CANCER OF THE ESOPHAGUS

Internal Medicine Grand Rounds

University of Texas Southwestern Medical

Center at Dallas

William V. Harford, M.D.

November 2, 1989

CANCER OF THE ESOPHAGUS

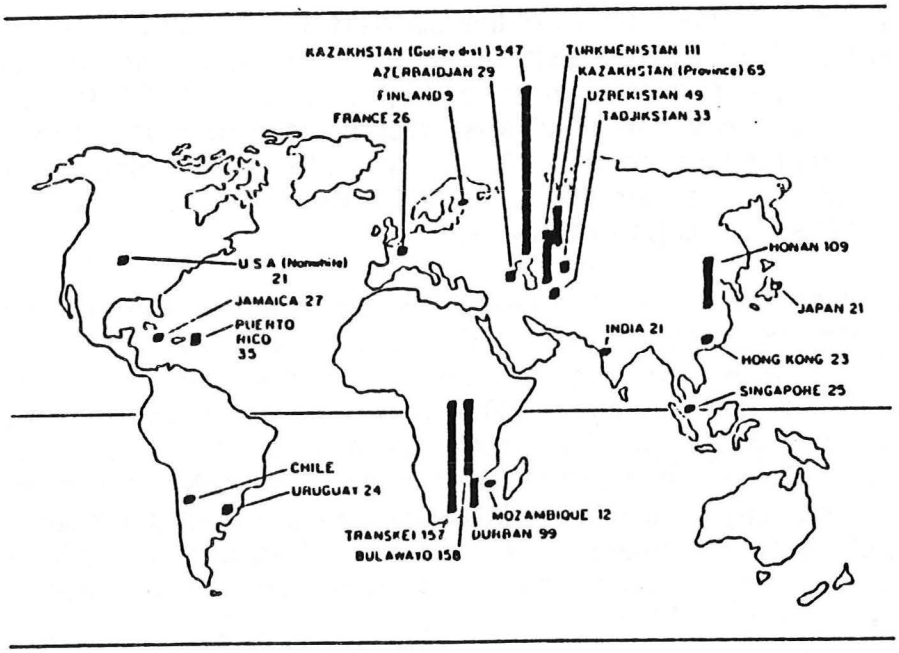
Introduction

Esophageal cancer is a terrible disease. The inability to eat and swallow normally, coughing, aspiration, pain, progressive cachexia, and weakness rob patients of their dignity and humanity. Five-year survival is less than 10%, and has improved little in recent years. Traditional therapy, such as surgery and radiation, cures few patients. There is little sound information to guide physicians in the choice of alternative treatments. All of this has led many physicians to face the problem of esophageal cancer with either benign neglect or studied despair.

Epidemiology

Cancer of the esophagus is a relatively infrequent disease in the United States. Approximately 9,000 cases a year are recorded. Incidence in American men is from 2.5 to 5 cases per 100,000 a year; in women from 1.5 to 2.5. In contrast, in certain other areas of the world, esophageal cancer is much more common, as in the Transkei region of South Africa where the rate in men reaches 357 cases per 100,000, and esophageal cancer is responsible for 1 out of 5 adult deaths.(1)

The distribution of squamous cell cancer of the esophagus shows wide variation from country to country, from region to region within countries, and among ethnic groups in the same regions. Based on epidemiological research, several potential risk factors have been identified, although no single environmental factor has been found to account for the patterns of esophageal cancer in all high incidence areas.



Incidence of Esophageal Cancer
From Curr. Probl. Surg. 1988

In certain areas of Northeastern China, around the Yellow River, cancer of the esophagus has been known for 2,000 years. In the Linxian area of Hebei Province it has been referred to as ge shi bing or "hard of swallowing disease." The incidence of cancer of the esophagus in this area is approximately 140 cases per 100,000 per year, about 100-fold higher than that found in neighboring provinces. Interestingly, chickens in the area develop carcinoma of the pharynx at a similar rate.

Considerable circumstantial evidence implicates nitrosamines, which are known to be carcinogenic in animals. In this arid area of China, man made ponds are used to collect runoff rainwater, which is then stored in large ceramic tanks. This stored water is found to have high levels of nitrosamines. The soil in Linxian is deficient in molybdenum and zinc. Molybdenum is a co-factor for nitrate reductase in plants, and deficiency leads to accumulation of nitrates. Zinc deficiency may favor nitrosamine production in humans. Other potential factors in endemic areas include mold contamination of stored grain, diets poor in fresh fruit, vegetables, and animal protein, deficiency of vitamins riboflavin, A, and C, and the practice of drinking very hot liquids.(2) The Chinese have performed large scale screening studies using a technique called "lawang", which involves passing a mesh-covered balloon into the esophagus, inflating the balloon, and retrieving scraped cells for cytology. Studies on more than 25,000 people have been reported, with up to 70% accuracy, based on endoscopy, in the diagnosis of esophageal cancer. Approximately 75% of discovered cases are early. Trials of primary intervention with diet changes and vitamin supplementation have been initiated.(3) Water supplies have been improved, better facilities for drying and storage of grain have been built, to prevent mold contamination, and molybdenum fertilizer is being used.

The area around the southern shore of the Caspian Sea in eastern Turkey, northern Iran, and the southern Soviet Union also has a high incidence of esophageal cancer. In Kazakhstan, esophageal cancer rates are as high as 263 per 100,000 in women and 206 per 100,000 in men. A variety of different factors have been implicated including the practice of ingesting opium dross, drinking very hot beverages, silica contamination of grain, and poor diet. As opposed to areas of the West, tobacco and alcohol use is very uncommon in this Muslim part of the world.(1)

Another area of high incidence is the Transkei in South Africa. Male members of the Xhosa tribe between the ages of 35 and 64 have an incidence of 357 cases per 100,000, which is 14 times more frequent than hepatoma, the next most prevalent cancer. Esophageal cancer represents 20% of all adult deaths in this area. As in China, the Xhosa have a diet poor in fresh fruit, vegetables, animal products, and vitamin A. Also as in China, the soil is deficient in zinc and molybdenum, which leads to an increased concentration of nitrates in maize, the predominant local crop. The maize may be further contaminated by a mold which appears to be carcinogenic. Drinking native maize beer or "cidiviki" has been associated with an increased risk of esophageal cancer, which the Xhosa consider to be the result of introducing a black

spider into their beer by sorcery. The Xhosa smoke locally grown tobacco in homemade pipes. They scrape out and ingest the stem residue or "injonga", which has been shown to be carcinogenic.(4)

In North America and Europe esophageal cancer is more common among people of low socioeconomic status, but the predominant contributing factors seem to be alcohol and tobacco. Together, these seem to account for 80 - 90% of cases. Combined exposure to alcohol and tobacco multiplies the risk, so that at high levels of exposure the relative risk is over 150 times normal.(1)

Relative Risk of Esophageal Cancer
Associated With Varying Levels of Consumption
of Alcohol and of Tobacco*

Grams of Ethanol Consumed Per Day	Grams Smoked Per Day			
	0-9	10-19	20-29	>30
0-40	1.0**	3.4	3.2	7.8
41-80	7.3	8.4	8.8	35.0
81-120	11.8	13.6	12.6	83.0
>121	49.6	65.9	137.6	155.6

* Adapted from Tuyns et al. (See Ref. 1)
** Risks are expressed relative to a risk of 1.0 in persons smoking less than 10 g per day and drinking no more than 40 grams per day.

Other Predisposing Conditions

There are a variety of relatively unusual conditions associated with an increased incidence of squamous carcinoma of the esophagus.

Conditions Associated With
Increased Risk of Esophageal Cancer

Tylosis
Plummer-Vinson Syndrome
Achalasia
Lye ingestion with stricture
Celiac sprue
ENT cancer
Barrett's esophagus

Tylosis is an autosomal dominant disease, reported in several families in Britain, which leads to hyperkeratosis of the palms and soles, as well as papillomatosis and carcinoma of the esophagus. Up to 95% of affected family members will develop esophageal cancer.(5)

The Plummer-Vinson syndrome consists of iron deficiency anemia, glossitis, esophagitis, esophageal strictures, and carcinoma of the pharynx and upper esophagus. This is felt to be due to nutritional deficiency. First reported in Scandinavia, it is much less common than when first described.

Achalasia is a disorder of the esophageal body and lower sphincter which leads to stasis of food in the esophagus. The risk of cancer of the esophagus has been estimated at up to 5%, after a 15 to 20 year latent period. However, a recent prospective study disclosed no cases of esophageal cancer in a large number of patients with achalasia, so this association has been questioned.(6)

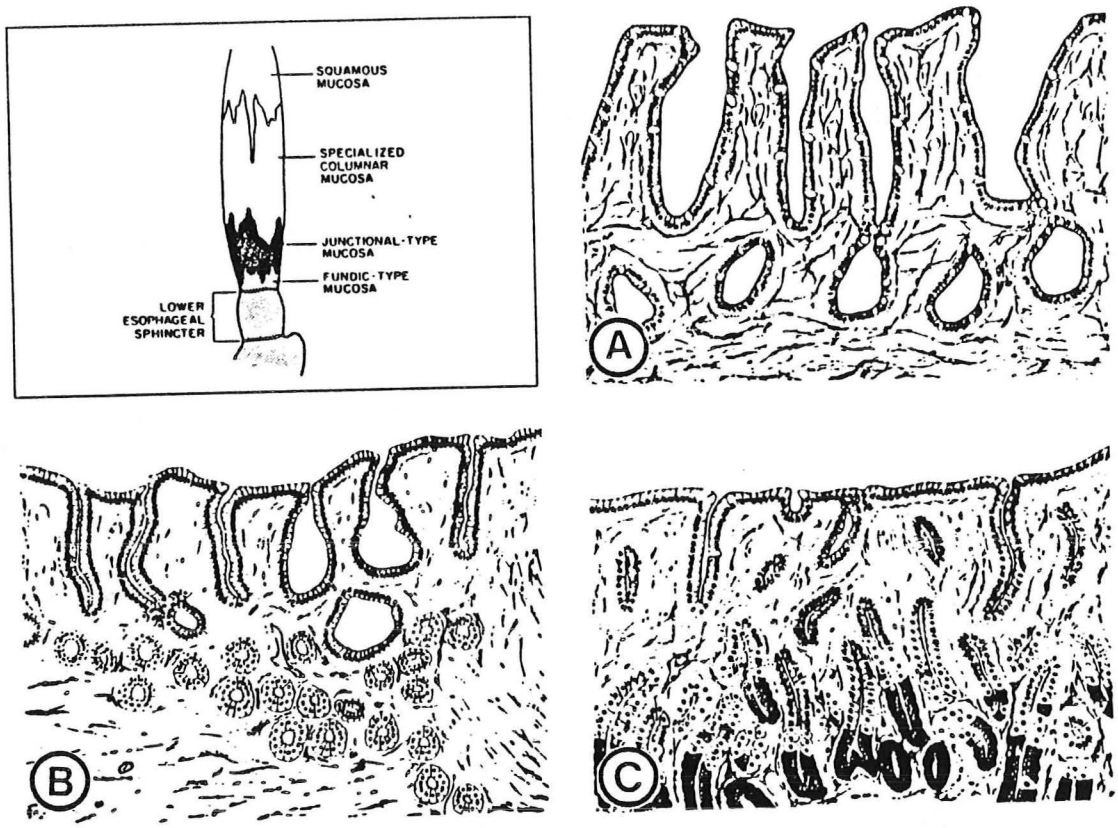
Patients with a history of lye ingestion with subsequent esophageal stricture may have an incidence of cancer estimated at from 1-4%. The latent period is long, up to 40 years after the ingestion.(7)

Celiac sprue is associated with increased risk of lymphoma, but also squamous cell carcinoma of the esophagus, and other GI malignancies.

