. This fact, along with infrequent posttherapy imaging and subclinical recurrences, likely underestimates local recurrence rates. These data clearly emphasize the need for improvements in local treatment modalities.

Clinical Presentation

Symptoms of esophageal cancer often start 3 to 4 months before diagnosis. Location of the primary tumor in the esophagus may influence presenting symptoms. Dysphagia is seen in more than 90% of patients regardless of location. Odynophagia (pain on swallowing) is present in up to 50% of patients (109). Weight loss is common, with 40% to 70% of patients reporting a loss of >5% of total body weight. This extent of weight loss has been associated with a worse prognosis. Less frequent symptoms may include hoarseness, cough, and glossopharyngeal neuralgia (92).

Advanced lesions can produce signs and symptoms from tumor invasion into local structures. Hematemesis, hemoptysis, melena, dyspnea, and persistent cough secondary to tracheoesophageal or bronchoesophageal fistula may occur. Compression or invasion of the left recurrent laryngeal nerve or the phrenic nerves can cause dysphonia or hemidiaphragm paralysis. Superior vena cava syndrome and Horner's syndrome can also occur. Pleural effusion and exsanguination resulting from aortic communication may also be seen (109). Abdominal and back pain may occur with celiac axis nodal involvement with lower esophageal tumors.

Diagnostic Work-Up

After a thorough history and physical examination, all patients with suspected esophageal cancer should have a work-up similar to that outlined in Figure 50.6. Attention should be paid to cervical and supraclavicular lymph nodes. Basic blood counts

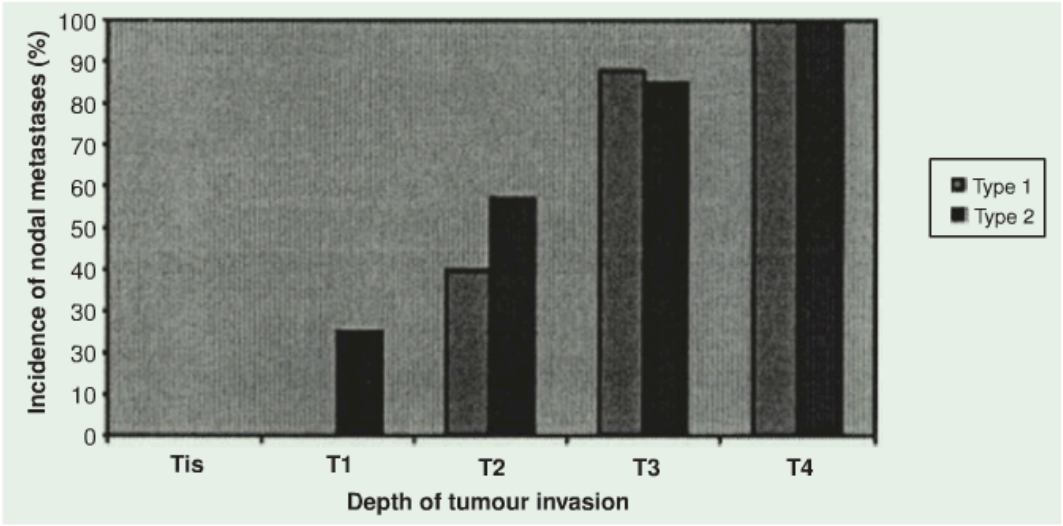


FIGURE 50.4. The incidence of nodal metastases related to depth of tumor invasion for adenocarcinoma.

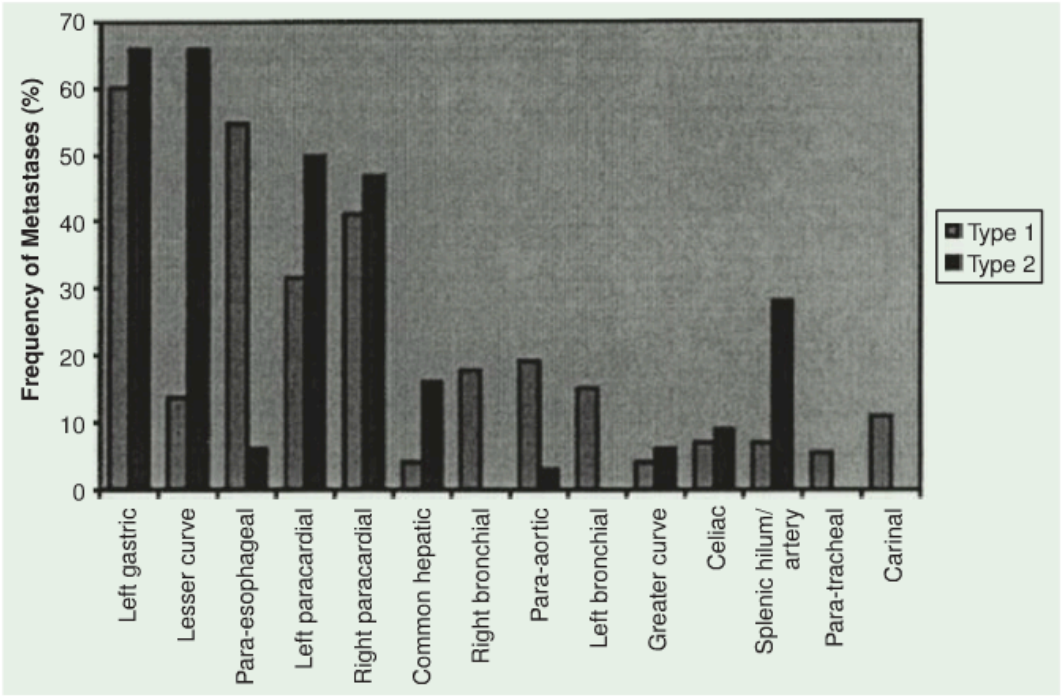


FIGURE 50.5. Distribution of nodal metastases by frequency of site involved for adenocarcinoma.

and a metabolic panel with liver function tests should be obtained.

Although the esophagogram may be used to define lesion extent, endoscopy is the best tool to diagnose and define such (129). During flexible endoscopy, biopsies and brushings should be taken of the primary site and suspicious areas harboring satellite lesions or submucosal spread. Additionally, accurate endoscopic measurement and characterization of tumor and gastroesophageal junction in relation to the incisors facilitates radiation treatment planning. Examination of the oral cavity, pharynx, larynx, and tracheobronchial tree may also be performed at the time of esophagoscopy in patients with squamous cell carcinomas given the high incidence of second tumors in the head and neck and upper airway (108). Additionally, bronchoscopy should be performed in patients with proximal malignancy to evaluate for the presence of tracheal or carinal invasion, particularly for patients with tumors abutting these structures on computed tomography (CT). CT of the thorax and abdomen is critical to identify metastases to the liver, upper abdominal nodes, or adrenals. However, CT may not adequately assess periesophageal lymph node involvement or accurately define the true extent of the primary tumor (78,102). Conventional CT scan can accurately determine resectability in only 65% to 85% of cases. Furthermore, CT accurately predicts T stage in approximately 70% of cases and nodal involvement in only 50% to 70% of cases (53,71,105).

To assess periesophageal and celiac lymph node involvement and transmural extent of disease, endoscopic ultrasonography (EUS) should be performed. EUS provides accuracy rates of 85% to 90% for tumor invasion (T stage) and 75% to 80% for lymph node metastases, when matched to surgical pathology (68,73,107). However, the accuracy of endoscopic

Table 50.2 PATTERNS OF FAILURE IN ESOPHAGEAL CANCER

Modality	No. of Patients	Recurrence (%)					
		Local	Marginal	Neck	Mediastinal	Local and Distant	Distant
Irradiation alone (30–80 Gy)	517	25–84	25	10–43	—	—	23–65
Radical surgery alone	266	21–50		44	33	—	17–65 33 abdominal nodes 17 liver 6 lung
Combined radiation therapy and surgery (primarily preoperative irradiation, 35–50 Gy usual dose)	2,078	22–87	53[a]	—	20[a]	—	7–43[b]
Radiation therapy and chemotherapy alone[c]	254	15–39	—	—	—	5–25	—
	—	—	—	—	—	—	6–25
Preoperative radiation therapy and chemotherapy[c]	150	2–36	—	—	—	5–38	16–29

[a]From one study.
[b]From two studies.
[c]Data from LePrise EA, Meunier BC, Etienne PL, et al. Sequential chemotherapy and radiotherapy for patients with squamous cell carcinoma of the esophagus. *Cancer* 1995;75:2.
Modified from Aisner J, Forastiere A, Aroney R. Patterns of recurrence for cancer of the lung and esophagus. In: Wittes RE, ed. *Cancer treatment symposia: proceedings of the Workshop on Patterns of Failure after Cancer Treatment*, vol 2. Washington, DC: U.S. Department of Health and Human Services, 1983:87, with permission.

Table 50.3 LOCAL FAILURE RATES FROM RANDOMIZED THERAPY TRIALS EVALUATING CHEMORADIATION THERAPY ALONE IN ESOPHAGEAL CANCER

Study (Reference)	Dose (Gy)	Local Failure (crude) (%)	Local Failure (2-year) (%)
RTOG 85-01 (6)	50	45	47
INT 0123 (91)	50	55	52
INT 0123 (91)	64	50	56
German (123)	>60	51	58

ultrasound following neoadjuvant therapy is significantly less, ranging from 27% to 48% for T staging and 38% to 71% for N staging. This is possibly due to the failure to discriminate tumor from postradiation inflammation and fibrosis (16,75,149).

Surgical staging procedures, including thoracoscopy, mediastinoscopy, and laparoscopy, may provide additional staging information and are considered in selected patients at some institutions (66). Patients with significant obstruction with inability to maintain their weight may require placement of feeding jejunostomy. If surgery is planned, gastric tube placement is generally avoided given the stomach will ultimately serve as the "neoesophagus" following resection.

More recently, positron emission tomography (PET) has proven to be a valuable staging tool in esophageal cancer patients. The addition of PET to standard staging studies such as CT can improve the accuracy of detecting stage III and stage IV disease by 23% and 18%, respectively (17,46). Overall, it is estimated that PET will detect distant metastatic disease in approximately 20% of patients who are considered to have local regional disease only by CT. However, PET also appears to have a lower accuracy in detecting local nodal disease compared to CT alone or in combination with endoscopic ultrasound. Importantly, emerging data suggest that PET can be used to predict response to therapy, with "PET responders" experiencing significantly improved outcomes compared to "nonresponders." Additionally, PET has been used to predict therapeutic response to treatment early in the treatment course. This has led to investigation of early treatment response as measured by PET as a surrogate for therapeutic efficacy and clinical outcomes (142).

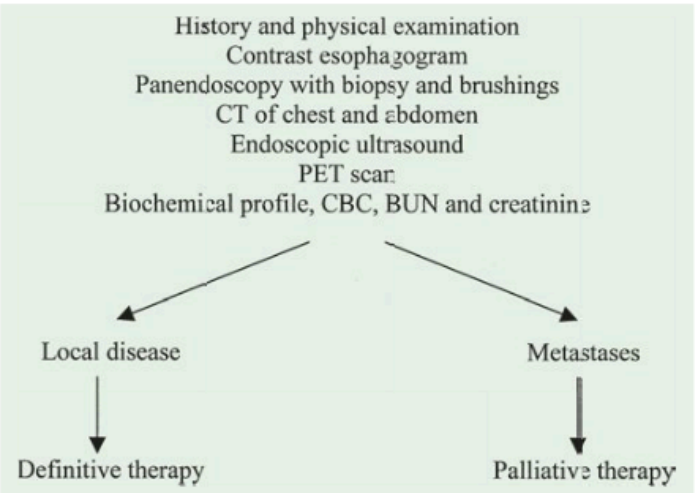


FIGURE 50.6. Diagnostic work-up for esophageal cancer. BUN, blood urea nitrogen; CBC, completed blood cell count; CT, computed tomography; PET, positron emission tomography

Staging Systems

Esophageal staging can be based on pathologic or clinical criteria. Pathologic staging is performed after invasive procedures including esophagectomy, mediastinotomy, or thoracotomy. Clinical staging is often employed with "definitive" and neoadjuvant chemoradiotherapy approaches and is less accurate. With the combination of CT, PET, and EUS, clinical staging closely correlates with pathologic stage (Table 50.4). Note the esophageal staging system is relatively unique in that celiac nodal metastases from a lower esophageal lesion and cervical nodal metastases from an upper esophageal lesion are designated M1a.

Pathologic Classification

Squamous cell carcinoma and adenocarcinoma comprise 95% of all esophageal tumors, although other rare histologic subtypes are occasionally seen (97) (Table 50.5).

For squamous cell carcinomas, some investigators have proposed that the degree of cellular differentiation influences survival (147), although others have reported no association of cellular differentiation to lymph node involvement or survival

Table 50.4 STAGING FOR CANCER OF THE ESOPHAGUS BY TUMOR, LYMPH NODE, AND METASTASIS

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)			
MX	Presence of distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Tumors of the lower thoracic esophagus			
M1a	Metastases in celiac lymph nodes		
M1b	Other distant metastases		
Tumors of the mid-thoracic esophagus			
M1a	Not applicable		
M1b	Nonregional lymph nodes and/or distant metastases		
Tumors of the upper thoracic esophagus			
M1a	Metastases in cervical nodes		
M1b	Other distant metastases		
Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
Stage III	T3	N1	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

Adapted from Fleming ID, Cooper JS, Henson DE, et al., eds. *American Joint Committee on Cancer: cancer staging manual*, 5th ed. New York: Spring-Verlag, 2002.

Table 50.5 PATHOLOGIC CLASSIFICATION OF MALIGNANT ESOPHAGEAL TUMORS

Epithelial tumors
- Squamous cell carcinoma
  - Well differentiated
  - Moderately differentiated
  - Poorly differentiated
- Variants of squamous cell carcinoma
  - Spindle cell carcinoma
  - Pseudosarcoma and carcinosarcoma
  - Verrucous carcinoma
  - *In situ* carcinoma
- Adenocarcinoma
  - Adenoacanthoma
- Adenoid cystic carcinoma (cylindroma)
- Mucoepidermoid carcinoma
- Adenosquamous carcinoma
- Carcinoid
- Small cell carcinoma

Nonepithelial tumors
- Leiomyosarcoma
- Malignant melanoma
- Rhabdomyosarcoma
- Myoblastoma
- Choriocarcinoma
- Lymphoma

From Rosenberg JC, Lichter AS, Leichman LP. Cancer of the esophagus. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: principles and practice of oncology,* 3rd ed. Philadelphia: J.B. Lippincott, 1989;499, with permission.

(108). Pseudosarcoma is a variant of a poorly differentiated squamous cell carcinoma with spindle-shaped cells in the stroma resembling fibroblasts. Verrucous carcinoma is a well differentiated, papillary variant of squamous cell carcinoma (108). Squamous cell carcinoma *in situ* is rarely seen in the United States and should be distinguished from dysplasia (26,87,120).

Adenocarcinoma is now the predominant histologic type of esophageal cancer. Adenocarcinoma may arise from foci of ectopic gastric mucosa or intrinsic esophageal glands. However, it is believed the vast majority arises from Barrett's esophagus. If a focus of squamous cell metaplasia is found in an adenocarcinoma, the tumor may be referred to as an adenoacanthoma (129).

Adenoid cystic carcinomas are rare, with an incidence of 0.75%. Patients with this malignancy present around the sixth decade of life and have a median survival of only 9 months (44). Mucoepidermoid tumors (adenosquamous carcinomas) are more aggressive and carry a poor prognosis (131). The incidence of small-cell carcinoma is approximately 2%. Patients with these malignancies present in the sixth to eighth decades of life, and the lesion is usually located in the middle to lower esophagus in males (24,65). These are believed to originate in the argyrophilic cells in the esophagus and may produce paraneoplastic syndromes, such as antidiuretic hormone secretion and hypercalcemia (38). The clinical course of small-cell carcinoma is similar to that of small-cell carcinoma of the lung and may be responsive to chemotherapy and radiation therapy (65,131).

Nonepithelial tumors of the esophagus are rare. Among these, leiomyosarcomas are the most common. Twenty-five percent of patients with this tumor present with metastases (48,99,104). Histologically, these tumors have interlacing bundles of spindle-shaped cells. Less aggressive forms have fewer mitotic figures and less anaplasia. Prognosis has been reported to be more favorable than that of squamous cell carcinoma (131). In patients with Kaposi's sarcoma, gastrointestinal involvement of the esophagus can be seen (50).

Malignant melanoma is rare and can occur as a primary esophageal tumor or as a metastasis. These lesions are usually large and often covered by intact squamous mucosa with focal areas of ulceration. Spread is usually submucosal. Mean survival is approximately 7 months (83,121). Lymphoma comprises approximately 1% of esophageal malignancies. It is usually associated with direct extension from other organs, although primary esophageal lymphoma has been reported (98).

Prognostic Factors

Stage is the most important prognostic factor in estimating survival of esophageal cancer patients. Increasing depth of penetration (T stage), nodal involvement (N stage), and absence or presence of distant metastases (M stage) significantly influence outcome. Patients with distant metastases are very rarely curable. In addition to stage, other factors portend outcome. Tumor location in the esophagus has been reported to influence survival, with upper-third lesions experiencing improved outcomes versus lesions in the lower two-thirds (64,101). Tumor size may also impact outcome. One study reported a 2-year survival rate of 19.2% for patients with tumors <5 cm in size versus 1.9% for patients with tumors >9 cm (64). Increasing tumor size is also correlated with unresectability and higher rates of distant metastases. Histologic tumor type has also been reported as an independent prognostic factor in patients undergoing resection. Siewert et al. (118) analyzed over 1,000 patients undergoing resection and found a 5-year survival rate of 47% for patients with adenocarcinoma versus 37% with squamous cell carcinoma. Patients with early stage adenocarcinoma had a much lower incidence of nodal involvement versus their squamous cell carcinoma counter parts. However, other series have reported no survival differences by histology (6).

Women tend to fare better than men with regards to survival (64,101). Race may also be a factor; Hussey et al. (64) reported higher survival rates in Caucasians than African Americans. In contrast, a recent analysis of patients treated with radiation and chemotherapy showed no statistical survival difference between races (125). Age has also been found to be significant, with patients older than 65 years of age faring less well (101). Weight loss and low overall performance status also indicate poor prognosis (64). Deep ulceration of the tumor, sinus tract formation, and fistula formation are other poor prognostic factors (109). Lymphatic vessel invasion portends advanced stage and worse long-term survival (137).

The importance of obtaining uninvolved pathologic margins at resection is of significant importance with regards to long-term outcomes. An Intergroup study (discussed below) evaluating chemotherapy preceding and following esophagectomy showed outcomes were similar in patients undergoing R1 resection (positive microscopic margins), R2 resection (gross residual disease), or patients not undergoing resection at all. Only patients undergoing R0 resection (uninvolved margins) had a substantial chance of long-term disease-free survival (69). A patterns of care survey examined the outcomes of patients with adenocarcinoma and squamous cell carcinoma of the esophagus between 1996 and 1999. Patients were treated with radiation therapy across 59 institutions. On multivariate analysis, significant improvements in survival were seen in patients treated at centers with ≥500 new cancer patients per year, compared to centers seeing <500 (hazard ratio 1.32; $p = 0.03$) (126).

General Management

Treatment for esophageal carcinoma is characterized as curative or palliative. According to Pearson (101), only 20/100

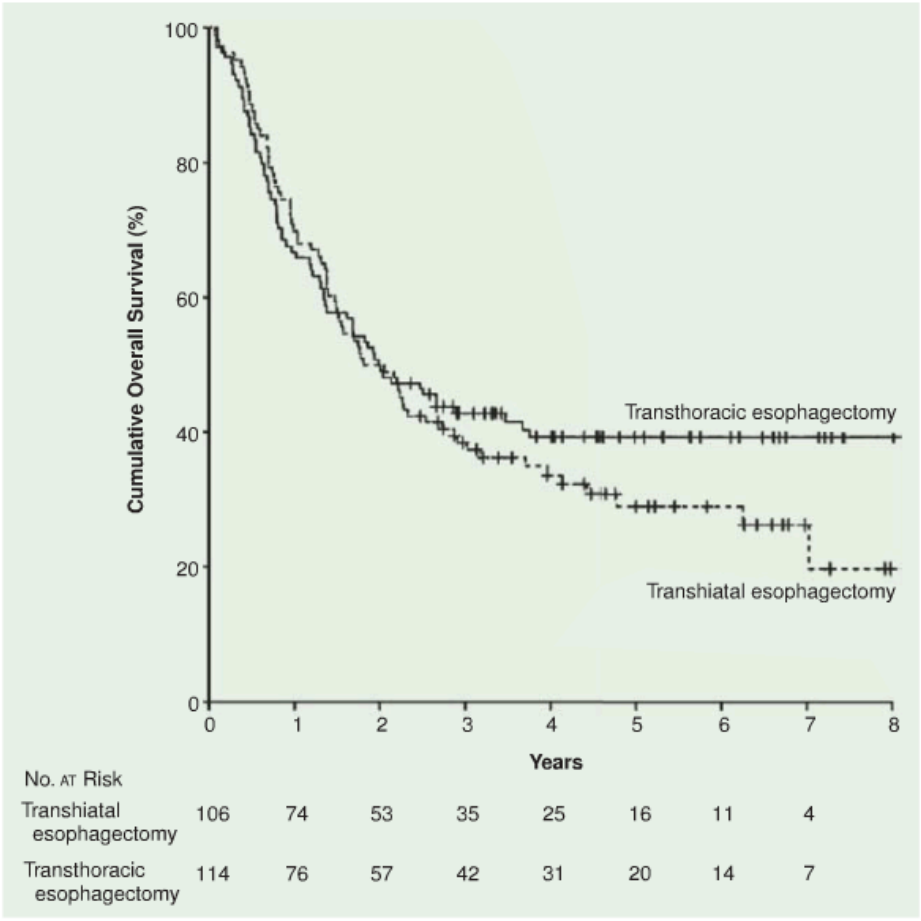


FIGURE 50.7. Overall survival among patients randomly assigned to transhiatal esophagectomy or transthoracic esophagectomy with extended en bloc lymphadenectomy. (Hulscher)

patients present with cancer of the esophagus that is truly localized to the esophagus, indicating that at the time of diagnosis, approximately 80/100 patients have locally advanced or distant disease.

Surgery with Curative Intent

Surgery of the thoracic esophagus requires a subtotal or total esophagectomy and is usually undertaken for lesions of the mid- to lower third of the thoracic esophagus and gastroesophageal junction. Patients with stage I to III and selected IVa tumors are often considered for potentially curative resection; however, aortic, tracheal, heart, or great vessel invasion may preclude resection. Esophagectomy may be accomplished by a number of techniques, including a transhiatal esophagectomy, right thoracotomy (Ivor-Lewis), left thoracotomy, or radical esophagectomy. Each technique has its advantages and disadvantages. Advantages of the transthoracic approach include better visualization with access and resection of the upper two thirds of the esophagus and mediastinal lymph nodes. Alternatively, the transhiatal approach has less morbidity than thoracotomy (including respiratory compromise) with easier access to anastomotic leaks (neck versus thorax). In any instance, achievement of negative margins at resection has been reported to be a significant prognostic factor and should be the goal of esophageal resection. In a study of 500 patients undergoing transthoracic resection, patients undergoing margin negative resection had a 5-year survival rate of 29% versus no 5-year survivors in patients with involved margins (43).

The Ivor-Lewis procedure is the classic approach to expose mid-esophageal lesions. A left thoracotomy procedure exposes lesions of the gastroesophageal junction. Transhiatal esophagectomy is performed without a thoracotomy and is useful in lower esophageal lesions, although direct visualization and dissection of varying mediastinal lymph nodes cannot be achieved. The optimal surgical approach is unknown. A randomized trial comparing transhiatal versus transthoracic approaches in patients with adenocarcinoma showed no significant survival advantage to the later, although a possible trend was noted (5-year survival 29% vs. 39%; Fig. 50.7). However, perioperative mortality was also increased with the transthoracic approach (63).

Laparotomy can be performed before or concurrently with esophagectomy to rule out any disease below the diaphragm. Multiple reconstruction options are available following definitive surgery; esophagogastrostomy is the most widely used, using the stomach as a conduit to replace the esophagus. Patients with significant obstruction and inability to maintain their weight often require placement of feeding jejunostomy. If possible surgery is planned, gastric tube placement is generally avoided given the stomach will ultimately serve as the "neoesophagus" following resection. Colon interposition, preferably with the left colon, can also be used; however, this approach is generally reserved for patients who have previously undergone gastric surgery or other procedures that have devascularized the stomach (108).

Squamous cell carcinoma of the cervical esophagus presents a difficult management situation. If surgery is performed, resection of portions of the pharynx, the entire larynx, thyroid gland, and the proximal esophagus is often required. Radical neck dissections are also carried out (109). Because of the significant morbidity and loss of organ function with surgery, chemoradiation alone has been frequently employed. The survival probability with definitive chemoradiotherapy is similar, without the major functional impairments, morbidity, and mortality associated with surgery (56).

Curative Combination Therapy

In the treatment of patients with esophageal cancer, an approach of radiation therapy with concurrent chemotherapy, with or without surgery, is frequently adopted. Multiagent

chemotherapy with cisplatin and 5-fluorouracil (5-FU) is utilized most frequently. Taxanes, topoisomerase inhibitors, and antiepidermal growth factor receptor inhibitors with radiation therapy are under investigation.