Patients with head and neck cancer, presumably due to their exposures to tobacco and alcohol, have a 2% risk of cancer of the esophagus, as well as an increased incidence of other upper airway cancers. It is the practice of most ear, nose, and throat surgeons to perform both esophagoscopy and bronchoscopy before operating on patients with head and neck cancer.(8)

Barrett's Esophagus and Adenocarcinoma

All of the above conditions are unusual, and do not contribute significantly to the total number of patients with carcinoma of the esophagus. On the other hand, Barrett's esophagus is known to be associated with high frequency of adenocarcinoma of the esophagus. Barrett's esophagus is a condition in which normal squamous mucosa of the esophagus is replaced by columnar epithelium. It was originally felt to be congenital, but is now known to be the result of chronic reflux esophagitis. There are three types of metaplastic epithelium; specialized columnar, junctional, and fundic. Specialized columnar epithelium resembles intestinal mucosa. The surface is villiform, with crypts, and goblet cells are seen. This is felt to be a form of incomplete intestinal metaplasia. Junctional type mucosa resembles the epithelium of gastric cardia, and fundic type resembles the epithelium of the normal fundus, with secreting parietal and chief cells. These epithelia are distributed in a characteristic way in Barrett's esophagus, with specialized columnar most proximal, then junctional, and fundic most distal.(9)



Distribution (Top Left Panel) and Morphologic Features (A, B, and C) of the Three Types of Epithelia in Barrett's Esophagus. Part A shows specialized columnar epithelium, in which both the villiform surface and the crypt-like glands are lined by (clear and oval) goblet cells and by cells that may resemble small intestinal absorptive cells but that contain mucous granules similar to those in gastric foveolar cells. B shows gastric junctional-type epithelium, in which the surface, the pits, and the glands are lined by mucus-secreting cells. C shows gastric fundic-type epithelium, in which the pitted surface is lined by mucus-secreting cells and the glands contain (large, clear) parietal cells and (dark) chief cells, as well as mucus-secreting cells. All three epithelial types commonly have evidence of inflammation and atrophy.

From Spechler and Goyal
NEJM 1986

Some authors feel that specialized columnar epithelium is the characteristic tissue of Barrett's esophagus, with the other types being simply a proximal displacement of normal gastric mucosa. The overall prevalence of Barrett's in the general population is not known. In a large series of patients undergoing endoscopy for a variety of reasons, 1.5% of patients were found to have Barrett's esophagus.(10) In patients with symptoms of heartburn coming to endoscopy for symptoms resistent to medication, 12% had Barrett's, and up to 44% of patients with strictures of the esophagus were found to have Barrett's.(9)

The importance of Barrett's esophagus is its relationship to adenocarcinoma. Barrett's esophagus is a precancerous condition. Virtually all cases of adenocarcinoma

of the esophagus are related to Barrett's. The risk of cancer of the esophagus is increased 30 to 40 times the patients with columnar lined esophagus.

Many patients are first found to have Barrett's esophagus when they present for evaluation of complications of gastroesophageal reflux such as stricture or esophageal ulcer. In this group of patients the prevalence of cancer at the initial examination has been reported to be in the range of 7-14%. Because of this, all patients found to have Barrett's esophagus should have multiple biopsies at the time of their initial endoscopy.

The incidence of adenocarcinoma, that is, the number of new cases developing each year in Barrett's esophagus, has been estimated to be from 1 in 50 to 1 in 441 cases per patient year. Small cancers may be inapparent on examination, and systematic biopsies were not done in all these studies. If only those studies in which biopsies were done are considered, the incidence can be estimated to be 1 in 77 per patient per year.

Incidence of Cancer in Barrett's Esophagus

Hameeteman	Gastro. 1989	1/50
Ovaska	Dig. Dis. Sci. 1989	1/52
Van DerVeen	Gut 1989	1/170
Robertson	Brit. J. Surg. 1988	1/56
Spechler	Gastro. 1984	1/175
Cameron	NEJM 1985	1/441
Achkar	Am. J. Gastro. 1988	1/166
Wellinger	Gastro. 1989	1/217

Patients with Barrett's esophagus seem to progress through a sequence of epithelial dysplasia to adenocarcinoma. Although small numbers of patients have been reported, high grade dysplasia is associated with carcinoma in about 50% of cases.(11,12)

Because of the increased risk of development of adenocarcinoma, and the potential to identify patients at risk for the development of cancer, many gastroenterologists recommend surveillance of patients with Barrett's esophagus with yearly endoscopy and biopsy.(13) If mild dysplasia is found, a repeat endoscopy is done in 6 months. If high grade dysplasia is found, endoscopy and biopsies are repeated immediately, and if dysplasia is confirmed, many physicians would recommend esophagectomy.

Whether this approach will improve patient survival has not been determined. There have been no studies of the natural history of severe dysplasia. It is not known how many cases will regress, and how many will progress to cancer. If esophagectomy is done on all patients with high grade dysplasia, approximately one-half will not have

cancer at the time of resection. The morbidity and mortality of esophagectomy is substantial. This approach is also expensive. Using an estimated incidence of 1 in 166, a cost per case discovered was estimated to be approximately $62,000.(14) Efforts are being made to find a more exact marker of malignant potential in cases with dysplasia. Flow cytometry is a technique with which the average DNA content of a population of cells can be measured. Aberrations of DNA content in dysplastic mucosa may identify patients most likely to develop overt carcinoma.(15)

Until more information is available, I believe patients found to have Barrett's esophagus should be carefully informed of the increased risk of cancer. Patients who are relatively young and fit, and who might be surgical candidates, should be offered yearly screening, after an explanation of the limits of this approach. Hopefully, screening of patients with Barrett's esophagus will result in a larger proportion of cancers being discovered at an early, asymptomatic stage. However, even with screening, many patients with Barrett's are unaware of their condition, and so will present with advanced tumors.

There is considerably less information about the therapy of adenocarcinoma of the esophagus than squamous cell carcinoma in large part because adenocarcinoma represents only about 8% of all esophageal cancers. There are few reports of treatment options, and no randomized trials.

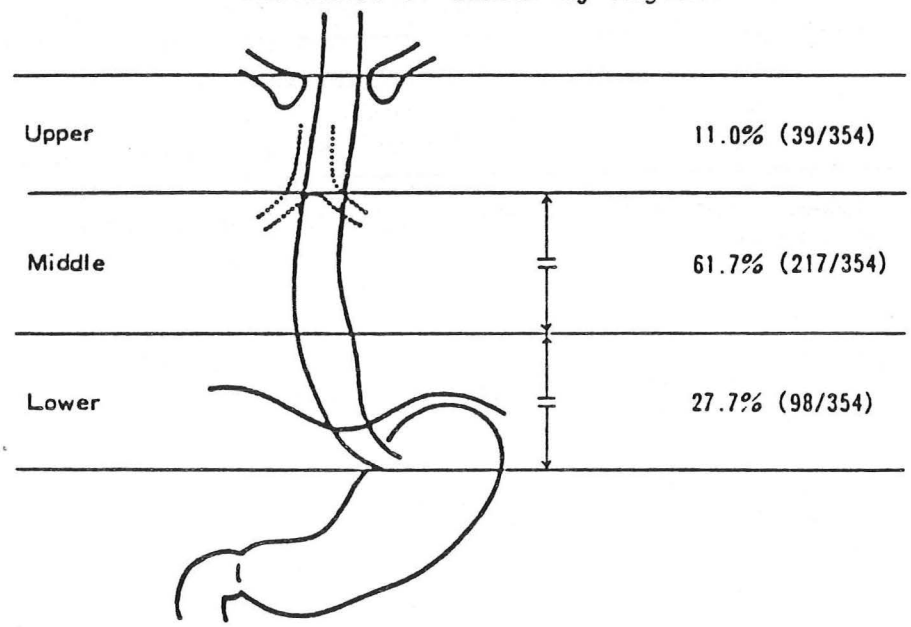
Most esophageal adenocarcinomas occur in the lower third of the esophagus. In this area, surgical resection is more readily accomplished than in the mid or cervical esophagus. Most tumors are locally advanced, but surgical resectability rates of over 80% are reported, with operative mortalities of less than 10%. Reports of the response to radiation treatment have been conflicting, and trials of 5-FU adriamycin and mitomycin have been discouraging, with only 22% of patients responding.(16) Surgery should be regarded as the primary therapy for adenocarcinoma of the esophagus. Various forms of palliation, including dilatation, BICAP tumor probe, and laser therapy have been reported. One small non-randomized trial of radiotherapy, 5-FU, and mitomycin reported palliation of dysphagia in 6 of 9 patients for a mean of 8 months.(17)

Although esophageal adenocarcinoma is an important problem, this histological type represents only, at most, 8% of esophageal cancers. The remainder of this review will focus on squamous cell tumors, which account for more than 90% of esophageal malignancies.

Anatomic Considerations

The esophagus is divided into three principal regions; cervical, upper and mid thoracic region, and the lower thoracic esophagus. About 15% of esophageal cancers appear in the upper third, 50% in the middle third, and 35% in the lower third.