Palliative Treatment

Palliative treatment is frequently used for the relief of symptoms of esophageal carcinoma, especially dysphagia (119). Surgical palliation involves resection and reconstruction, if possible, removing the bulk of the disease, potentially preventing abscess and fistula formation as well as bleeding. Substernal bypass with the colon or entire stomach has also been carried out (119). However, given the poor prognosis in patients with advanced disease and morbidity associated with resection, this approach is not commonly adopted and should be avoided in patients who can be managed with nonsurgical modalities.

Endoscopic dilatation is a reasonable alternative. When the lumen of the esophagus is dilated to 15 mm, dysphagia is often no longer experienced. Repeat dilatation is often required (109). Esophageal stenting with either conventional plastic stents or metallic self-expanding stents can also be used to maintain patency (112).

Palliative irradiation is frequently used to control the primary disease as well as distant metastases. Resolution of symptoms, especially pain and dysphagia, can be accomplished in up to 80% of patients (108). Palliative treatment regimens range from 30 Gy over 2 weeks (92) to 50 Gy over 5 weeks (108). Chemotherapy is also often used for palliation, either alone or in combination with radiation.

Radiation Therapy Techniques

Simulation

When patients are simulated, the radiation oncologist must know the extent of disease based on imaging (barium swallow, CT, PET) as well as endoscopy. During simulation, the patient is positioned, straightened, and immobilized on the simulation table. Arms are generally placed overhead. Palpable neck disease should be marked with a radio-opaque wire. Conventional simulation using fluoroscopy or CT-based simulation is appropriate. With either technique, the administration of oral contrast to delineate the esophagus is used. With conventional simulation (two-dimensional planning), frontal and lateral radiographs of the patient in the treatment position are obtained. For cervical and upper thoracic lesions, an immobilization mask may assist in an accurate reproducibility. Some authors recommend placing the patient in the prone position for treatment to displace the esophagus away from the spinal cord (120).

When three-dimensional (3D) conformal radiation therapy is used, the patient is placed on the CT simulator in the same treatment position, and a scan of the entire area of interest with margin is obtained. At minimum, 5-mm slices should be used, allowing accurate tumor characterization as well as improved quality of digitally reconstructed radiographs. Arterial phase IV contrast is generally used to delineate mediastinal and abdominal vascular nodal basins, including the celiac axis. The tumor and vital structures are then outlined on each slice on the treatment planning system, enabling a 3D treatment plan to be generated.

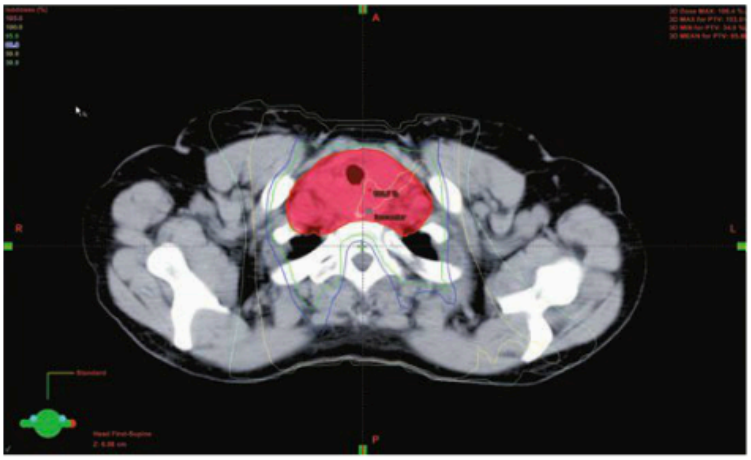
Treatment Planning

The fusion of CT-PET has been shown to prompt treatment modification of the gross tumor volume (GTV) and planning target volumes in a majority of patients, including lung volume considerations (148). A margin of 5 cm above and below the tumor is usually recommended to cover subclinical submucosal/nodal disease, as well as an approximate 2.5-cm radial margin. For disease located in the lower esophagus, the celiac axis and gastrohepatic ligament are often included based on patterns of spread data. The celiac axis is generally located at the level of T12 and can be identified on CT. Similarly, supraclavicular nodal basins are often included for upper esophageal lesions (109).

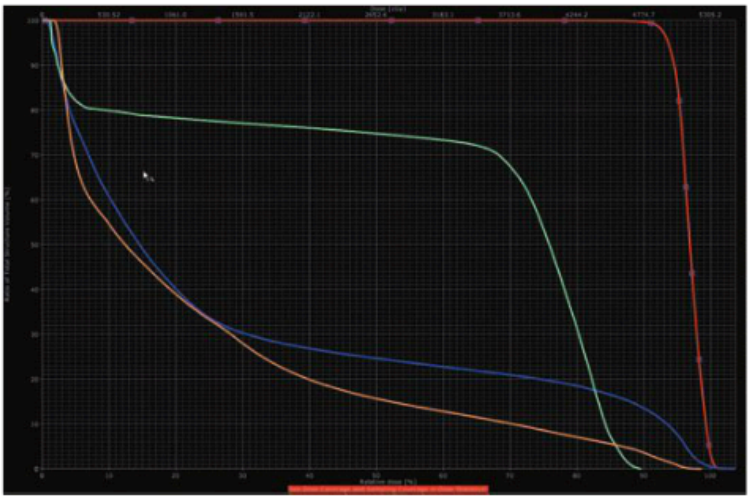
Because of the changing contour from the neck to the thoracic inlet, treatment of lesions in the upper third of the esophagus can present a difficult technical problem. Often, lesions in the upper cervical or postcricoid esophagus are treated from the laryngopharynx to the carina, depending on extent of disease. Supraclavicular and superior mediastinal nodes are irradiated electively. This can be achieved with lateral parallel opposed or oblique portals to the primary tumor and a single anterior field for the supraclavicular and superior mediastinal nodes (64). Another technique treats lesions in this region by means of a four-field box technique. A wax bolus is used to build up the lack of tissue above the shoulders, acting as a compensator. A high-energy beam (>15 MV) is used, and both sides of the neck are treated prophylactically. Other methods of treating lesions at the thoracic inlet include 140-degree arc rotations, anterior wedged pairs, and three- or four-field techniques using posterior oblique portals combined with a single anterior portal or anteroposterior-posteroanterior (AP) fields (64). More recently, intensity-modulated radiation therapy (IMRT)–based planning has facilitated the treatment of upper esophageal lesions (Fig. 50.8A,B). Strict normal tissue constraints, including normal lung and spinal cord, are important considerations using these techniques.

Lesions in the thoracic esophagus may be more simply approached. The inferior margin of the initial fields includes the gastroesophageal junction and, for lower or middle-third lesions, the celiac axis nodal basins as well as gastrohepatic ligament. Initial fields include anteroposterior-posteroanterior opposed portals and are treated to 30 to 36 Gy, after which oblique fields may be used, including an anterior field with posterior oblique pair (left and right posterior oblique) or opposed right anterior and left posterior oblique fields to 45 Gy, inclusive of the above nodal basins. Care should be taken to avoid as much of the heart as reasonably possible. Additionally, the kidney volume in the radiation field should be considered when treating the celiac axis in lower esophageal tumors. Reduced fields encompassing gross disease with an approximate 2-cm margin through oblique or lateral fields may then be used for an additional 5.4 Gy. Doses usually do not exceed 50 Gy (see below). Figures 50.9 and 50.10 show digitally reconstructed radiographs for a typical lower esophageal adenocarcinoma. Figure 50.11A,B illustrates dose distributions and a dose–volume histogram for a patient with lower esophageal adenocarcinoma using this approach.

In radiation therapy planning, normal tissue tolerance should always be considered. The spinal cord dose should generally be limited to 45 Gy using 1.8 Gy fractions. Efforts to minimize radiation to the heart, in particular the left ventricle in lower esophageal lesions, should be made. Adopting an "off heart" approach using oblique orientations (including right anterior and left posterior) may help facilitate this. Efforts to minimize dose to normal pulmonary tissues should be made, given there are emerging data suggesting volume of irradiated lung may correspond to postoperative complications and worsened pulmonary function (below). Frequently, the volume of irradiated lung can be minimized using a simple AP/PA approach. However, this often results in significant cardiac dose, particularly in lower esophagus and gastroesophageal junction tumors. Therefore, oblique orientations are used, resulting in increased volumes of normal lung being irradiated. When



A



B

DVH Line	Structure
	CTV
	Lung
	Spinal Cord
	heart

FIGURE 50.8. A: Isodose curves of a patient with cervical esophageal lesion treated with an eight-field IMRT plan. **B:** Dose–volume histogram for patient treated to 50 to 40 cGy using an eight-field IMRT technique. CTV, clinical target volume. (Both photos courtesy of Zhiheng Wang, Ph.D.)

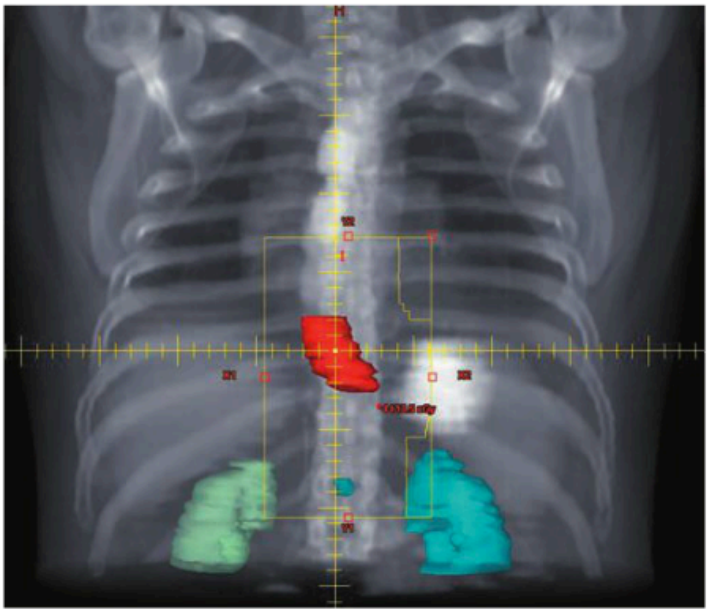


FIGURE 50.9. Digitally reconstructed radiograph for a typical lower esophageal lesion—AP view. gross tumor volume, red; celiac trunk, blue; right kidney, green; left kidney, blue (Courtesy of Rhonda May, CMD and Shiva Das, Ph.D.)

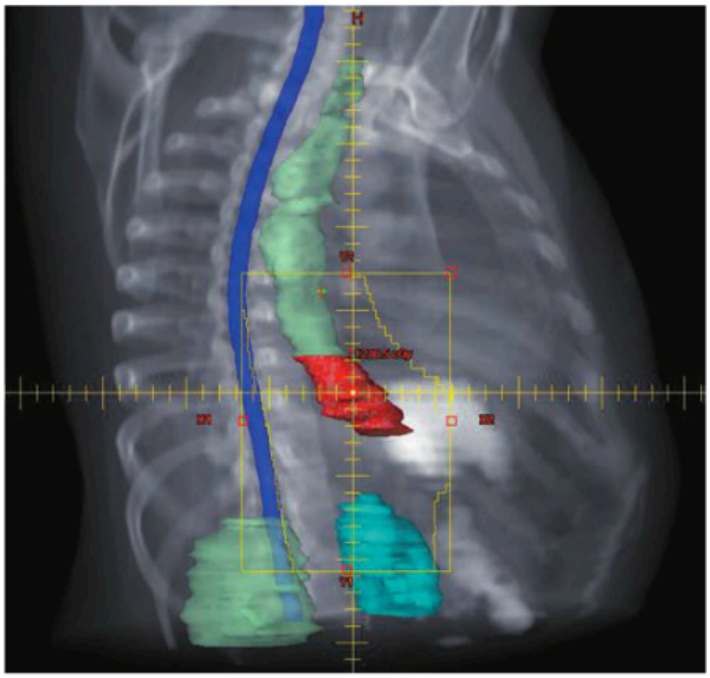
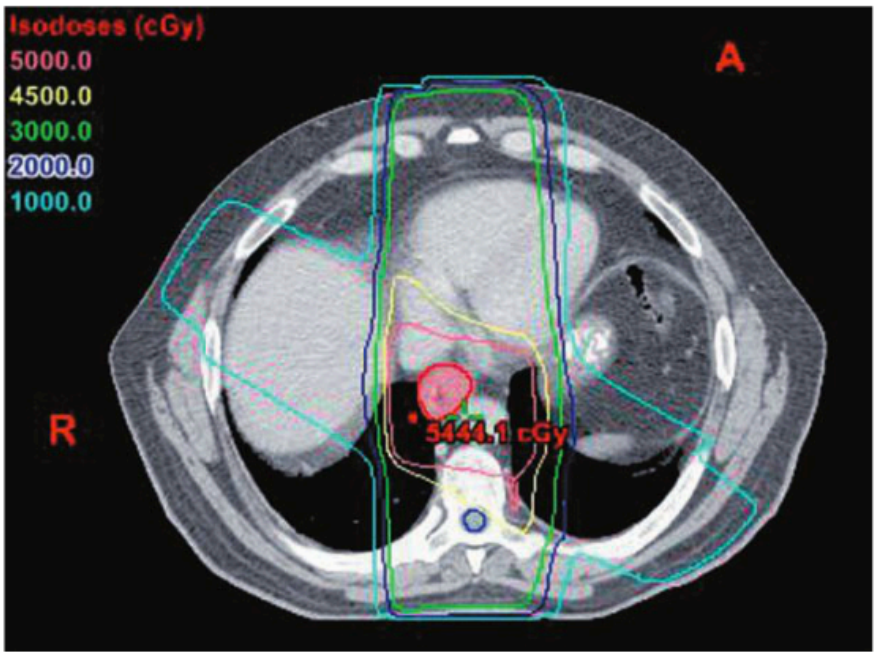


FIGURE 50.10. Right anterior oblique fields used to spare the left ventricle and spinal cord following initial AP/PA fields. (Courtesy of Rhonda May, CMD and Shiva Das, Ph.D.)



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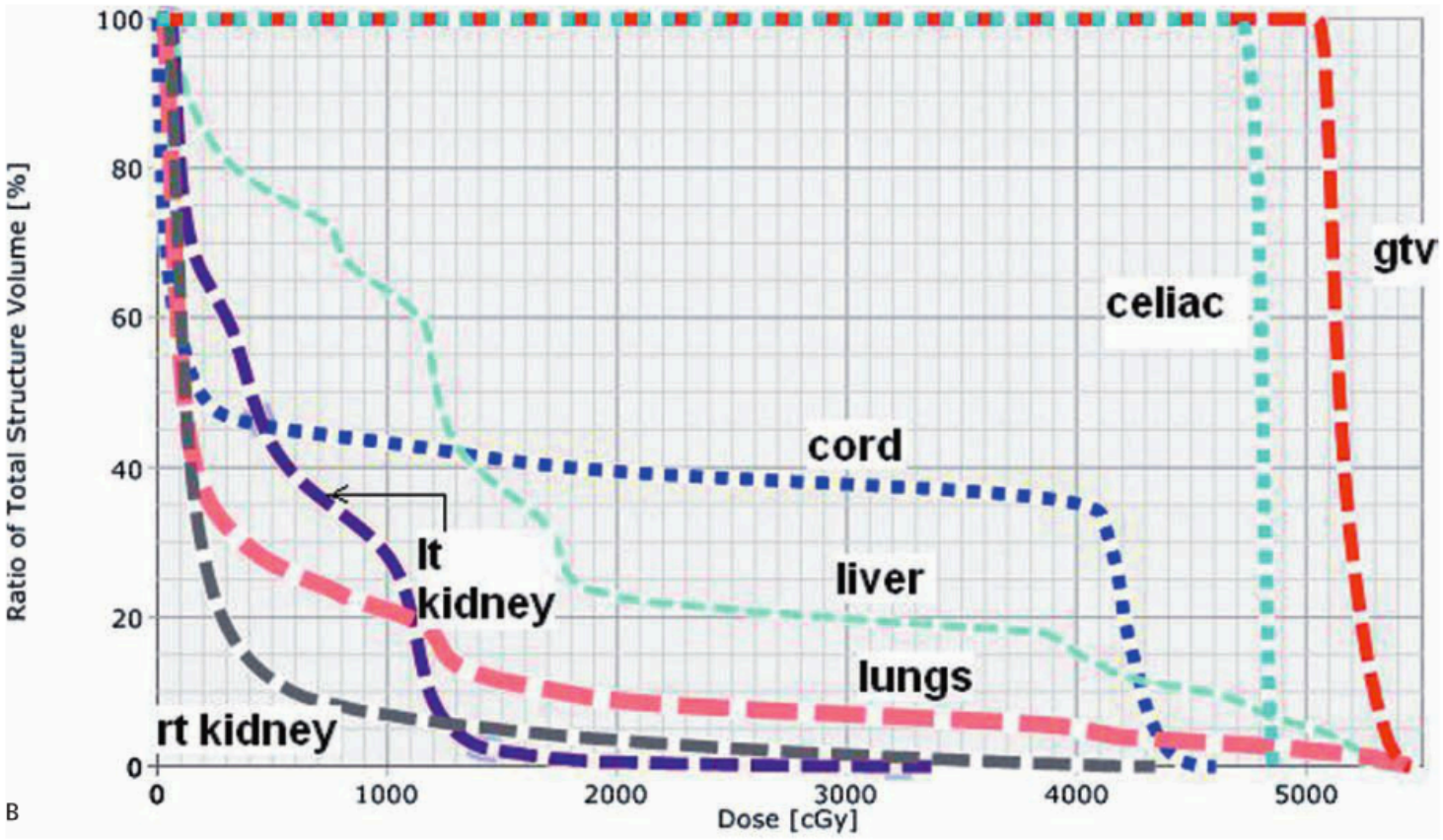


B

FIGURE 50.11. A: Dose distributions using computed tomography–generated dosimetry for a patient with an adenocarcinoma involving the lower esophagus. **B:** Dose–volume histogram for patient with a lower esophageal adenocarcinoma. (Both courtesy of Rhonda May, CMD and Shiva Das, Ph.D.)

given concurrent chemotherapy, dose to these fields should generally be limited to 13 to 15 Gy.

Doses of Radiation

Because local-regional failure is common after conventional chemoradiation, investigators have evaluated dose-escalation techniques. Minsky et al. (91) reported the results of Intergroup 0123, which randomized 236 patients with clinical stage T1-4, N0/1, M0 squamous cell or adenocarcinoma of the esophagus selected for nonsurgical therapy. Patients were randomized to receive 64.8 Gy versus 50.4 Gy, both with concurrent 5-FU and cisplatin chemotherapy. Patients with cervical, mid-, or distal esophageal cancer were eligible with the exception of tumors within 2 cm of the gastroesophageal junction. Approximately 85% of patients had squamous cell histology. This study was closed after interim analysis showed no probability of superiority in the high-dose arm. No significant difference in median survival (13 vs. 18.1 months), 2-year survival (31% vs. 40%), or local-regional failure/persistence of disease (56% vs. 52%) was seen between the high-dose and standard-dose arms. Eleven treatment-related deaths occurred in the high-dose arm compared with two in the standard-dose arm, with 7/11 high-dose arm deaths occurring in patients who received 50.4 Gy or less.

The authors performed a separate survival analysis including only patients receiving the assigned radiation dose. Despite this, no survival advantage was noted in the high-dose arm. These authors concluded that higher radiation doses did not increase survival or local/regional control, and that the standard radiation dose for patients treated with concurrent 5-FU and cisplatin chemotherapy is 50.4 Gy.

Brachytherapy

In addition to external beam radiation therapy (EBRT), intracavitary therapy can be used with curative or palliative intent. The advantage of brachytherapy centers on exploitation of the inverse square law and quick dose falloff, thus sparing surrounding tissues from radiation while providing focal dose escalation. The radioactive source of choice is usually iridium-192 (^{192}Ir). High–dose-rate (HDR) techniques can deliver 100 to 400 Gy per hour, allowing treatment to be given in 5 to 10 minutes.

With brachytherapy, an afterloading catheter is introduced through the nose into the esophagus to the primary tumor site under fluoroscopic guidance. This is often performed with the patient on the simulation table. Contrast is used to define the tumor site. CT scan can also be used to discern tumor location. After localization films are taken and dosimetry generated, the catheter is then attached to a remote afterloader through a guide cable and the ^{192}Ir source inserted through remote control. Doses of 5 to 20 Gy are usually delivered to a depth of 1 cm from the center of the catheter. Dose can be shaped and modified through the use of dwell times.

Results of Therapy

The best survival results have been reported in patients who have esophageal tumors that are truly localized. Survival rates range from 25% to 35% at 5 years, and these results have been attained using an array of treatment approaches. Problems arise in comparisons of various modalities, however, because of patient selection factors. A review of the Princess Margaret Hospital data (15) supports the concept that extent of tumor rather than therapy is the most important factor influencing survival. They found a significant correlation between tumor (T) stage and response to treatment: T1 lesions showed a 100% response rate, whereas T2 and T3 lesions had response rates of 68% and 58%, respectively. They also found differences in survival according to T stage, metastasis (M) stage, and overall stage. Almost 20% of patients with stage I disease were alive at 3.5 years, whereas only 11% of stage II patients were alive after the same interval. All patients with stage III disease died within approximately 1.5 years following therapy.

Surgery Alone

Surgery remains the benchmark to which other modalities are compared. Surgery removes the tumor, a length of normal esophagus, and lymph nodes. Although multiple techniques exist in the resection of esophageal cancer, no clear "preferred" approach has emerged. Proponents of more extended resection (including transthoracic approaches) have advocated that such procedures result in a superior nodal clearance and therefore offer a more complete "oncologic" resection. As described previously, a trial from the Netherlands randomized 220 patients with esophageal adenocarcinoma to transhiatal esophagectomy alone or transthoracic esophagectomy with extended lymph node dissection. Patients undergoing transhiatal resection experienced significantly fewer pulmonary complications, chylous leaks, as well as significantly reduced ventilator dependence, intensive care unit, and hospital stays. At a median 4.7 year follow-up, no significant difference in local–regional recurrence was seen between the two groups (32% transhiatal vs. 31% transthoracic). Furthermore, no significant differences were seen in median disease-free survival (1.4 years vs. 1.7 years; $p = 0.15$) or median overall survival (1.8 vs. 2.0 years; $p = 0.38$). However, there did appear to be a nonsignificant trend favoring the transthoracic approach in improved disease-free survival (5-year 27% vs 39%) and overall survival (5-year 29% vs. 39%) (see Fig. 50.7). The authors concluded that a transhiatal approach was associated with less morbidity relative to transthoracic surgery with no apparent survival advantage with either technique, although a trend toward improved survival with longer follow-up was seen (63). In summary, none of the surgical approaches to localized esophageal cancer has clearly been shown to be superior with regards to complications or outcomes, and no one standard surgical approach exists for esophageal cancer resection.

Following resection alone, local–regional relapse is a common mode of failure. Contemporary randomized trials with surgery-alone arms have reported local–regional failure rates of 32% to 45% (63,69,77,133). It should be remembered that patterns of failure reports often describe first site of failure only, potentially underreporting the true incidence of local–regional recurrence. These and other data suggest that even with modern surgical techniques, local–regional persistence of disease following resection remains a major problem. Additionally, studies pooling large surgical experiences have reported poor overall survival rates. One series reviewed 122 papers involving more than 83,000 patients treated primarily by surgery (41,42). The overall 5-year survival rate for patients with resected tumors was 12%. Patients treated with palliative intent had a survival range of 2 to 6 months. Whyte and Orringer (144) reviewed 583 patients undergoing transhiatal esophagectomy alone; the 5-year overall survival rate was 27%. Other studies are in basic agreement with these findings (2,76,101,114,119). Furthermore, prospective randomized trials using surgery alone in the treatment of esophageal cancer have reported 3-year survival rates ranging from 6% to 35% (69,133,139) (Table 50.6). Given these high rates of relapse and poor long-term survival, the integration of adjuvant or neoadjuvant chemoradiation approaches into the treatment of esophageal cancer is rational and indicated.

Radiation Therapy Alone

There are no randomized studies comparing surgery alone with radiation alone, and, radiation therapy alone has been usually delivered when lesions are deemed inoperable because of tumor extent or medical contraindications and/or when palliative treatment is indicated. In general, patients receiving radiation as a sole treatment modality have a median survival of 6 to 12 months and a 5-year survival rate of <10%.

In a report by Pearson (101) in 1977, 208 patients were treated with radiation alone. Patients received 50 Gy and had an unduplicated 5-year reported survival rate of 20%. An updated Edinburgh experience reported 2- and 5-year survival rates of 19% and 9%, respectively (95). A large review analyzing 49 series involving more than 8,400 patients treated primarily with radiation therapy found overall survival rates at 1, 2, and 5 years to be 18%, 8%, and 6%, respectively (42). Hancock and Glatstein (56) reviewed 9,511 patients and found only 5.8% were alive at 5 years. Okawa et al. (96) reported 5-year survival rates by stage. For patients with stage I disease, the 5-year survival rate was 20%; stage II, 10%; stage III, 3%; and stage IV, 0%. Overall, the 5-year survival rate was 9%. For cervical esophageal lesions treated with radiation alone, the cure rates are comparable with those in patients treated with surgery alone. Lederman (79) treated 263 patients with radiation therapy alone and reported 3- and 5-year survival rates of 11% and 7%, respectively. In more contemporary series, an

Table 50.6 COMPARISON OF SURGERY ALONE ARMS IN RANDOMIZED STUDIES

Author (Reference)	Patients (Total)	Patients (Surgical)	Median Survival (Months)	2-Year Survival	3-Year Survival
Walsh et al. (139)	110	55	11	26	6
Urba et al. (133)	100	50	18	NA	15
Bosset et al. (23)	282	139	19	40	35
Kelsen et al. (69)	440	227	16	37	23
Medical Research Council (89)	802	402	13	34	NA

NA, not applicable

Intergroup randomized study (discussed below) comparing combined chemotherapy with 5-FU and cisplatin with radiotherapy (50 Gy) versus radiotherapy only (64 Gy) showed 3-year survival with radiotherapy alone was 0%. These and other data suggest that treatment with radiation therapy alone for esophageal cancer patients is palliative in the vast majority of patients (Table 50.7).