Incidence of Cancer by Region

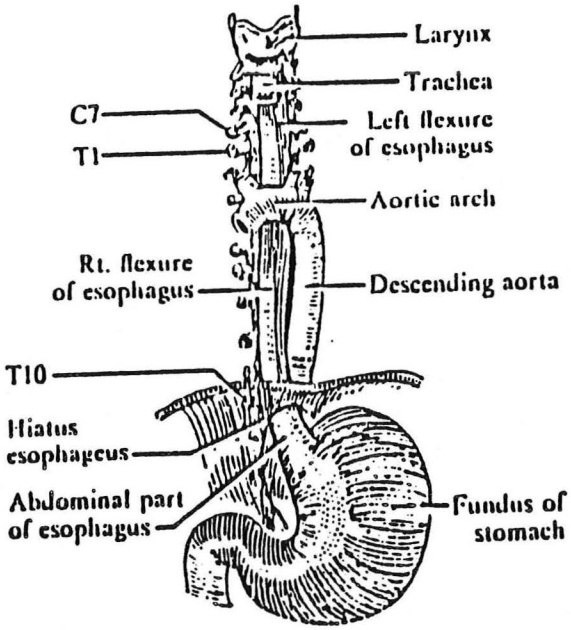


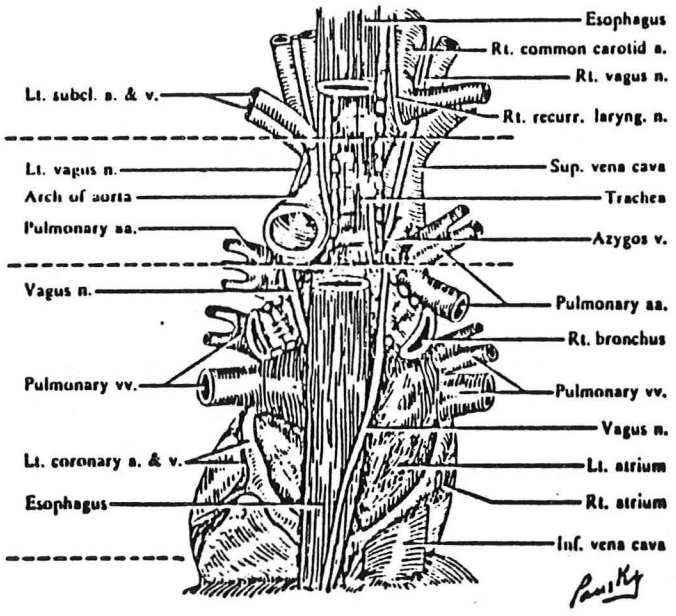
From Ann. Surg., Akiyama

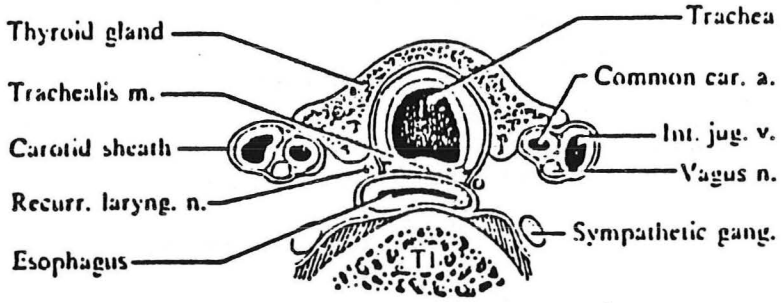
Throughout its course, the esophagus is in close proximity with structures of the neck and chest;

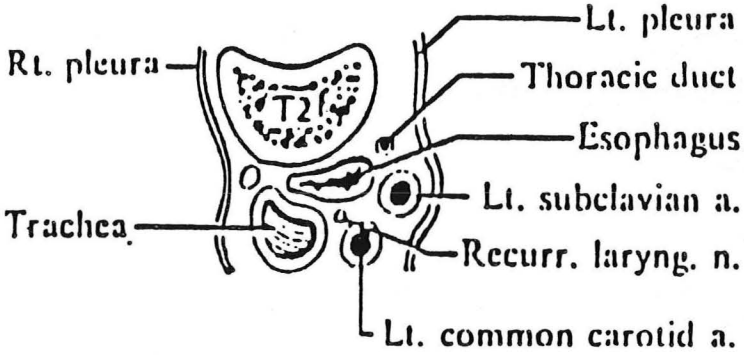
in the neck - trachea, spine, recurrent laryngeal nerves, and carotid sheaths;
in the mid chest - bifurcation of the trachea and the left mainstem bronchus, aorta azygous vein, and thoracic duct;
in the lower chest - the aorta, both pleural surfaces, pericardium, and diaphragm.

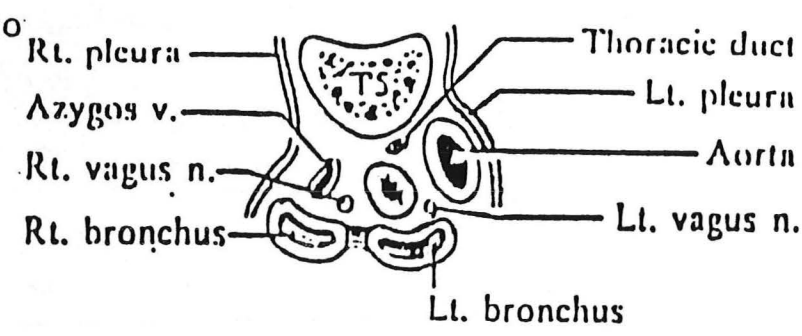
RELATIONAL ANATOMY OF THE ESOPHAGUS

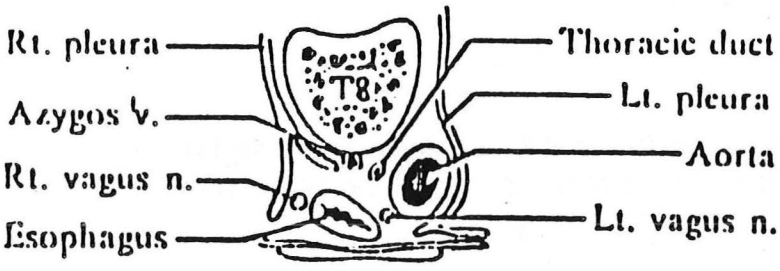


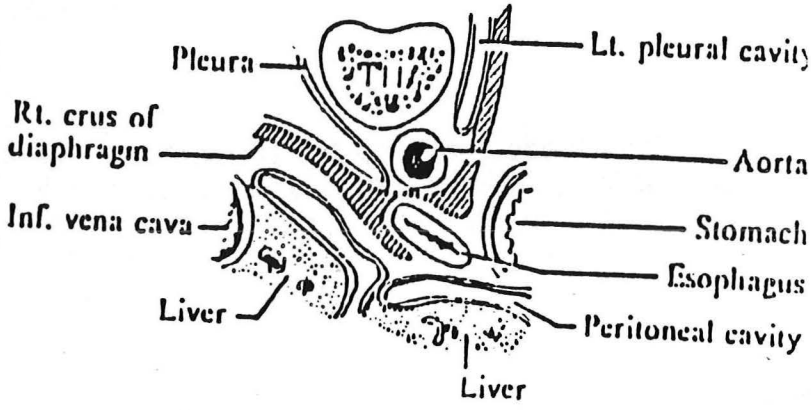










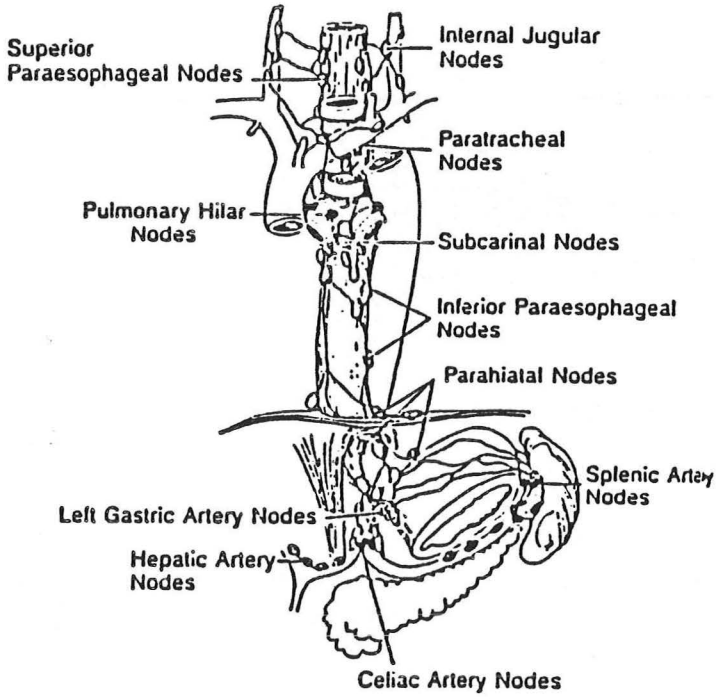


From Pansky: Review of Gross Anatomy

The esophagus, unlike the rest of the gut, has no serosa. Tumors which penetrate the muscularis quickly spread to involve adjacent structures.

Lymphatics

Networks of lymphatic vessels are located in the mucosa, submucosa, and muscularis of the esophagus. These networks interconnect freely, and the flow of lymph is unpredictable, but the general pattern favors a longitudinal rather than a circumferential spread.



Esophageal Lymphatic Drainage
From Curr. Probl. Surg. 1988

Skip areas occur, so foci of tumor can be found as far as 4-8 cm. from the margins of the primary tumor.(18) Because of this esophageal resection must be done with wide margins. In most cases this implies near total esophagectomy.

Nodal metastases are common and often can be widespread. For example, subdiaphragmatic nodes can be found in up to 32% of tumors located in the upper third and are present in more than 62% of tumors of the lower third.

Frequency of Subdiaphragmatic Nodal Metastases

Location of Tumor	Frequency of Occurrence (%)	Frequency of Subdiaphragmatic Nodes (%)
Upper third	17	32
Middle third	47	33-46
Lower third	36	>62

Modified from Akiyama H,Tsurumaru M, Kawamura T, Ono Y: Principles of surgical treatment for carcinoma of the esophagus. Analysis of lymph node involvement. Ann. Surg. 194:438-446, 1981.

Natural History

The early course of squamous cell carcinoma in Western Countries is not known, since most tumors are advanced at the time of diagnosis. More is known about early disease in China, where screening programs have identified large numbers of early lesions. In areas of high incidence, up to 20% of the population can be found to have epithelial dysplasia, and early cancer is common. The course of severe dysplasia have been followed in Chinese patients. In one study done over a period of 5-9 years, 34% patients with severe dysplasia progressed to cancer. The rest remained stable.(2) In another study, 90 patients with early cancer who refused treatment were followed for 19 to 78 months. Interestingly, 52 (58%) continued to have superficial tumors, while 35 progressed to advanced disease or died. The estimated mean survival time was 6 years.(19) In China there seems to be a clear progression from dysplasia, to early cancer, which has a long presymptomatic period and a good prognosis when resected. Surgical cure rates of close to 90% have been reported in China.

We can only speculate whether natural history of squamous cell carcinoma of the esophagus in China, or other areas of high prevalence, bears any similarities to squamous cell carcinoma in the United States. Early squamous cell cancers in the

West are found only by accident. Nevertheless, the few cases which have been reported suggest that there is high cure rate.(20)

In the United States the great majority of patients present with dysphagia. Unfortunately, in 90% of cases this is associated with advanced local or metastatic disease. Most tumors are greater than 4 cm. in length when first diagnosed. Tumors less than 5 cm. in length have a 60% incidence of local invasion or distant metastases, and tumors longer than 5 cm have up to a 90% incidence of invasion or metastases. Overall, by the time of diagnosis only 40% of esophageal cancer is surgically resectable, and of cases in which resection is done, up to half will have positive margins or positive lymph node invasion.(21) The course of esophageal cancer is dominated by symptoms of local spread, but autopsy studies have shown that up to 85% of patients will have metastatic disease at the time of death, most frequently to lymph nodes, lung, and liver.(22)

Clinical Presentation

As mentioned, dysphagia is the presenting symptom in the great majority of cases. Dysphagia occurs late in esophageal carcinoma. The esophagus is an elastic organ, and up to two-thirds of the wall must be involved before significant obstruction occurs. In addition, there is usually a 3-4 month delay between the onset of dysphagia and patient presentation. Some patients may have early clues, such as a transient hang-up with swallowing, especially with certain foods such as beef, apples, or bread. Most patients respond to this by chewing their food more thoroughly, increasing their fluid intake, and altering their diet. By the time patients seek care many are on a soft or liquid diet, and most have lost 10 to 20 pounds.

Pain occurs less commonly. There is often discomfort associated with the passage of food through the stricture. Malignant ulceration can result in pain from the topical effect of alcohol, citrus juices, and medications. The most ominous of esophageal pain is a steady aching pain in the mid chest or back, which indicates extensive local invasion.

Pulmonary symptoms such as regurgitation and cough are common and can be due to aspiration from obstruction, tracheal or bronchial involvement, or tracheoesophageal fistula.

Hoarseness, Horner's syndrome, diaphragmatic paralysis, and superior vena cava obstruction also imply extensive involvement of the mediastinum. Malignant pleural effusions and ascites may occur.

Diagnosis and Staging

The diagnosis of cancer of the esophagus is straightforward when it is suspected. A barium swallow will frequently reveal mucosal irregularity, ulceration, or mass. However, small tumors may be missed. The best diagnostic tool is esophagoscopy with biopsies and brushings. Very early carcinomas may be subtle, presenting as changes in the color, texture, or vascular pattern of the esophagus, but most cancers diagnosed in symptomatic patients are readily apparent. Biopsies may be difficult if the tumor has caused an esophageal stricture with a prominent submucosal component, but the combination of brushings and biopsies will yield a positive diagnosis in more than 95% of cases.

Staging

The classification recommended by the American Joint Committee on Cancer is presented below.(23)

-- TNM Definitions --

Primary tumor (T)
TX: Primary tumor cannot be assessed
TO: 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
NO: No regional lymph node metastasis
N1: Regional lymph node metastasis

*For the cervical esophagus, the cervical nodes (including the supraclavicular nodes) are considered regional; for the intrathoracic esophagus, the mediastinal and perigastric lymph nodes (excluding the celiac nodes) are considered regional.

Distant metastasis (M)
MX: Presence of distant metastasis cannot be assessed
MO: No distant metastasis
M1: Distant metastasis

-- AJCC Stage Groupings --

-- Stage 0 --5-year survival: excellent
Stage 0 is defined as the following TNM grouping:

Tis, NO, MO

-- Stage I --5-year survival: >50%
Stage I is defined as the following TNM grouping:

T1, NO, MO

-- Stage II --5-year survival:
IIA: 15%
IIB: 10%
Stage IIA is defined as any of the following TNM groupings:

T2, NO, MO
T3, NO, MO

Stage IIB is defined as any of the following TNM groupings:

T1, N1, MO
T2, N1, MO

-- Stage III --5-year survival: <10%
Stage III is defined as any of the following TNM groupings:

T3, N1, MO
T4, any N, MO

-- Stage IV --5-year survival: rare
Stage IV is defined as the following TNM grouping:

any T, any N, M1

The classification is based on operative or autopsy findings.

Staging of esophageal carcinoma has important implications for prognosis and therapy. As mentioned, the great majority of patients have metastatic disease at the time of presentation, and for these patients, palliative therapy is appropriate. However,

it is also important to select those patients who appear to have localized disease and who may have a chance for cure.

The most important factors in prognosis are depth of invasion and the presence of lymph node or distant metastases. Histological type and differentiation do not contribute. One of the most important roles of evaluation and staging is to determine resectability. Overall, about 60% of the patients are operable, but of those taken to surgery up to one-third will be found to be unresectable because of advanced disease.(21) Accurate clinical or preoperative staging will minimize patients having unnecessary surgery and alternative treatments can then be recommended.

Clinical symptoms which imply advanced carcinoma of the esophagus include pain radiating to the back on swallowing, hoarseness from laryngeal paralysis, diaphragmatic paralysis from involvement of the phrenic nerve, coughing when swallowing due to tracheoesophageal fistula, superior vena cava syndrome, palpable supraclavicular cervical nodes, malignant pleural effusion or ascites, and bone pain.

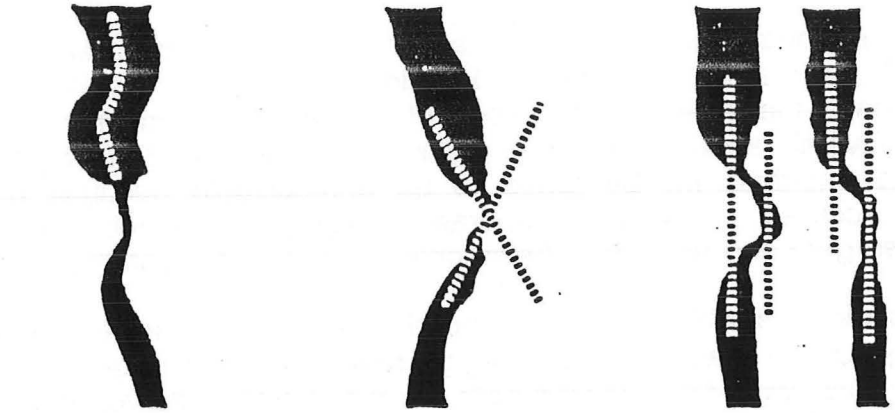
Signs and Symptoms Produced by
Advanced Esophageal Cancer

Pain radiating to the back on swallowing
Dysphonia (laryngeal paralysis)
Diaphragmatic paralysis (involvement of phrenic nerve)
Coughing when swallowing (tracheoesophageal fistula)
Superior vena cava syndrome
Palpable supraclavicular or cervical nodes
Malignant pleural effusion
Malignant ascites
Bone pain

From Cancer, ed. DeVita

Barium Swallow

The length of the tumor measured on barium swallow may give some indication of stage but this may not always be reliable. Deformity of the esophageal axis has been said to indicate fixation to adjacent structures and imply unresectability.(24)



Three types of esophageal axis abnormalities originally described by Akiyama. The deviation is due to a carcinoma that has extended through the wall and caused contraction of periesophageal tissues.

CT

CT has been proposed as a reliable indicator of transmural spread of esophageal cancer, as well as lymph node metastases. The esophagus is easily demonstrable with CT throughout its entire length, and fatty tissue interfaces separate the esophagus from its adjacent mediastinal structures. Esophageal wall thickness of more than 5 mm, displacement and fixation of the trachea or left bronchus, increased area of contact between the esophagus and aorta, and obliteration of the fat plane between the esophagus and pericardium have been found to indicate invasion.(25) However, in cachectic patients the normal fat planes may be lost. CT is less sensitive in the diagnosis of regional lymphadenopathy than in the diagnosis of local invasion. Lymph nodes less than 5 mm are often below the resolution of CT. Furthermore, small nodes may contain cancer, and, conversely, large nodes may be inflammatory. The overall accuracy of CT in several studies is indicated in the table below. Some authors have had less favorable experience.(26)

Overall accuracy: results of evaluation for local invasion and distant metastases on CT.

Reference	Tracheobronchial involvement (%)	Aortic invasion (%)	Mediastinal invasion (%)	Regional lymph adenopathy (%)	Abdominal lymph adenopathy (%)	Hepatic metastases (%)	Gastric extension (%)	Pericardial invasion (%)
Daffner et al (1979)	—	—	82	—	57	—	—	—
Moss et al (1981)	—	—	100	—	87	—	—	—
Coulomb et al (1981)	—	—	83	—	86	—	—	—
Picus et al (1983)	—	100	—	0	80	—	—	—
Thompson et al (1983)	93	90	98	—	82	97	—	96
Lea et al (1984)	88	94	77	72	39	94	83	—
Quint et al (1985a and b)	97	55	95	61	85	100	79	97

— = not specified

From Reeders Bailliere's Clin. Gastro. 1987

Sonography

Conventional ultrasonography is impeded in the thorax by pulmonary gas and by ribs. Prototype endoscopic ultrasound probes have been developed, which use frequencies in the range of 7.5 to 12 MHz. With these frequencies the wall of the esophagus can be resolved into 5 layers. The first two represent the mucosa, the third the submucosa, the fourth the muscularis propria, and the fifth the adventitial fat. Tumors can be visualized as hyperechoic, inhomogeneous areas, and the integrity of the esophageal wall can clearly be assessed. In several studies, endoscopic ultrasound has been found to be substantially more accurate than CT in staging the depth of tumor infiltration, especially for tumors limited to the esophageal wall. As can be seen from the table below in the assessment of lymph node metastases, endoscopic ultrasound tends to overstage, while CT tends to understage.(27)

Staging Esophageal Cancer:
Endoscopic Ultrasound (EUS) vs CT

	Invasion		Lymph Nodes	
Accuracy (%)	EUS	CT	EUS	CT
Stages I, II	82	12	-	-
Stages III, IV	93	88	80*	51**

* EUS 16% false +, 7% false -
** CT 7% false +, 48% false -

Adapted From
Tio, Gastroenterology 1988

Endoscopic ultrasound can visualize small lymph nodes (less than 5 mm in diameter), separate them from adjacent tumor mass, and give some assessment of node texture. One very important limitation of endoscopic ultrasound is inability to pass the probe through malignant strictures, which occurs frequently with the current 13 mm Olympus sonoendoscope. Endoscopic ultrasound requires considerable skill in both endoscopy and ultrasonography and is available in only a few centers.

Bronchoscopy

When the primary esophageal tumor is in the upper thorax, involvement of the trachea and bronchus can be found in up to 30% of cases. Invasion of the tracheobronchial tree means that only palliative treatment can be offered. When evaluating a patient for resection of a thoracic tumor, bronchoscopy should be performed to assess for impingement on the tracheobronchial tree or the presence of mucosal invasion.