Preoperative Radiation Therapy

The use of preoperative radiation therapy has potential biologic and physical advantages, including increased resectability of tumors, increased tumor radioresponsiveness secondary to improved tumor oxygenation, a theoretical decreased likelihood of dissemination at the time of surgery, as well as avoidance of surgery in patients with rapidly progressive disease.

There are numerous nonrandomized studies reporting patient survival with preoperative radiation therapy. Hancock and Glatstein (56) reviewed 1,181 patients treated with preoperative irradiation. In their analysis, the overall 5-year survival rate was 6%, although in patients who completed preoperative therapy and esophageal resection, the 5-year survival rate was 14%. Marks et al. (88) treated 332 patients (101 resectable) with preoperative therapy and found 2- and 5-year survival rates of 23% and 14%, respectively.

There are at least five randomized studies comparing preoperative irradiation followed by surgery with surgery alone. These studies demonstrate no apparent clinical benefit to the use of preoperative radiation therapy alone (Table 50.8). Launois et al. (76) reported delivering 40 Gy over 8 to 12 days with surgery 8 days later versus surgery alone. Resection rates were similar—70% and 58% for preoperative irradiation and for surgery alone, respectively. The 5-year survival rate after resection was 11.5% for those treated with surgery alone, compared with 9.5% for those treated with irradiation and surgery. The second randomized study, published by the European Organisation for Research and Treatment of Cancer (EORTC), used 33 Gy over 12 days (52). There was no significant difference in survival between those receiving preoperative irradiation and those receiving surgery alone. Arnott et al. (13) reported on 176 patients, 86 of whom were treated with esophagectomy alone versus 90 who were treated with preoperative radiation therapy. Preoperative radiation therapy was delivered with 4-MV photons using opposed fields, delivering 20 Gy at 2 Gy per fraction. Resectability and local failure were not reported. Patients receiving low-dose radiation therapy did not demonstrate a benefit in 5-year overall survival rates (17% vs. 9% for surgery and preoperative radiation, respectively; $p = 0.4$). Wang et al. (140) randomized 206 patients to surgery alone versus 40 Gy in 2-Gy fractions delivered preoperatively. No significant survival advantage was seen for patients receiving radiation therapy (35% vs. 30%; $p > 0.05$).

A recent meta-analysis from the Oeosophageal Cancer Collaborative Group updated data from five randomized trials of >1,100 patients comparing preoperative radiotherapy alone versus surgery alone. The majority of patients had squamous cell carcinoma. At a median follow-up of 9 years, the hazard ratio was 0.89, suggestive of an overall reduction in the risk of death of 11% and absolute survival benefit of 4% at 5 years with the use of preoperative radiotherapy. However, this was not statistically significant ($p = 0.06$). The authors concluded that there

Table 50.7 RESULTS WITH EXTERNAL BEAM RADIATION THERAPY ALONE FOR ESOPHAGEAL CANCER

Author (Reference)	No. of Patients	Dose	2-Year Survival	5-Year Survival
Pearson (101)	288	50 Gy/4 wk (2.5 Gy/fr)	NR	17% (48/288)
Beatty et al. (15)	344	>40 Gy/<19 fr, >45 Gy/<23 fr, >50 Gy/<3 mo	21%	0%
	176 curative[a]			
	168 palliative	Less than the curative doses	0%	0%
Schuchmann et al. (114)	127	>4,500 R	—	0%
		<4,500 R	—	0%
Newaishy et al. (95)	444 (all curative)	50–55 Gy/4 wk (2.5–2.75 Gy/fr)	—	9%
Okawa et al. (96)	288		NR	9%
DeRen (36)	678	60–69 Gy/6–8 wk, 5–10 Gy boost	11.4%	8%

fr, fraction; NR, not reported
[a]Thirty of the 176 radically treated patients had surgery plus irradiation.

Table 50.8 RANDOMIZED TRIALS OF PREOPERATIVE RADIATION THERAPY FOR ESOPHAGEAL CANCER

Author (Reference)	Patients	Dose (Gy)	Fraction (Gy)	Local Failure		Survival (5-Year)	
				Surgery	RT + Surgery	Surgery	RT + Surgery
Launois et al. (76)	109	40	NA	NA	NA	12	10
Gignoux et al. (52)	229	33	3.3	67	46	8	10
Arnott et al. (13)[a]	176	20	2	NA	NA	17	9
Wang et al. (140)	160	40	2	NA	NA	30	35

NA, not applicable; RT, radiation therapy
[a]Both squamous and adenocarcinoma.

was no clear evidence that preoperative radiotherapy improves survival of patients with potentially resectable esophageal cancer (12).

In general, there were no differences in resectability rates, local failure, or survival in almost all reported individual studies. Interpretation of these varying studies is complicated by differences in radiation techniques, suboptimal radiation dose, and inadequate radiation volumes. Although preoperative radiation therapy alone may improve local control, there is no convincing data that it results in improved survival in esophageal cancer patients.

Postoperative Radiation Therapy

The main advantage to adjuvant versus neoadjuvant approaches is the knowledge of the pathological staging to appropriately select patients for therapy. Postoperative therapy may allow the radiation oncologist to treat areas at risk for recurrence while sparing otherwise normal radiosensitive structures, thereby decreasing toxicity. In addition, patients with pathologic T1N0 or metastatic disease may be spared treatment. Postoperative irradiation has historically been delivered to patients with esophageal cancer who have bulky tumors with gross residual disease or histologically proven microscopic residual disease. Potential disadvantages of postoperative radiation include limited tolerance of normal tissues following gastric pull-up or intestinal interposition and irradiation of a devascularized tumor bed.

Three randomized trails have assessed surgery alone versus surgery followed by postoperative radiation therapy. In a French trial, 221 patients with squamous cell carcinoma of the mid-lower esophagus undergoing esophagectomy were randomized to postoperative radiation therapy or no further treatment. Patients were stratified by extent of nodal involvement. Total dose was 45 to 55 Gy at 1.8 Gy per fraction, beginning within 3 months of surgery. Five-year survival in node negative patients was 38% versus 7% with involved nodes. No significant survival difference was seen in patients receiving postoperative radiation versus surgery alone. Rates of local regional recurrence were lower in patients receiving radiation therapy (85% vs. 70%; P = NS). However, in patients without nodal involvement, local–regional recurrence was significantly improved in patients receiving postoperative therapy (90% v. 65%; $p < 0.2$). The authors concluded that postoperative radiation therapy did not improve survival following resection for squamous cell carcinoma (127).

Investigators from the University of Hong Kong reported the results of 130 patients treated with postoperative radiation therapy versus surgery alone. Patients who underwent either curative or palliative resections were included in this trial. Radiation therapy was delivered to a total dose of 49 Gy (curative patients) or 52.5 Gy (palliative patients) using 3.5-Gy fractions. Most patients had squamous cell histology. Local recurrence was noted in 15% of patients receiving radiation and 31% of patients with surgery only ($p = 0.06$). In patients with squamous cell carcinoma, the local recurrence rate was 15% with radiation therapy versus 36% with surgery alone ($p = 0.02$). Median survival in patients was worse in patients receiving postoperative radiotherapy versus control patients (8.7 vs. 15.2 months; $p = 0.02$). A total of 10 patients undergoing surgery alone had tracheal bronchial recurrence resulting in death versus three patients receiving adjuvant radiation therapy ($p = 0.07$). The authors concluded that postoperative radiation therapy was associated with increased morbidity and death caused by irradiation injury as well as the early appearance of metastatic disease and a reduced overall survival, although patients receiving radiation therapy were less likely to have a tracheobronchial recurrence. The high rate of complications associated with radiation therapy in this study may possibly be related to the high dose per fraction and total dose delivered (47).

Lastly, a study conducted by Xiao et al. (146) randomized 549 patients to radical resection vs radical resection followed by radiation therapy. All patients had squamous cell carcinoma. The radiation dose delivered was 60 Gy in 6 weeks. Patients were classified into three groups: Group 1, no lymph node involvement; Group 2, one to two lymph nodes involved; Group 3, three or more lymph nodes involved. Results showed T stage, stage group, and the number of lymph nodes involved by tumor were highly predictive of survival. The 5-year survival for groups 1, 2, and 3 were 58.1%, 30.6%, and 14.4%, respectively. Local control and survival were improved in patients receiving postoperative irradiation. For patients with involved lymph nodes, 5-year survival for resection only patients versus patients receiving resection and radiation therapy were 17.6% and 34.1%, respectively ($p = 0.04$). In summary, postoperative radiation therapy may decrease local recurrence, particularly in the setting of involved margins, although the impact of this adjuvant treatment on overall survival remains less clear.

Postoperative Combined Chemoradiation

The role of adjuvant combined chemoradiation following resection of esophageal cancer has remained ill-defined. A large randomized Intergroup trial evaluating the role of adjuvant chemoradiation following surgery versus surgery alone for patients with adenocarcinoma of the stomach and GE junction was reported in 2001. In this study, a total of 556 patients with resected, margin-negative gastric or gastroesophageal junction adenocarcinoma were randomly assigned to surgery alone versus surgery with postoperative chemoradiotherapy. Treatment consisted of one cycle of 5-FU and leucovorin, followed by 45 Gy external beam irradiation concurrent with 5-FU, followed by two additional cycles of 5-FU and leucovorin. Approximately 20% of patients had lesions in the gastroesophageal

junction. A significant survival advantage was seen in the adjuvantly treated group (median survival 27 months vs. 36 months; $p = 0.005$). On subset analysis, this benefit was detected in patients with gastroesophageal cancer (84). Therefore, in patients with stage Ib to IV, nonmetastatic GE junctional carcinoma, it is appropriate to advise adjuvant chemoradiotherapy in efforts to potentially improve upon local control and ultimate survival.

Preoperative Chemotherapy

Three large randomized trials have shown conflicting results with the use of neoadjuvant chemotherapy alone in the treatment of esophageal cancer. Kelsen et al. (69) reported the results of an Intergroup study randomizing 440 patients with squamous cell carcinoma and adenocarcinoma to receive either combined cisplatin or 5-FU chemotherapy for three cycles followed by resection, followed by a similar regimen of adjuvant chemotherapy, versus immediate resection with no chemotherapy. Results of this trial showed patients receiving neoadjuvant chemotherapy had a pathologic complete response rate of 2.5% at resection. There was no apparent survival advantage (3-year survival of 23% vs. 26%) in patients receiving chemotherapy. Additionally, rates of local failure (32% vs. 31%) and distant metastases development (41% vs. 50%) were not significantly different between the two groups. The authors concluded that neoadjuvant chemotherapy with cisplatin and 5-FU did not improve survival in patients with resectable esophageal cancer.

In contrast to the Intergroup study, a similar trial from the Medical Research Council (MRC) randomized 802 patients with squamous cell carcinoma or adenocarcinoma of the esophagus to either two cycles of combined cisplatin/5-FU chemotherapy versus surgery alone. Preoperative staging CT was not required, and radiation therapy was allowed in both treatment arms. Patients receiving neoadjuvant chemotherapy had a statistically improved 2-year survival (43% vs. 34%) (89). The reason for outcomes differences in these trials is not clear.

A recent large European study randomly assigned patients with resectable adenocarcinoma of the stomach, gastroesophageal junction, or lower esophagus to preoperative and postoperative chemotherapy with epirubicin, cisplatin, and 5-FU (ECF) versus surgery alone. Approximately one fourth of the patients had adenocarcinoma involving the lower esophagus or gastroesophageal junction. Patients receiving perioperative chemotherapy had a hazard ratio for death of 0.75, which was highly significant. Five-year survival in patients receiving chemotherapy was 36% versus 23% in patients undergoing surgery alone ($p = 0.009$). Subgroup analysis of patients with lower esophageal or gastroesophageal junction tumors showed benefit to the delivery of perioperative chemotherapy (33).