Treatment

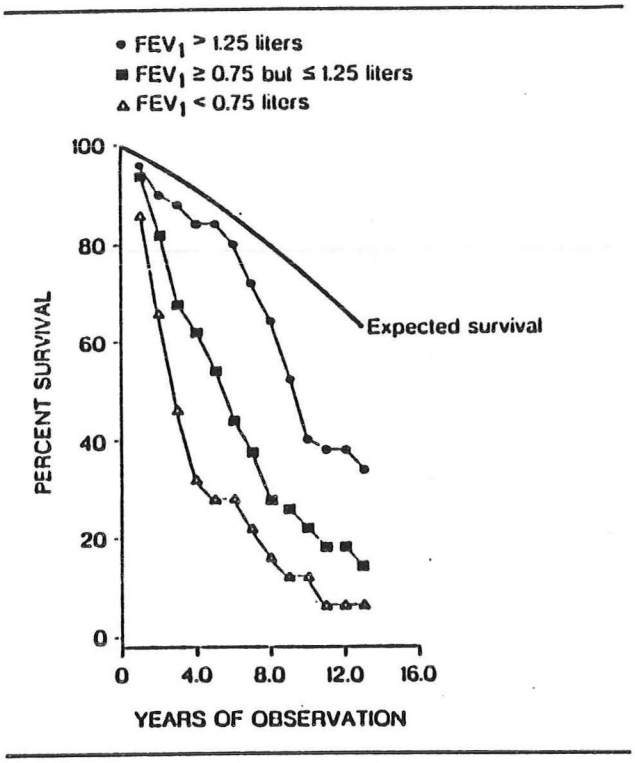
Surgery

In 1913, Franz Torek accomplished the first successful subtotal esophagectomy for cancer of the thoracic esophagus. A cervical esophagostomy and gastrostomy were done. The patient lived for 13 years, feeding herself by connecting her cervical esophagostomy to her gastrostomy with a rubber tube. However, this remained an isolated case until after World War II, when the development of closed system general anesthesia brought about the ability to control pneumothorax during thoracic procedures.

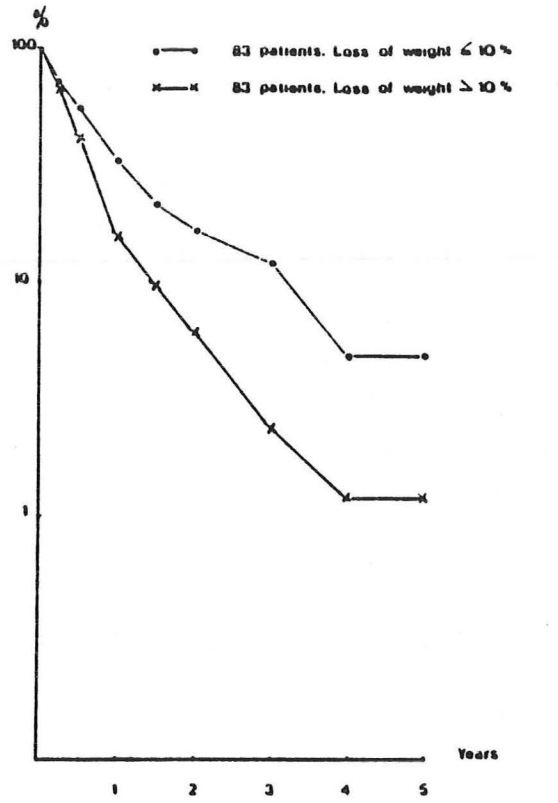
Since that time, many surgical series have been published. These series are largely retrospective, with no controls, or only historical controls. Patient selection varies greatly, and there has been little uniformity in reporting results, so that it is difficult to compare therapies and draw firm conclusions.

In a review of 122 papers including data on 83,783 patients done by Earlham and Cunla-Melo in 1980, the authors concluded that, on average, 58% of patients were considered operable. Of those explored, 67% could have the tumor resected. Operative mortality was 22%. Of the 26% leaving the hospital after resection, 1-year survival was 18%, 2-year survival was 9%, and 5-year survival was 4%.(21)

Selected series report better results. For example, Kasai reported his experience with 430 patients treated between 1963 and 1977.(28) He noted that during this period his operative mortality fell from 16% to 4.5%. During this time his criteria for operability changed, so that after 1972 he required a vital capacity of >1800 ml/m^2, a normal blood pressure, normal EKG, and normal renal function for consideration of resection of upper and mid thoracic tumors. He reported an overall 5-year survival of 16.5% for these patients, which is an example of the influence which selection may have on reported surgical outcome. Age, pretreatment weight loss, and pulmonary function are a few of the factors which can be expected to influence survival.



Diener, Am. Rev. Resp. Dis. 1975



Pedersen, ACTA Chir. Scand. 1982

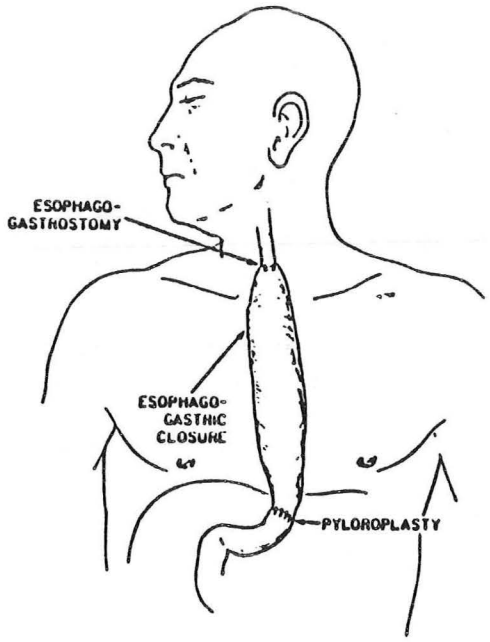
Another example of difficulties in interpreting these reports is illustrated by a study by DeMeester in 1988.(29) In this series, actuarial 5-year survival of a curative en bloc resection of an esophageal cancer of the distal one-third was reported in 14 patients to be 53%. Closer reading reveals careful patient selection. All patients taken to surgery were less than 75 years old, with a left ventricular ejection fraction of more than 40% and an FEV_1 of >1.5 liters. Of the 52 patients screened, 19 were not resected. Nineteen others had palliative surgery only, and had a 1-year survival of 31%. Fourteen had curative resections, one of whom died. The 53% 5-year survival is based on the 13 of the 52 original patients who had survived the curative resection. The projected 5-year survival expressed as the percentage of the original group would be 15%.

There are several surgical approaches to cancer of the esophagus. The Ivor-Lewis operation consists of initial laparotomy during which the liver and diaphragmatic area are explored for metastases. Dissection of the right gastric nodes is done, and stomach is mobilized. The right chest is opened. A resection of the tumor and esophagus is done with wide margins. The mobilized stomach is pulled into the chest and an esophagogastrostomy is done. If positive nodes or metastases are found, and the tumor is in the lower one-third, a palliative resection can be done, using a transhiatal approach, which is described later.

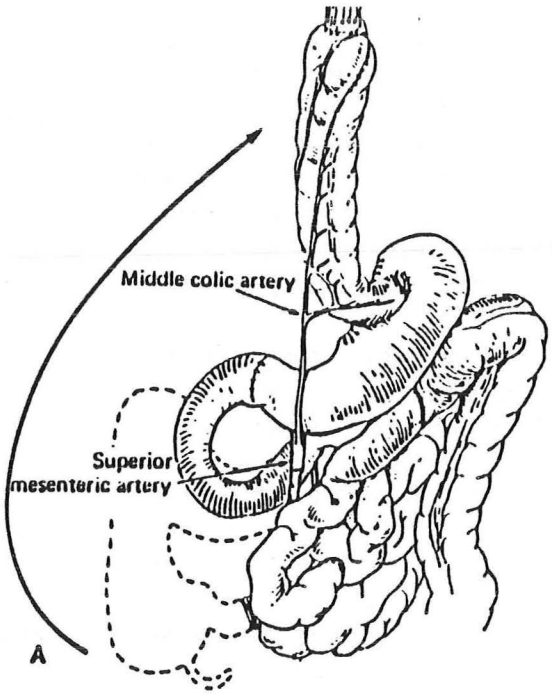
The approach favored by Skinner is a radical or total esophagectomy with an anastomosis in the neck, using either the stomach or a colonic interposition. The arguments for a total esophagectomy and cervical anastomosis include the possibility of wider margins, especially for tumors of the midthorax, and the fact that cervical anastomotic leaks are less disastrous than thoracic anastomotic leaks. However, a randomized prospective trial comparing cervical and thoracic anastomosis showed that although cervical anastomoses yielded better margins, leaks were more common. Surgical mortality and mean survival were not different.(30)

Orringer and others have written concerning extrathoracic or transhiatal esophagectomy.(31) This procedure begins with a laparotomy. The abdomen is explored and the stomach mobilized. Blunt dissection of the lower half of the esophagus is done through the hiatus. A cervical incision is then made and blunt dissection of the upper esophagus is done through this incision. The esophagus is transected at both ends and pulled out, with the tumor. The mobilized stomach is then drawn up through the bed of the esophagus and a cervical esophagostomy is made. This approach avoids the morbidity and mortality of a thoracotomy. It may be useful in tumors of the lower third, where much of the dissection can be done under direct vision. It is more hazardous in tumors in the mid and upper thorax, because dissection is blind, and if there is unrecognized mediastinal invasion, damage to the trachea, thoracic duct, or great vessels can occur, with disastrous consequences. This approach can be used as a palliative resection for tumors of the lower third, when abdominal spread is found at laparotomy in a patient who was felt to be resectable at preoperative evaluation. Transhiatal esophagectomy does not seem to be different from thoracic esophagectomy with respect to surgical morbidity or actuarial survival.(44)

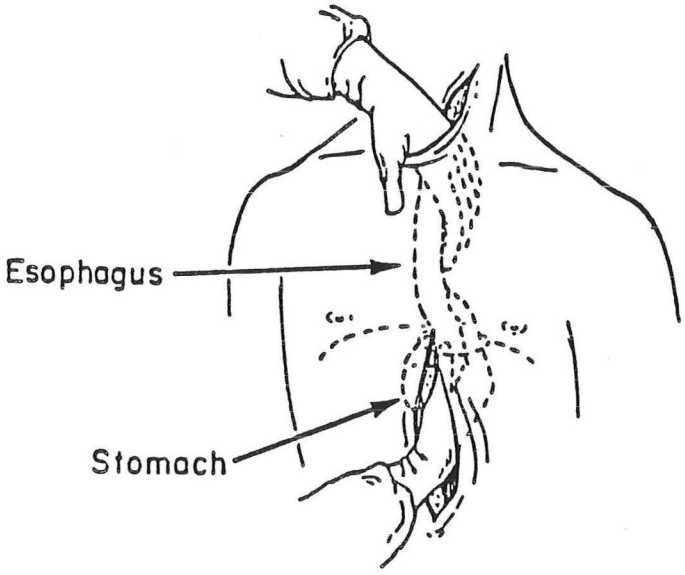
Bypass of the tumor, with substernal pull-up has been done as palliation for unresectable esophageal cancer. A series reported by Orringer had a postoperative mortality of 24%, and 59% of patients had a major postoperative complication, such as an anastomotic leak, abscess, or mucocele. It seems unreasonable to subject a patient with an unresectable tumor and a short life expectancy to surgery with such morbidity and mortality.(32) Other alternatives, such as dilatation, and stenting, are available except in patients who are completely obstructed.