Urshel et al. (135) performed a meta-analysis of 11 randomized controlled trials including nearly 2,000 patients treated with neoadjuvant chemotherapy and surgery versus surgery alone in patients with resectable esophageal cancer. These authors did not demonstrate a survival benefit with the addition of neoadjuvant chemotherapy. In summary, the role of neoadjuvant chemotherapy alone in the setting of potentially resectable esophageal cancer remains controversial.

Preoperative Chemoradiation versus Surgery Alone

Walsh et al. (139) reported the first randomized study to evaluate the role of concurrent preoperative chemoradiation combined with surgery. One hundred ten patients with adenocarcinoma of the esophagus were randomized to receive cisplatin, 5-FU, and concurrent radiation therapy followed by surgery versus surgery alone. Combined modality patients received two courses of chemotherapy weeks 1 and 6. Patients were treated using anteroposterior-posteroanterior fields (later changed to a three-field technique) to a total dose of 4,000 cGy in 15 fractions. Surgery was performed 4 to 6 weeks later, using five separate approaches. Median survival was 16 months with preoperative chemoradiation therapy compared to 11 months for the patients treated with surgery alone ($p = 0.01$). The 1-, 2-, and 3-year survival rates were 52%, 37%, and 32%, respectively, for patients who received multimodality therapy, and 44%, 26%, and 6%, respectively, for those patients assigned to surgery. These results were significant at 3 years ($p = 0.01$). The authors concluded neoadjuvant chemoradiation was superior to surgery alone in patients with resectable esophageal adenocarcinoma. This trial has been criticized for its poor surgery alone results, short follow-up, and lack of prerandomization CT staging.

Urba et al. (133) reported the results of 100 patients with nonmetastatic esophageal carcinoma (squamous and adenocarcinoma histology) randomized to receive preoperative chemoradiation followed by surgery versus transhiatal esophagectomy alone. Chemotherapy consisted of cisplatin, 5-FU, and vinblastine. Only 69% of the patients were able to receive the intended chemotherapy dose. Radiation was delivered at 1.5 Gy twice daily for 3 weeks to a total dose of 4,500 cGy. No elective nodal irradiation was performed. Surgery was performed on day 42. Tumors >5 cm, patient age >70 years, and squamous cell histology were associated with inferior survival. At median follow-up of 8 years, no significant difference in survival was seen between treatment arms, with a median survival of 17 months. However, 3-year survival rate was 16% in the surgery-alone arm versus 30% in the combined-modality arm ($p = 0.15$). A higher incidence of locoregional failure as first site of failure was seen in surgery-alone patients (42% vs. 19%;, $p = 0.02$). In patients experiencing pathologic complete response, a median survival of 50 months and a 3-year survival rate of 64% was seen, versus patients with residual tumor in the surgical specimen where median survival was 12 months with a 3-year survival rate of 19% ($p = 0.01$). The investigators stated that "Although this is not statistically significant, this suggests a possible trend to the benefit of multimodality therapy, but the sample size was too small to detect a more subtle survival difference," and that surgery should be continued as a standard of care.

Bosset et al. (23) reported an EORTC trial randomizing 282 patients with squamous cell carcinoma of the esophagus to either immediate surgical resection or preoperative therapy using concurrent cisplatin chemotherapy with radiation therapy. Patients were treated with split course radiotherapy with a 2-week interval, using 3.7 Gy per fraction to a total of 37 Gy. Postoperative mortality was significantly higher in patients receiving preoperative therapy (12% vs. 4%). Outcomes showed patients receiving neoadjuvant therapy experienced a significant improvement in disease-free survival, cancer-related mortality, margin-negative resection, and local control; however, no improvement in overall survival was seen versus patients undergoing surgery alone (median survival 18.6 months both groups). The authors concluded that neoadjuvant chemoradiation improved disease-free survival and local control in patients with squamous cell carcinoma of the esophagus, but had no impact on overall survival. The authors judged that the increase in postoperative mortality in the combined group "could be due to deleterious effects of the high-dose of radiation per fraction," among other factors, and believed that the dose of 3.7 Gy per fraction "probably had a detrimental effect." This trial has also been criticized for the split-course treatment approach as well as suboptimal chemotherapy.

Burmeister et al. (27) reported an Australian study randomizing 257 patients with adenocarcinoma and squamous cell carcinoma of the esophagus to surgery alone versus neoadjuvant therapy using concomitant 5-FU and cisplatin. Patient received 2.33 Gy per fraction to a total dose of 35 Gy. Patients undergoing

Table 50.9 RESULTS OF PREOPERATIVE COMBINED CHEMORADIATION VERSUS SURGERY ALONE–PHASE III TRIALS

Author (Reference)	Median Follow-Up (years)	Path	Regimen	No. of Patients	Path CR	3-Year Survival	Survival Difference
Urba et al. (133) (Mich)	8.2	SCC + adeno	5-FU-CDDP-Vinb/45 Gy S	50 50	28 —	CMT/S: 30% S alone: 16%	$p = 0.15$
Bosset et al. (23) (EORTC)	4.6	SCC	CDDP/37 Gy S	143 138	20 —	CMT/S: 33% S alone: 36%	NS
Walsh et al. (139) (Ire)	1.5	adeno	5-FU-CDDP/ 40 Gy S	58 55	22 —	CMT/S: 32% S alone: 6%	$p = 0.01$
Burmeister et al. (27) (Aus)	5.4	SCC+adeno	5-FU-CDDP/35 Gy S	128 128	16 —	CMT/S: 35% S alone: 31%	NS
Tepper et al. (128) (CALGB)	6.0	SCC+adeno	5-FU-CDDP/ 50 Gy S	30 26	40 —	CMT/S: 39% (5 y) S alone: 16% (5 y)	$p = 0.008$

adeno, adenocarcinoma; CDDP, cisplatin; CMT, combined modality therapy; 5-FU, 5-fluorouracil; S, surgery; SCC, squamous cell carcinoma; Vinb, vinblastine

neoadjuvant therapy had a 16% pathologic complete response rate at resection. Patients receiving neoadjuvant therapy were more likely to undergo curative resection and have negative lymph nodes on histologic examination. However, no significant improvement in median survival was seen (19 months vs. 22 months; hazard ratio 0.89; $p = 0.57$). On subset analysis, there appeared to be a trend toward improved survival in patients with squamous cell carcinoma undergoing neoadjuvant therapy versus surgery alone (progression-free survival hazard ratio 0.47; $p = 0.01$; overall survival hazard ratio 0.69; $p = 0.16$). The authors concluded that neoadjuvant chemoradiation as delivered in their study provided no obvious survival benefit in patients with esophageal cancer, although further study was warranted in patients with squamous cell carcinoma. Potential criticisms of this trial include delivery of a single chemotherapy cycle as well as delivery of lower radiation doses.

Preliminary trial results by the Cancer and Leukemia Group B (CALGB) described 56 patients (75% with adenocarcinoma) randomized to either surgery alone or neoadjuvant chemoradiation followed by surgical resection (128). Patients in the neoadjuvant therapy arm received cisplatin/5-FU based chemotherapy and 50.4 Gy of external beam radiation therapy at 1.8 Gy per fraction. This trial was closed prematurely due to poor accrual. In patients undergoing neoadjuvant therapy, pathologic complete response rate was 40%. A significant improvement in local control and survival was seen in patients receiving neoadjuvant combined-modality therapy (5-year survival 39% vs. 16%; $p = 0.008$). The authors concluded that neoadjuvant chemoradiation in patients with esophageal cancer significantly improves progression-free and overall survival (Table 50.9).

Because of the conflicting results in these studies, meta-analyses have been carried out. Fiorica et al. (45) analyzed six randomized controlled trials comparing neoadjuvant chemoradiation versus surgery. Some of these trials included suboptimal radiation techniques and sequential (versus concurrent) chemoradiation. The authors reported the odds ratio of death with neoadjuvant chemoradiation was significantly improved compared to surgery alone (0.53; $p = 0.03$). Additionally, patients undergoing neoadjuvant therapy experienced significant down-staging. The authors concluded chemoradiotherapy plus surgery significantly reduces mortality compared to surgery alone in patients with resectable disease. Urschel and Vasan (134) performed a meta-analysis of nine randomized controlled trials comparing neoadjuvant chemoradiation therapy with surgery versus surgery alone, comprising more than 1,100 patients. As above, multiple trials were deemed to have suboptimal radiation techniques and delivered sequential therapy. The 3-year survival odds ratio was 0.66, significantly in favor of patients receiving neoadjuvant therapy. Additionally, when concurrent (as opposed to sequential) therapy alone was analyzed, an odds ratio of death of 0.45 was seen. These authors concluded that preoperative chemoradiation improves overall survival, margin negative resection rates, and local failure versus surgery alone. In summary, the available data suggest that neoadjuvant concurrent chemoradiation improves local control and modestly improves survival versus surgery alone in patients with resectable esophageal cancer.

Radiation Therapy Alone versus Chemoradiation

There are multiple randomized studies comparing radiation therapy alone with concurrent radiation and chemotherapy (6,11,110) as definitive therapy. However, many of these studies are handicapped by small patient numbers, substandard chemotherapy delivery, and the use of suboptimal radiotherapy techniques. This makes treatment results difficult to interpret. The landmark trial establishing the superiority of concurrent chemoradiation to radiation therapy alone was RTOG 8501. Herskovic et al. (59) reported results of this two-arm trial that treated 60 control patients with radiation alone to a total dose of 64 Gy versus 61 patients with 50 Gy of radiation therapy with concurrent chemotherapy. The chemotherapy protocol consisted of four planned courses of infusional 5-FU and cisplatin. Although less radiation was delivered in the concurrent-therapy arm, the results demonstrated a significant advantage of the combined-modality arm over the radiation-alone arm. The median survival in patients treated by radiation alone was 8.9 months compared with 12.5 months for those treated with combined therapy. The 2-year survival rate with the addition of chemotherapy improved from 10% to 38%, the incidence of local recurrence decreased from 24% to 16%, and the 2-year distant metastases rate decreased from 26% to 12%. Because of this highly significant survival difference, the randomization was stopped, and 69 additional patients were treated on the chemoradiation arm. Updated trial results from Al-Sarraf et al. (6) showed that at 5 years, survival rates were 30% and 0%, respectively, for chemoradiation and radiation therapy alone. Local recurrence rates were also decreased with the use of combined-modality therapy versus radiation alone (45% vs. 69%), and distant metastases were more frequent in the radiation-alone arm at 40% versus 12% for the combined-modality group. The incidence of acute toxicity, however, was higher for the combined-modality arm versus the radiation-alone arm (44% vs. 25%). Similarly, the incidence of life-threatening side effects, including hematologic toxicity and fistula formation, was increased from 3% to 20%. In conclusion, this study demonstrated a significant improvement in local

control, median and overall survival, and distant metastases development with the addition of chemotherapy to radiation therapy, at the cost of increased side effects.

Comparison of outcomes data from "definitive" chemoradiation approaches suggests that survival with combined chemoradiation therapy is similar to that achieved by surgery alone. In previously discussed studies, median survivals of 14 to 20 months and 5-year survival rates of 20% to 30% were achieved with chemoradiation therapy alone; in comparison, with the MRC and Intergroup trials evaluating surgery alone, median survival rates were 13 to 16 months with 5-year survivals of approximately 20%. Additionally, local failure rates appear similar. For example, in the RTOG/Intergroup studies using chemoradiation therapy alone, local failure rates as a first site of failure range from 39% to 45%. In comparison, local failure rate for the Intergroup study evaluating surgery alone was 31%. However, this analysis was limited to patients undergoing R0 resection only (59% of patients) (69). This would undoubtedly be higher if considering all patients. Therefore, local failure and survival rates appear similar between "definitive" chemoradiation and surgical approaches.

Chemoradiation versus Chemoradiation Followed by Surgery

Two randomized trials have examined whether surgery is necessary following combined modality therapy. A report from French investigators randomized 445 patients with clinically resectable squamous cell or adenocarcinoma of the esophagus. All patients received concurrent 5-FU and cisplatin-based chemoradiation. Patients were allowed to be treated with one of two radiation regimens: 46 Gy over 4.5 weeks (continuous), or 30 Gy at 15 Gy per week (split course). Two hundred fifty-nine patients who had at least a partial response were then randomized to either surgery or additional combined modality therapy of 5-FU and cisplatin delivered concurrent with radiation (either an additional 20 Gy at 2 Gy per day or split course of 15 Gy). No significant difference in 2-year survival (34% vs. 40%; $p = 0.44$) or median survival (18 vs. 19 months) was seen between the groups. The death rate at 3 months following treatment was 9% in the surgery group versus 1% in the combined modality therapy alone group. Additionally, patients undergoing surgery were found to have a worse quality of life. However, the rate of stent and dilatation requirement was higher in the nonsurgical arm. The results of this trial suggest that surgery following chemoradiation in responding patients does not further enhance survival (22).

In a study from Germany, 172 patients with potentially resectable squamous cell carcinoma of the esophagus received induction chemotherapy with 5-FU, leucovorin, etoposide, and cisplatin for three cycles, followed by concurrent etoposide and cisplatin with 40 Gy of external beam radiation therapy. Patients were then randomized to receive surgery versus continuing with combined chemoradiation (total radiation dose increased to 60 to 65 Gy, with or without brachytherapy). Local control was significantly improved in patients undergoing surgery (2-year local control 64% vs. 41%; $p < 0.05$). Despite this, no significant difference in survival was seen (median survival 16 vs. 15 months, 3-year survival 31% vs. 24%; p = NS). The "severe" postoperative complication rate (including infection, leak) was 70%, and the hospital mortality rate was 11%. Overall treatment-related mortality was significantly higher in patients undergoing surgery (13% vs. 3.5%). In patients who did not respond to induction chemotherapy, 3-year survival was improved in patients undergoing surgery (18% vs. 9%). On regression analysis, only tumor response to induction chemotherapy was found to be a significant prognostic factor. An important caveat to this trial was that only approximately two thirds of patients in the surgery arm actually had surgery. The authors concluded that (a) surgery following combined modality therapy improves local control but had no impact on overall survival (Fig. 50.12A,B) and (b) nonresponders to induction chemotherapy may benefit from surgery, and it may be appropriate to individualize therapy based on response to induction treatment (123).

In a study describing national patterns of care from 1996 to 1999, practice standards for patients receiving radiation therapy for esophageal cancer were evaluated (126). The authors found that contemporarily treated patients had a decreased risk of death (hazard ratio 0.32) if treated with concurrent chemoradiotherapy followed by surgery compared with patients treated with chemoradiotherapy alone. In summary, although surgery following combined chemoradiation for esophageal cancer appears to improve local control of disease, its impact on ultimate survival remains controversial.

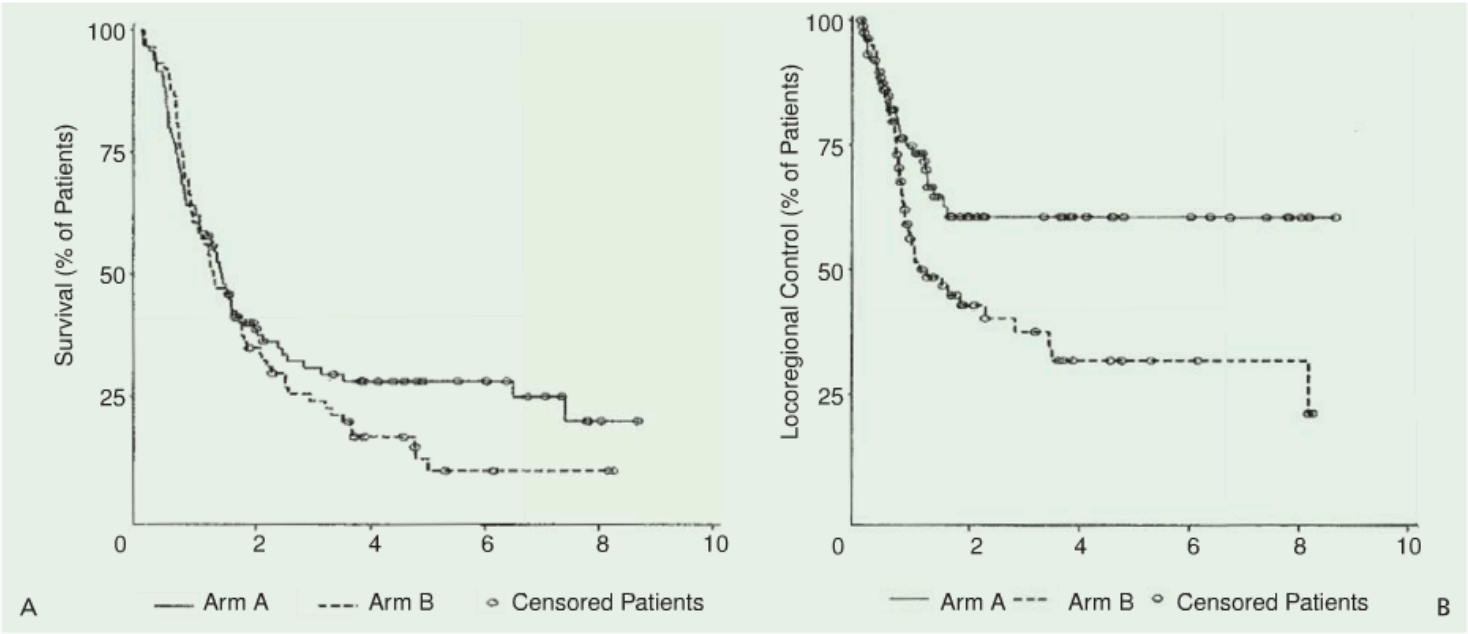


FIGURE 50.12. **A:** Overall survival-neoadjuvant therapy followed by surgery (arm A) versus chemoradiation alone (arm B). **B:** Local–regional control in patients undergoing neoadjuvant chemoradiation followed by surgery (arm A) versus "definitive" chemoradiation (arm B). (Stahl).

Brachytherapy

Gaspar et al. (49) reported the results of a prospective trial evaluating intraluminal brachytherapy in patients with nonoperable esophageal cancer. Patients initially received 50 Gy of external irradiation with concurrent chemotherapy, followed by a 2-week break and brachytherapy administration. Patients received either 15 Gy using HDR techniques over 3 consecutive weeks (5 Gy per fraction) or a single administration of 20 Gy using low-dose-rate (LDR) techniques. Dose was prescribed to 1 cm from the source axis. Treatments were accomplished by placement of a 10 to 12 French applicator inserted transnasally or transorally. The target length was defined as the pretreatment tumor length with 1-cm margin proximally and distally as determined by CT, barium swallow, and endoscopy. Both external irradiation and brachytherapy were given concurrently with 5-FU chemotherapy. Following the development of fistulas in six patients, the HDR dose was reduced to 10 Gy in two fractions, and the LDR arm was ultimately closed because of poor accrual. Results showed a median survival of 11 months in all patients. Local persistence/recurrence was observed in 63% of 49 eligible patients receiving HDR therapy. Six patients developed esophageal fistulas resulting in three deaths. These fistulas were deemed treatment related. The 1-year actuarial fistula development rate was 18%. The investigators conclude that esophageal brachytherapy, particularly in conjunction with chemotherapy, should be approached with caution (49). Review of other combined brachytherapy/EBRT series suggests fistula formation rates range from 0% to 12%, with a possible trend toward a higher incidence in patients receiving concurrent chemotherapy with brachytherapy. The incidence of brachytherapy-related mortality varies from 0% to 8%, with most series reporting rates at 4% or less (138).

Other studies have suggested that HDR brachytherapy is effective for palliation of dysphagia in up to 90% of patients (60). Danish investigators reported the results of a randomized trial of 209 patients with dysphagia due to inoperable esophageal or gastroesophageal junctional tumors. Patients were randomized to either endoscopic stent placement or single-dose HDR brachytherapy. Patient exclusion criteria included tumors >12 cm, tumors within 3 cm of the upper esophageal sphincter, deeply ulcerated tumors, tracheoesophageal fistula/tracheal involvement, presence of a pacemaker, and previous radiation treatment or stent placement. Brachytherapy was delivered through a flexible 1 cm applicator, delivering a dose of 12 Gy prescribed to 1 cm from the source axis. The treatment length was defined as gross disease plus 2 cm proximally and distally. Although trial results showed a more rapid improvement in dysphagia following stent insertion, long-term dysphagia relief was significantly improved in the group receiving brachytherapy. Patients undergoing brachytherapy experienced more days with low grade/no dysphagia versus patients with stent placement. Complications rates were higher following stent placement (33% vs. 21%), primarily due to an increased incidence of late hemorrhage in the stent group. The authors concluded that single-dose brachytherapy is preferable to stent placement as the initial treatment for patients with progressive dysphagia due to inoperable esophageal or gastroesophageal junction carcinoma (60).

For patients treated with curative intent (unifocal thoracic tumors <10 cm, no distant metastases, no airway involvement or cervical esophageal location), the American Brachytherapy Society recommends a brachytherapy dose of 10 Gy in 2 weekly fractions of 5 Gy each (HDR) or 20 Gy in a single course at 0.4 to 1 Gy per hour (LDR). The dose is prescribed to 1 cm from mid-source and delivered through a 6 to 10 mm applicator. The recommended active length is the visible mucosal tumor with a 1- to 2-cm proximal and distal margins (Fig. 50.13). Ideally, brachytherapy is started 2 to 3 weeks following completion of concurrent external irradiation/chemotherapy to allow mucositis resolution. Concurrent chemotherapy with brachytherapy is not recommended. In palliative cases, a similar approach is recommended, with delivery of 10 to 14 Gy in one or two fractions (HDR) or 20 to 25 Gy in a single course (LDR). In previously untreated patients with a short life expectancy (<3 months), a dose of 15 to 20 Gy in two to four fractions (HDR) or of 25 to 40 Gy (LDR) without external irradiation is recommended (Tables 50.10–50.12). In summary, the use of brachytherapy in the curative approach to esophageal cancer does not appear to significantly improve results achieved with combined external beam radiation therapy with chemotherapy alone.

Palliative Treatment

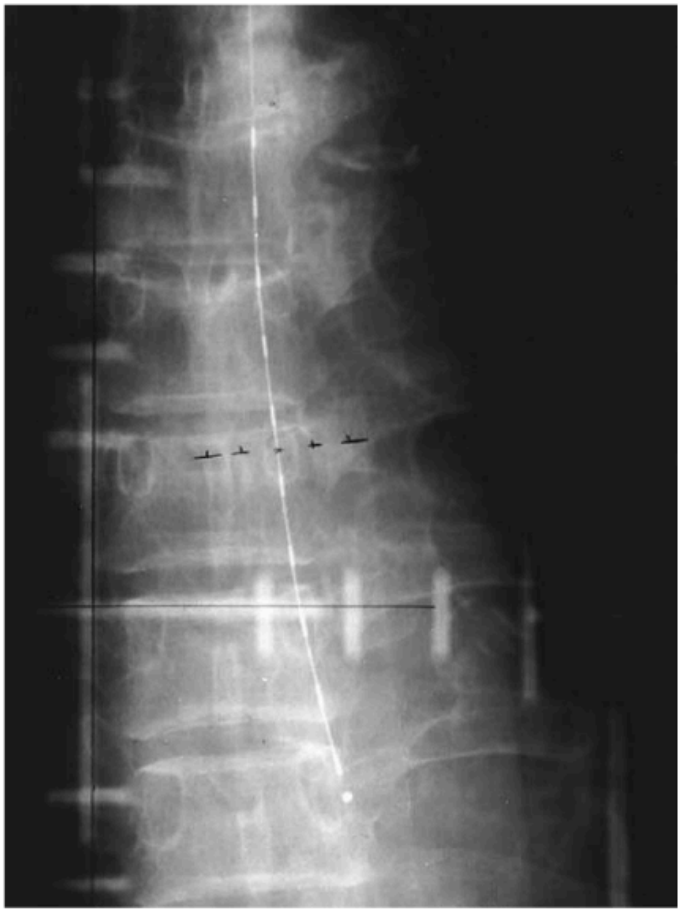
Although treatment advances have occurred in esophageal cancer over the past 20 years, the majority of patients diagnosed with this disease will die of their malignancy. Therefore, palliation remains an important goal. Dysphagia is a common presenting symptom and may significantly impair patient's quality of life. Radiation therapy has been used as an effective treatment for palliation. Many studies report a 60% to >80% rate of relief from dysphagia. Coia et al. (30) reported that nearly half of patients with baseline dysphagia experienced an improvement in swallowing within two weeks of treatment initiation. By the completion of the sixth week, over 80% experienced improvement. A median time to maximal improvement was approximately 1 month. Given the superior outcomes of patients receiving concurrent chemotherapy with radiation therapy in nonmetastatic disease, palliative chemoradiation is likely preferable to radiation alone for patients with advanced-stage esophageal carcinoma who have a good performance status. As described above, intraluminal brachytherapy has also been used for palliation of dysphagia. The previously described randomized trial from the Netherlands comparing intraluminal brachytherapy to stent placement showed that although patients undergoing stenting experienced a more rapid improvement in dysphagia, long-term palliation was significantly improved in patients treated with brachytherapy (60).

The palliative management of patients with tracheoesophageal fistula presents a clinical dilemma. Fistulization usually precludes surgery. These patients are often treated effectively with the placement of silicone-covered self-expanding metal stents, often obviating palliative surgery. Additionally, placement of feeding gastrostomy or jejunostomy may be appropriate. Although considered a "relative" contraindication to radiation therapy, limited data from a Mayo Clinic series suggest that radiation therapy may not increase fistula severity and can be administered safely in this setting; however, the presence of fistula is a poor prognostic factor (54).