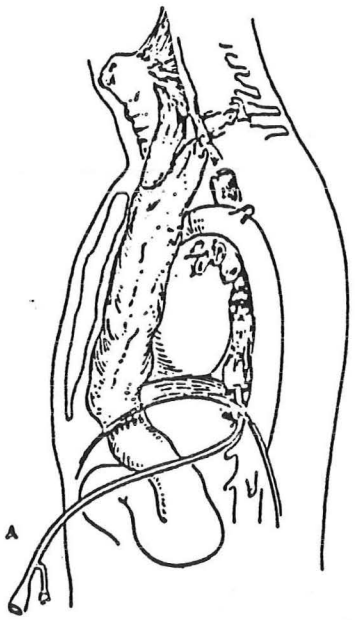
Esophagogastrostomy
From Cancer, ed. DeVita



Colon Interposition
From Cancer, ed. DeVita



Transhiatal Esophagectomy
From Cancer, ed. DeVita



Retrosternal Gastric Bypass
From Cancer, ed. Devita

To quote Earlham and Cunla-Melo from their 1980 paper:

"Out of any 100 patients, including all in the community who actually go to visit a doctor, 58 will be explored, 39 resected, 26 leave the hospital with the tumor excised, 18 survive for 1 year, 9 for 2 years, and 4 for 5 years. If there is any surgeon, accepting all the patients in the population he serves, who can improve upon these figures, he has not yet written an article with his results. The first question to be asked is whether these figures can be accepted as correct by surgeons. If they are taken as true, the second question follows; would the patient, being properly informed, consent to surgical exploration with a 29% operative mortality and an 18% chance of surviving one year, or would he ask whether there was any other available treatment?"(21)

The possibility of surgery should not be discarded in esophageal cancer. Surgical results are better in young, fit patients with early disease. However, as mentioned earlier, most patients with esophageal cancer are older, and many have been heavy smokers and drinkers. In addition, clinical preoperative staging can be difficult, and up to one-third of patients felt to be candidates for resection will be found to have extensive disease at surgery, having thus been subjected to surgery without benefit. Clearly then, alternatives to surgery should be considered.

Radiotherapy

Radiotherapy has been used in esophageal cancer since radium Bougies were first reported in 1909. The use of radiotherapy as primary therapy is supported by the observation that the survival rates for patients treated with radiotherapy have been no different than those treated with surgery.(33)

	Survival		
	1 yr	2 yr	5 yr (%)
Radiotherapy	18	8	6
Surgery	18	9	4

In a disease where less than 10% of patients will be cured, it seems reasonable to offer that therapy with the least morbidity and mortality.

In an extensive review of radiotherapy by Earlam and Cunla-Melo the authors comment that "There has been no controlled trial of radiotherapy versus surgery for squamous cell carcinoma of the esophagus", and "there are no results available to suggest what would happen if a patient with a localized tumor, technically suitable for surgical resection, were treated instead by radiotherapy."(33) Since that review, little additional information is available.

Radiotherapy has virtually no treatment-related mortality, and morbidity is controlled simply by stopping treatments. Disadvantages of radiotherapy include the fact that with most treatment regimens, 4-5 weeks of daily therapy are required, and in most series, control of local disease is not as good with radiotherapy as with surgery. No randomized studies have been done, and other retrospective studies(34) have shown results essentially the same as those reported in review of Earlam and Cunla-Melo.

In cancer of the cervical esophagus, or the upper third, radiotherapy may clearly be preferable to surgery. For cancer of the upper third, surgical therapy requires resection of the larynx, pharynx, and esophagus, with a pharyngogastrostomy. Cure rates of 10-20% are reported. With radiotherapy, survivals of up to 15% have been reported.(35) The enormous functional and cosmetic impairments of the surgical procedure would seem to favor radiotherapy as the primary treatment.

Various external radiotherapy regimens have been used. Most involve three fields, designed to minimize exposure of the spinal cord, heart, and lungs, while maximizing tumor dose.

Complications of radiotherapy, such as esophagitis and pneumonitis, are uncommon, and spinal cord and myocardial damage should be rare.

A variety of doses are used. Tumor response increases with increasing dose, and examination of resected tissue after preoperative radiotherapy has shown that, in some cases, all discernable macroscopic and microscopic tissue can be eliminated with radiation,(36) but tissue tolerance is exceeded before local control is likely, and complication rates are higher with large doses. Most programs use total doses of 4,500 to 5,500 rads for both palliation and attempted cure.

Fraction size is another variable which has been studied. Conventional programs give 200-250 rads five times a week for 4-5 weeks. Larger fraction sizes, up to 500 rads a day, have been used, which have the advantage of shortening treatment time in patients with a short life expectancy.(36,37)

Radiation can also be delivered to the lumen of the esophagus by inserting iridium or cesium pellets into a tube which is placed in the esophagus. Intracavitary radiotherapy offers a means of providing palliation with a very short course. In a series reported in 1985, 65% of patients with advanced disease had relief of dysphagia for an average of 4 months after one treatment with intracavitary radiotherapy.(38)

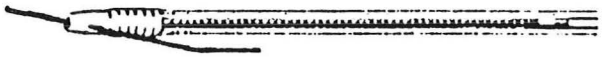
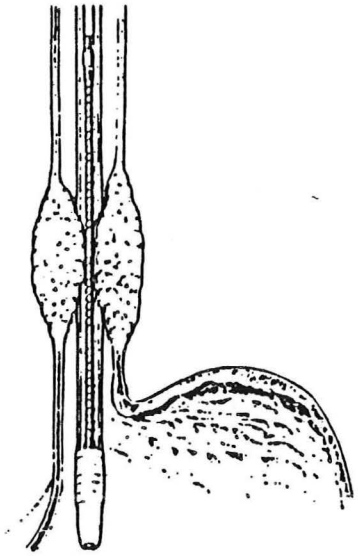


Fig 1—Applicator design.



Applicator in treatment position.

Intracavitary Radiation
From Rowland, Lancet, 1985

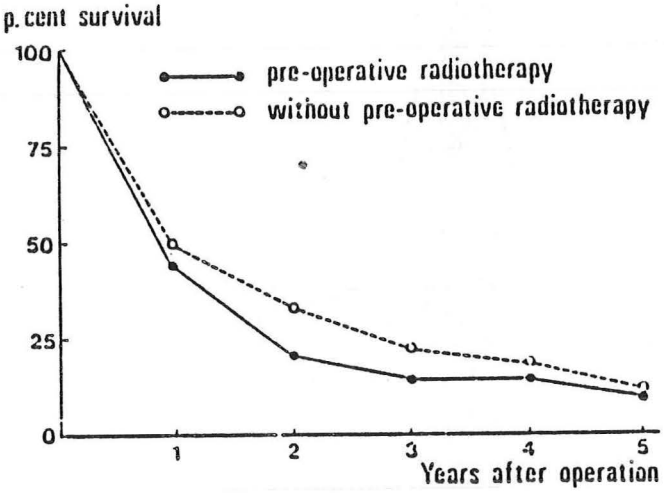
Palliation of dysphagia can be expected in up to 70% of patients treated with external radiotherapy, and up to 54% will remain improved until death. Recurrent dysphagia in patients treated with radiotherapy is due to progression of malignancy in 75% of cases, which reflects failure of local tumor control. The response to radiotherapy depends on the stage of the tumor. For tumors less than 5 cm in length, nearly 100% will respond, whereas if the tumor is greater than 10 cm in length, only 29% will respond. The same authors reporting these results found that none of their patients with metastatic disease responded.(39)

The presence of tracheoesophageal fistula is one of the few absolute contraindications to radiotherapy.

Perioperative Radiation

The rationale of preoperative radiation therapy includes the possibility of decreasing tumor size and increasing resection rates. Radiotherapy may treat periesophageal disease beyond the margins of resection, but surgery can treat greater lengths of tumor. Nonrandomized studies showed some improvement with preoperative therapy, but three randomized controlled studies have failed to confirm this.(40,41,42) The best

information suggests, then, that preoperative therapy is not beneficial, and should not be recommended.



Actuarial survival rate after surgical resection of carcinoma of esophagus. In the irradiated patients, the five year actuarial postoperative survival rate was 9.5 per cent versus 11.5 per cent for the nonirradiated patients.

From Launois, S.G.O., 1981

The rationale for postoperative radiotherapy includes the possibility of controlling disease at the positive margins of resected tumor. A single randomized prospective trial of surgery and postoperative radiotherapy compared to surgery alone in patients undergoing curative resections has been reported in abstract form. Five-year survival was not improved with radiation, regardless of clinical stage.(43) Based on the information available, postoperative radiation cannot be recommended.

Attempts to improve the results of radiotherapy with single-agent chemotherapy or radiosensitizers, such as methotrexate, bleomycin, or misonidazole, have shown no benefit.(44,45,46)

Chemotherapy and Combined Therapy

The poor results of surgery alone and radiotherapy alone have been due in large part to failure to control either local spread or distant metastases. This has led a number of investigators to use a multimodality approach in an attempt to improve local control and cure rates. Combinations of radiotherapy and surgery have already been discussed.

A variety of chemotherapeutic agents have been found to have activity against squamous cell carcinoma of the esophagus, with response rates in the 12-25% range.

The most commonly used have been 5-FU and cisplatin. Response rates with combined chemotherapy range from 30-80%.(47) Studies have been done using chemotherapeutic agents alone or in combination with surgery or radiotherapy.

Regimens Involving Chemotherapy

1. Chemotherapy, radiation, and surgery
2. Chemotherapy and surgery
3. Chemotherapy and radiation
4. Chemotherapy alone

Very few randomized controlled studies have been done in this area. Almost all published studies are single-arm, non-randomized pilot trials with a few patients, and no controls, or, at best, historical controls. Patient selection bias is difficult to assess in these studies, and the results should be interpreted cautiously.

Chemotherapy and Surgery

The rationale for using chemotherapy before and after surgery is that surgery controls local disease, while the majority of patients with symptomatic tumors have systemic disease at presentation. Several non-randomized studies of preoperative chemotherapy have shown survivals of 14-20 months.(48,49,50) However, a single, controlled, randomized study comparing chemotherapy and surgery to surgery alone was reported in 1988 from M. D. Anderson, Walter-Reed and the National Cancer Institute.(51) In this study, treatment with cisplatin, vindesine, and bleomycin before surgery was compared to surgery alone. There was a trend toward increased 3-year survival with chemotherapy, but it was not significant. At this time then, the benefit of preoperative chemotherapy has not been proven.

	Survival	Complications		
	Mean (Mo)	2 yr (%)	3 yr	(%)
Chemotherapy and surgery	9	27	25	29
Surgery alone	9	17	5	47

Roth 1988

Chemotherapy, Radiotherapy, and Surgery

The impetus for trials of chemotherapy, radiotherapy, and surgery for carcinoma of the esophagus came in part from the success of preoperative chemotherapy and irradiation for squamous cell carcinoma of the anal canal and adenocarcinoma of the rectum at Wayne State University Medical Center in Detroit.