Treatment Sequelae

Advances in surgical technique as well as improved pre- and postoperative management have decreased treatment-related mortality. Contemporary operative mortality rates are generally <10% (123,130). Complication rates can exceed 75%, including pulmonary and cardiac complications, anastomotic leak (5% to 10%), and recurrent laryngeal nerve paralysis (5% to 10%). Stricture formation can occur in 14% to 27% of patients. The addition of preoperative radiation therapy and chemotherapy may enhance surgical complication rates. More than 75% of patients receiving such treatments have transient esophagitis and dysphagia and may require some type of nutritional support. Leukopenia and thrombocytopenia are common.

The acute toxicities of radiation therapy include esophagitis, epidermitis, fatigue, and weight loss in most patients. Nausea and vomiting are common, particularly in patients with lower



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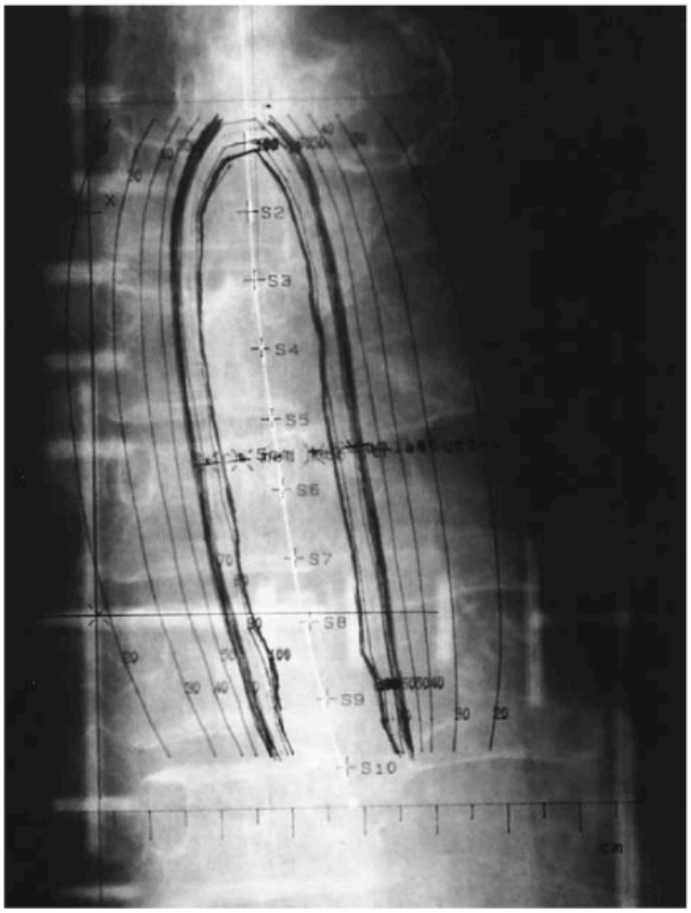

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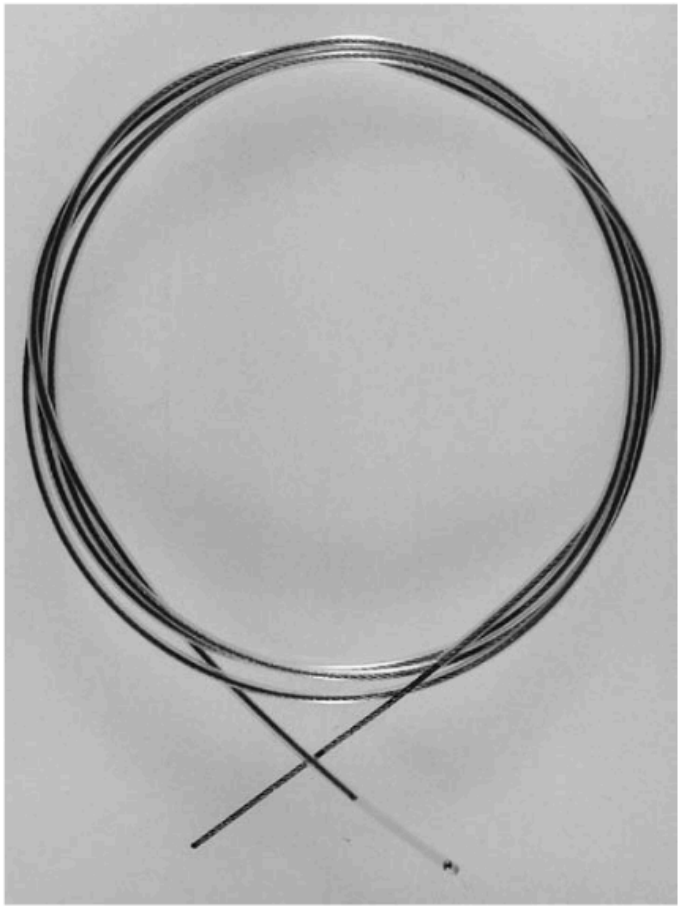

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FIGURE 50.13. Iridium-192 (^{192}Ir) afterloading technique. **A:** Anterior dosimetry film for ^{192}Ir boost to mid-thoracic lesion. **B:** Anterior dose distribution for mid-thoracic lesion. **C:** ^{192}Ir afterloading catheter with closed end and guide wire in place. (Courtesy of the Department of Radiation Oncology, The Graduate Hospital, Philadelphia, with special thanks to Joan Pellak and Steve Yan.)

Table 50.10 SELECTION CRITERIA FOR BRACHYTHERAPY IN THE TREATMENT OF ESOPHAGEAL CANCER

Good Candidates	Poor Candidates	Contraindications
Primary tumor ≤10 cm length	Extra esophageal extension	Esophageal fistula
Tumor confined to the esophageal wall	Tumor >10 cm in length	Cervical esophageal location
Thoracic esophagus location	Regional lymphadenopathy	Stenosis which can not be bypassed
No regional lymph node or systemic metastases	Tumor involving gastroesophageal junction or cardia	

esophageal and gastroesophageal junction tumors. Many symptoms resolve within 1 to 2 weeks of treatment completion. Pneumonitis has been seen, but is rare. A perforated esophagus is life threatening and may be characterized by substernal chest pain, a high pulse rate, fever, and hemorrhage (64). The addition of chemotherapy can significantly increase acute complications. Moderate to severe and even life-threatening toxicities have been reported in 50% to 66% of patients (29,59). In the previously discussed RTOG study of chemoradiation alone, patients treated with combined therapy had a higher incidence of acute grade 3 (44% vs. 25%) and grade 4 toxicity (20% vs. 3%) compared to patients receiving radiation therapy alone (6). Chemoradiation treatment-related mortality rates range from 0% to 3% (27,29,59,123,139).

The most common late effects following radiation therapy are stenosis and stricture formation. Stenosis can occur in more than 60% of patients. Stricture requiring dilatation has been reported to occur at least 15% to 20% of treated patients. Dysphagia may be relieved with two to three dilatations (29). Long-term results from the RTOG study showed that ≥late grade 3 toxicity was similar in the combined arm versus radiation-alone arm (29% vs. 23%). However, ≥grade 4 toxicity was higher in patients receiving combined modality therapy (10% vs. 2%) (32). Other complications include damage to organs within the radiation therapy volume, although this is uncommon. Recent studies have shown that significant declines in lung diffusion capacity and total lung capacity may occur in patients irradiated for esophageal cancer (51). In a report describing complications in patients receiving neoadjuvant combined modality therapy, 18% experienced pulmonary complications. These were significantly higher in patients where greater ≥40% of the lung volume received at least 10 Gy, and further increased in patients in whom ≥30% of the lung received at least 15 Gy (80). Chemotherapy may further increase the risk of late treatment-related toxicities.

Table 50.11 SUGGESTED SCHEMA FOR DEFINITIVE EXTERNAL BEAM RADIATION AND ESOPHAGEAL BRACHYTHERAPY[a]

External beam radiation:
45–50 Gy in 1.8–2.0 Gy fractions, five fractions/wk, weeks 1–5

Brachytherapy:
HDR: total dose of 10 Gy, 5 Gy/fraction, one fraction/wk, starting 2–3 weeks following completion of external beam
LDR: total dose of 20 Gy, single course, 0.4–1.0 Gy/h, starting 2–3 weeks from completion of external beam

HDR, high-dose rate; LDR, low-dose rate
[a]All doses specified 1 cm from mid-source or mid-dwell position.

Table 50.12 SUGGESTED SCHEMA FOR EXTERNAL BEAM RADIATION AND BRACHYTHERAPY IN THE PALLIATIVE TREATMENT OF ESOPHAGEAL CANCER

Recurrent after external beam radiation and short life expectancy:
Brachytherapy:[a]
HDR: total dose of 10–14 Gy, one or two fractions
LDR: total dose of 20–40 Gy, one or two fractions, 0.4–1.0 Gy/h

No previous external beam radiation:
External beam radiation:
30–40 Gy in 2–3 Gy fractions
Brachytherapy:[a]
HDR: 10–14 Gy, one or two fractions
LDR: total dose of 20–25 Gy, single course, 0.4–1.0 Gy/h

No previous external beam radiation, life expectancy > 6 months:
External beam radiation:
45–50 Gy in 1.8-2.0 Gy fractions, five fractions per week, weeks 1–5
Brachytherapy:[a]
HDR: total dose of 10 Gy, 5 Gy/fraction, one fraction/week, starting 2–3 weeks following completion of external beam
LDR: total dose of 20 Gy, single course, 0.4–1.0 Gy/h, starting 2–3 weeks following completion of external beam

HDR, high-dose rate; LDR, low-dose rate
[a]All doses specified 1 cm from mid-source or mid-dwell position.

Future Considerations

Although modest improvements in survival have been achieved by combining neoadjuvant chemoradiation therapy and surgery, patients treated with chemoradiation alone or with surgery alone have unacceptably high-local regional relapse rates and mortality rates (see Tables 50.3 and 50.6). Ultimately, approximately 75% of patients will succumb to metastatic disease. As described previously, efforts at radiation dose escalation have not resulted in significant gains in this disease. Given these data, clinical trials have turned to studies evaluating new and potentially more effective chemotherapeutic agents with radiation therapy, including traditional cytotoxic agents as well as "targeted" agents. Multiple phase II trials have evaluated preoperative combinations of cisplatin with paclitaxel with radiation therapy (3,18,111,132). With encouraging early results, the RTOG initiated protocol E-0113, a randomized phase II study assessing nonoperative therapies. The randomization included induction chemotherapy consisting of 5-FU, cisplatin, and paclitaxel versus induction paclitaxel and cisplatin only. Both arms received continuous-infusion 5-FU with concurrent radiation therapy 1.8 Gy per day to 50.4 Gy (72). Preliminary results showed increased toxicity in both arms compared to historical controls without significant improvements in outcomes. Additionally, the RTOG is also performing a phase II study (RTOG 0246) using induction paclitaxel, 5-FU, and cisplatin followed by concurrent 5-FU and cisplatin with external irradiation. In this study, there is no planned surgery. Instead, serial imaging including CT, endoscopy, EUS, and PET are performed following treatment completion, with surgery reserved for "salvage."

Other agents, such as irinotecan, oxaliplatin, capecitabine, epirubicin, gemcitabine, and docetaxel are being investigated in the metastatic setting as well as "curative" settings in combination with radiation therapy. Furthermore, there is ongoing investigation of the use of the vascular endothelial growth factor inhibitor bevacizumab as well as inhibitors of the epidermal growth factor receptors, including the antibody cetuximab and small molecule inhibitors gefitinib and erlotinib, in the treatment of esophageal cancer. All of these agents have radiosensitizing properties. The investigation of these agents with radiation therapy is the subject of future trials.

Summary

The prognosis for patients with carcinoma of the esophagus remains poor despite recent advances in combined-modality therapies. No firm recommendation can be made for managing locally advanced disease. The available data suggest that neoadjuvant chemoradiation may modestly improve outcomes in patients who are candidates for surgery. However, many patients are not able to tolerate surgery and combined chemoradiation may be more appropriate in selected patients, as definitive chemoradiation has resulted in survival rates comparable to surgery alone. Locoregional failure remains a significant pattern of relapse. For patients with stage IV disease, palliation with single-modality therapy or several modalities should be used and tailored to the patient's specific symptoms. Current unresolved issues include the following:

1. Is esophagectomy necessary after chemoradiation, and are there subsets of patients more likely to benefit from the addition of surgery than others?
2. Can introduction of newer chemotherapy/targeted agents in the neoadjuvant or definitive setting improve the results over "standard" chemoradiation with cisplatin and 5-FU?
3. Will new technologies such as 3D conformal therapy, PET-based planning, intensity-modulated radiation therapy, and image guided radiation therapy decrease complication rates and influence cure rates?
4. Will the identification of molecular prognostic markers allow "individualization" of treatments among patients?

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