In 1977, Wayne State University began a preoperative combined modality pilot program for localized squamous cell cancers of the middle and distal esophagus. The regimen consisted of 5-FU 1,000 mg/m^2 as an infusion, mitomycin C 10 mg/m^2 as a bolus, and 3,000 rads given preoperatively. An Ivor Lewis esophageal resection was performed after 3-4 weeks. If residual tumor was found, postsurgical radiation was given. In most instances, dysphagia improved rapidly with the preoperative regimen. In only one patient who underwent the entire course of treatment could residual tumor be found at esophagoscopy. Twenty-three patients went to surgery. In 6 of these 23, or 26%, no residual microscopic tumor was found in the resected specimen. When these results were presented, there was keen interest in this treatment modality. However, it should be noted that 7 of the 23, or 30%, of patients operated on died as result of treatment, and although 3 patients survived more than 5 years, all 3 died later of recurrent esophageal cancer. Median survival for the entire group was only 12 months.(52)

	First WSU Protocol
Resected	42%
Complete tumor response	26%
Treatment mortality	30%
Median survival	12 months

In 1979 the same group of investigators at Wayne State University substituted cisplatin for mitomycin, to reduce marrow toxicity. Results were similar to the initial study. A good clinical response occurred in most patients.(53)

	Second WSU Protocol
Resected	72%
Complete tumor response	24%
Treatment mortality	27%
Median survival	18 months

In 1987, the results of a larger study using essentially the same protocol were reported by the Southwest Oncology Group. This study had virtually the same results as the other two, with a 14-month median survival.(54)

Trials of regimens involving preoperative chemotherapy and surgery, with postoperative radiotherapy and chemotherapy have also been published.(48,55)

None of these studies have been prospective, randomized, controlled trials. Good clinical responses have occurred in most patients. The toxicity of the chemotherapy regimens has been moderate. Treatment mortality has not been as high as in the early Wayne State University studies. In 10-35% of cases tumor sterilization is seen, but distant recurrences are the rule, and no study has shown as high as a 20% 5-year survival rate.

Chemotherapy and Radiation

Because of the high operative mortality rate experienced in earlier trials, the investigators at Wayne State University designed a pilot study of chemotherapy and radiotherapy without esophagectomy.(56) The radiotherapy was increased to 6,000 rads, and four courses of chemotherapy were planned. Initially, bleomycin and mitomycin-C were added to the original 5-FU and cisplatin, but had to be dropped because of toxicity, and additional courses of 5-FU and cisplatin were added. The median survival was 19.5 months. This result was better than the median survival of 9.5 months in their patients previously treated with chemotherapy, radiation, and surgery.

The group at the Fox/Chase Cancer Center in Philadelphia achieved an overall two-year survival of 47%, and good control of dysphagia in advanced cases, using chemotherapy and radiotherapy.(57) Other non-randomized, uncontrolled studies at the Princess Margaret Hospital in Toronto, the University of California in Fresno, and the Henry Ford Hospital in Detroit, suggested good responses to chemotherapy and radiotherapy alone, without surgery, and better responses with chemotherapy and radiotherapy than with radiotherapy alone.(58,59,60)

These studies have suggested that surgery may add little to an aggressive program of combined chemotherapy and radiotherapy. This makes sense, since chemotherapy and surgery are both directed at local control. Chemotherapy and radiotherapy may also offer acceptable palliation of advanced disease.

However, although the studies of chemotherapy and radiotherapy to date are encouraging, they must be interpreted with caution, and prospective, randomized, controlled studies will be needed to confirm them. In 1987, David Kelsen, from Memorial Sloan Kettering Cancer Center, wrote an editorial entitled, "Multimodality Therapy of Esophageal Cancer; Still an Experimental Approach," in which he concluded that "In the absence of an investigational trial, standard treatment for local regional esophageal carcinoma, unsatisfactory though it is, remains surgery or radiotherapy".(61) Since that time, little has been published to alter that view.

The difficulties in conducting a randomized trial for treatment for esophageal carcinoma can be illustrated by going through the exercise of determining the sample size required for a study to determine whether a particular treatment will improve survival from 10 to 30% in resectable patients. This magnitude of improvement is in line with the experience in combined treatment of other solid tumors. Using a standard table of sample sizes we can see that if we choose an alpha or significance level of 0.05 and a power of 80%, both of which are customary, our study will require 71 evaluable patients in each arm, or a total of 142.(62)

Sample Sizes (Per Arm) for Clinical Trials with Dichotomous Endpoints

Difference to be detected**	Power:	α = 0.01* 80%	α = 0.01* 90%	α = 0.05* 80%	α = 0.05* 90%
5% vs 10%		686	863	474	621
15%		228	285	160	207
20%		125	155	88	113
25%		83	102	58	75
10% vs 20%		316	397	219	286
30%		102	126	71	92
40%		54	66	38	48
20% vs 30%		456	576	313	412
40%		131	164	91	118
50%		64	79	45	57
30% vs 40%		550	695	376	496
50%		149	186	103	134
60%		69	86	48	62
40% vs 50%		597	754	407	538
60%		154	193	107	139
70%		69	86	48	62

*Two-tailed
**For larger baseline rates, use complements; e.g., 50% vs 80% is equivalent to 20% vs 50%

From Ellenberg, Oncology, 1989

Of every 100 patients presenting with esophageal cancer, we know that only 40 will be resectable, so that to enroll 142 patients we will have to evaluate 355. If only 20% of patients declined to enter the study, which is optimistic, 444 patients will be required.

The Dallas Veterans Administration Medical Center, which has a population at high risk for esophageal cancer, saw 22 new cases of esophageal cancer in 1988. In other words, five centers similar to the Dallas Veterans Administration Medical Center would take four years to enroll the patients for such a study. Such a coordinated effort is possible, and has been accomplished for other conditions, but is difficult to organize. We should also take into account that such a study will require, at a minimum, a gastroenterologist, radiotherapist, surgeon, and oncologist in each center, that these 20 physicians will have to work together for five years, and that they must all agree on the appropriate therapeutic program to test.

Several randomized studies are ongoing. One such study being conducted at M.D. Anderson in Houston involves treatment of squamous cell carcinoma of the thoracic esophagus with chemotherapy and surgery compared to surgery alone. Other studies planned in Houston include chemotherapy and surgery versus surgery alone for adenocarcinoma of the esophagus, and two courses of chemotherapy with radiotherapy compared to five courses of chemotherapy with radiotherapy in inoperable patients. The name of the oncologist responsible for the studies in the written protocol is included below: Jaffer Ajani, M.D., University of Texas M.D. Anderson Cancer Center, Box 078, 1515 Holcomb Blvd., Houston, Texas 77038, telephone 713-792-2121.

Other randomized studies are needed, including:

1. surgery versus radiotherapy, including early stages,
2. chemotherapy plus radiotherapy versus radiotherapy alone
3. chemotherapy plus radiotherapy versus surgery alone
4. chemotherapy plus surgery versus surgery alone

Palliation

Since 10% or less of patients with cancer of the esophagus will be cured, it follows that in 90% or more, treatment will be palliative. The palliative results of surgery, radiotherapy, and chemotherapy have been discussed. The principal symptom of esophageal cancer is dysphagia. One swallows an average of 500 times a day, and disruption of the ability to swallow is devastating. Restoration of the ability to swallow should be the first priority of treatment.

Esophageal Dilatation

Esophageal dilatation with mercury-filled Bougies or wire-guided dilators is the most expedient way of restoring patency of the esophageal lumen. Large series have confirmed the safety of dilatation of malignant strictures. Ninety percent of patients will have improved swallowing, and be able to take at least a soft diet. Complications should be rare, particularly if gradual dilation is used, with fluoroscopy and guidewires for the first sessions. The disadvantage of dilators is that treatments must be repeated often, on the average of once a week. However, outpatient treatment is usually possible, and dilation can be done while awaiting response to radiation or other treatment modalities. Dilation can also be done if dysphagia recurs after radiotherapy or combined treatment.(63)

Esophageal Stents

In about 10-15% of patients a tracheoesophageal fistula will form. This is a miserable complication of esophageal cancer. Oral intake of any kind, and even the swallowing of secretions, leads to incessant coughing, as well as uncontrollable aspiration pneumonia. Patients with tracheoesophageal fistulae have a dismal prognosis. The only reasonable option is placement of an esophageal stent. An esophageal stent is an incompressible tube, usually 10-12 mm in internal diameter, with a proximal flange. The malignant stricture is dilated, following which, using a guide wire and a pusher tube, the stent is placed across the tumor. If successful, the stent will provide a permanent lumen, which bypasses the fistula. If gradual dilatation is used, procedure-related mortality should be less than 5%. Patients cannot generally swallow solid food, but most can swallow liquids, and aspiration and pneumonia can be controlled.(64)

Laser Therapy

Lasers can be delivered into the gastrointestinal tract through fiberoptic endoscopes using quartz wave guides. Lasers were first used for treatment of gastrointestinal bleeding, but have been adapted to the ablation of esophageal tumors.

Several techniques have been used, but the most commonly used is to dilate the malignant stricture and pass the endoscope and wave guide beyond it. As the endoscope is withdrawn, the laser is used to coagulate or vaporize tumor, creating a lumen. With this technique, an adequate lumen can be restored in most patients in

one or two sessions. Palliation lasts, on the average, about 4 weeks, at which time the treatment can be repeated. Laser therapy works best with short, straight, bulky tumors. Risks include aspiration pneumonia, pneumomediastinum, and cardio-respiratory problems. Laser units are expensive, and require considerable operator expertise, but when available, may offer rapid palliation for patients with advanced disease.(61,66)

BICAP Tumor Probe

The BICAP tumor probe is a long, flexible shaft to which is attached a metal olive. The olive has alternating conducting strips through which a bipolar current can be passed, thus coagulating tissue. The technique used is similar to that for the laser, in that the malignant stricture is dilated, and the instrument is advanced through the area. Then, using fluoroscopic control, the probe is pulled back into the tumor. Current is applied, and a 1 cm. length of tumor is coagulated. The probe is withdrawn another centimeter, current is reapplied, and the process is repeated until the entire length of tumor has been treated. The BICAP tumor probe works well with long, circumferential tumors. Non-circumferential tumors are dangerous to treat because of the risk of perforating normal tissue. Palliation can be accomplished in one or two sessions, and is reported to last up to 6 weeks. BICAP tumor probes are much less expensive than lasers.(67)

It should be recognized that even though luminal patency can be restored with dilatation, laser therapy, and BICAP tumor probe, many patients will continue to lose weight because of tumor-related anorexia. Dysphagia may be palliated, but the natural history of the disease is not affected.

Summary and Conclusions

Cancer of the esophagus in Western countries will likely continue to present at an advanced stage, except perhaps in patients with Barrett's esophagus followed with screening programs.

All patients should have careful clinical staging to guide therapy, but current methods of staging are imperfect. New techniques, such as endoscopic sonography, may be useful.

The standard therapy of early (stage I and II) cancer is surgery in fit patients, and radiation in poor risk patients. However, no studies have been done to compare surgery and radiation in early cancer. Both treatments may be equally effective. The standard therapy of advanced (stage III and IV) esophageal cancer is radiation. Some patients felt to have early tumors may be found to have stage IIIa lesions at surgery, and receive palliative resection. Tumors of the upper third of the esophagus should be treated with radiation, and adenocarcinomas of the lower third should be resected when possible. Perioperative radiotherapy should not be recommended on a routine basis.

Preliminary, uncontrolled studies suggest that combination therapy with chemotherapy, radiation, and surgery might be better than radiation alone or surgery alone, both for attempted cure and palliation. Other pilot studies suggest that combined chemotherapy and radiation may be effective without surgery. However, controlled, randomized trials have not been done. Combined therapy should be regarded as experimental, and, when possible, should be done in the context of clinical research. Dilatation and stenting will continue to be important for palliation. Laser and BICAP tumor ablation may be useful tools in palliative therapy.

References

1. Epidemiology of cancer of the esophagus
Schotterfeld D
Seminars in Oncology 1984;11:92

2. Research on esophageal cancer in China: A review
Yang C
Cancer Research 1980;40:2633

3. Vitamin intervention in precancerous lesions of the esophagus in a high risk population of China
Wahrendorf J, Munoz N, Lu J
In: Cancer of the liver, esophagus, and nasopharynx, Wagner G, Zhang Y (eds.), New York, Springer-Verlag, 1987

4. The aetiology of esophageal cancer in Transkei
Sagar P, Ellwood R
Gastroenterology 1989:96 (No. 5, Part 2):A424

5. Carcinoma of the oesophagus with tylosis
Harper PS, Harper RM, Howel-Evans AL
Quarterly J. Med. 1970;34:317

6. Achalasia as a risk factor for esophageal carcinoma - A reappraisal
Chuong J, DuBovik S, McCallum R.
Dig. Dis. Sci. 1984;29:1105

7. Caustic burns and carcinoma of the esophagus
Hopkins R, Postlethwait R
Ann. Surg. 1981;194:146

8. Identification of synchronous esophageal tumors in patients with head and neck cancer
Abemayer E, Moore D, Hanson D.
J. Surg. Oncol. 1980;38:94

9. Barrett's esophagus
Spechler SJ, Goyal RK
New Engl. J. Med. 1986;315:362

10. Barrett's esophagus: clinical, pathological, histochemical features and risk of adenocarcinoma
G.O.S.P.E.
Gastroenterology 1989;96 (No. 5, Part 2):A186

11. Endoscopic biopsy can detect high grade dysplasia in early adenocarcinoma in Barrett's esophagus without grossly recognizable neoplastic lesions
Reid BJ, Weinstein WM, Levin KJ, et al
Gastroenterology 1988;94:81

12. High grade dysplasia in Barrett's esophagus - A report of experience with 43 patients
Schnell T, Santos S, Chejfec L, et al
Gastroenterology 1989;96:A452

13. Barrett's oesophagus - to screen or not to screen?
Atkinson M
Gut 1989;30:2

14. The cost of surveillance for adenocarcinoma complicating Barrett's esophagus
Achkar E, Carey W
Am. J. Gastro. 1988;83:291

15. Barrett's esophagus: Correlation between fluorocytometry and histology in detection of patients at risk for adenocarcinoma
Reid B, Haggett R, Rubin C, Rabinovitch P
Gastroenterology 1987;93:1

16. Adenocarcinoma of the esophagus and gastroesophageal junction
Fein R, Kelsen D, Gellen N, et al
Cancer 1985;56:2512

17. Combined radiation and chemotherapy as primary management of adenocarcinoma of the esophagus and gastroesophageal junction
Coia L, Paul A, Ergstrom D
Cancer 1988;61:643

18. Carcinoma of the esophagus
Cuckingham R, Carey J
Ann. Thorac. Surg. 1978;26:224

19. Natural history of early esophageal squamous carcinoma and early adenocarcinoma of the gastric cardia in the People's Republic of China
Guanrei Y, SongLiang Q, He H, Guizen F
Endoscopy 1988;3:95

20. Superficial squamous cell carcinoma of the esophagus
Bogomoletz W, Molas G, Gayet B, Potet F
Am. J. Surg. Pathol. 1989;13:535

21. Oesophageal squamous cell carcinoma: 1. A critical review of surgery
Earlam R, Cunla-Melo J
Brit. J. Surg. 1980;67:381

22. Autopsy findings in squamous cell carcinoma of the esophagus
Anderson L, Lad T.
Cancer 1982;50:1587

23. Manual for staging and cancer, 3rd edition
American Joint Committee on Cancer
J. B. Lippincott Company, Philadelphia, PA., 1988, pp. 63

24. The esophageal axis and its relationship to the resectability of cacinoma of the esophagus
Akiyama H, Kogure T, Itai Y
Ann. Surg. 1972;176:30

25. CT of esophageal neoplasms
Halvorsen R, Thompson W
Radiologic Clinics of North America 1989;27 (No. 4):667

26. Diagnosis and preoperative staging of oesophageal malignancies
Reeders J, Tio J
Bailliere's Clinical Gastroenterology 1987;1:869

27. Endosonography and computed tomography of esophageal carcinoma
Tio T, Cohen P, Coene P, et al
Gastroenterology 1988;96:1478

28. Follow-up results after resection of thoracic esophageal carcinoma
Kasai M, Mori S, Watanabe T
World J. Surg. 1978;2:543

29. Selective therapeutic approach to cancer of the lower esophagus and cardia
DeMeester T, Zaninotto G, Johansson K
J. Thorac. Cardiovasc. Surg. 1988;95:42

30. Cervical or thoracic anastomosis for esophagectomy for carcinoma
Chasseray V, Kiroff G, Buard J, Launois B
Surg. Gynecol. Obstet. 1989;169:55

31. Carcinoma of the esophagus: A comparison of the results of transhiatal versus transthoracic resection
Hankins J, Attar S, Coughlin T, et al
Ann. Thorac. Surg. 1989;42(5):700

32. Substernal gastric bypass of the excluded thoracic esophagus - Results of an ill-advised operation
Orringer M
Surgery 1984;96:467

33. Oesophageal squamous cell carcinoma: II - A critical review of radiotherapy
Earlam R, Cunla-Melo J
Brit. J. Surg 1980;67:457

34. Ten-year follow-up of esophageal cancer treated by radical radiation therapy: Analysis of 869 patients
De-Ren S
Int. J. Radiation Oncol. Biol. Phys. 1989;16:329

35. Carcinoma of the esophagus - A review of 108 cases treated by radical radiotherapy
Slevin N, Stout R
Clin. Radiol. 1989;40:200

36. Radiation therapy of esophageal cancer
Hancock S, Glatstein E
Seminars in Oncology 1984, Vol II, No. 2, p 144

37. Multiple fraction per day radiation therapy for inoperable esophageal cancer
DePaoli A, Boz G, Trov'o M, et al
Int. J. Radiat. Oncol. Biol. Phys. 1988;14:855

38. Intracavitary irradiation in palliation of carcinoma of oesophagus and cardia
Rowland C, Pagliero K
Lancet 1985;November 2:1981

39. Carcinoma of the esophagus. Pretreatment assessment, correlation of radiation treatment parameters with survival, and identification of management of radiation treatment failure
Beatty J, DeBoer G, Rider W
Cancer 1979;43:2254

40. Preoperative radiotherapy for carcinoma of the esophagus
Launois B, DeLarue D, Campion J, Kerbaol M
Surg. Gynecol. and Obstet. 1981;153:690

41. The value of preoperative radiotherapy in esophageal cancer: Results of a study by the EORTC
Gignoux M, Roussel A, Paillot B, et al
Recent Results in Cancer Research 1988;110:1

42. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of esophageal carcinoma: report on 106 patients
Mei W, Xian-Zhi G, Weibo Y, et al
Int. J. Radiation Oncol. Biol. Phys. 1989;16:325

43. Does postoperative radiation therapy increase survival after curative resection for carcinoma of the esophagus? A prospective, controlled, multicenter trial
Lacaine P, Tenieres P, Hay J
Gastroenterology 1989;96 (No. 2, Part 2):A280

44. Palliative therapy of inoperable oesophageal carcinoma with radiotherapy and methotrexate: Final results of a controlled clinical trial
Roussel A, Bleiberg H, Dalesio O, et al
Int. J. Radiat. Oncol. Biol. Phys. 1989;16:67

45. A controlled evaluation of combined radiation and bleomycin therapy for squamous cell carcinoma of the esophagus
Earle J, Gelber R, Moertel L
Int. J. Radiat. Oncol. Biol. Phys. 1980;6:821

46. Esophageal carcinoma: the final results of a multicenter and controlled German study with misonidazole and radiation
Scherer E, Bamberg M, Godehard E, et al
Strahlenther-Onkol. 1986;162:661

47. Chemotherapy of esophageal cancer
Kelsen, D
Seminars in Oncology, Vol 11, No. 2, 1984, pp 159

48. Cisplatin, vindesine, and mitoguazone in the treatment of esophageal cancer
Kelsen D, Fein R, Cooney C, et al
Cancer Treat. Rep. 1986;70:255

49. Preoperative chemotherapy followed by surgery with possible postoperative radiotherapy in squamous cell carcinoma of the esophagus: evaluation of the chemotherapy component
Carey R, Hilgenberg A, Wilkens E, et al
J. Clin. Oncol. 1986;4:697

50. Cisplatin, vinblastine, and mitoguazone chemotherapy for epidermoid and adenocarcinoma of the esophagus
Forastiere A, Gennis M, Orringer M, et al
J. Clin. Oncol. 1987;5:1143

51. Randomized clinical trial of preoperative and postoperative adjuvant chemotherapy with cisplatin, vindesine, and bleomycin for carcinoma of the esophagus
Roth J, Pass H, Flanagan M, et al
J. Thor. Cardiovasc. Surg. 1988;96:24

52. Combined modality therapy for esophageal squamous cell carcinoma
Franklin R, Steiger Z, Vaishampayar G, et al
Cancer 1983;51:1062

53. Preoperative chemotherapy plus radiation therapy for patients with cancer of the esophagus: Potentially curative approach
Leichman L, Steiger Z, Seyde H, et al
J. Clin. Oncol. 1984;2:75

54. Combined therapies for squamous cell cancer of the esophagus: A Southwest Oncology Group (SWOG 8037) study
Poplin E, Fleming T, Leichman L, et al
J. Clin. Oncol. 1987;5:622

55. Treatment of esophageal carcinoma by combined preoperative chemotherapy
Bains M, Kelsen D, Beattie E, et al
Ann. Thorac. Surg. 1982;34:521

56. Chemoradiation with and without surgery in the thoracic esophagus: The Wayne State experience
Herskovic A, Leichman L, Lattin P, et al
Int. J. Radiat. Oncol. Biol. Phys. 1988;15:655

57. Nonsurgical management of esophageal cancer: Report of a study of combined radiotherapy and chemotherapy
Coia L, Engstrom P, Paul A
J. Clin. Oncol. 1987;5:1783

58. Radiotherapy alone and chemoradiation for nonmetastatic esophageal carcinoma
John M, Flam M, Mowry P, et al
Cancer 1989;63:2397

59. Comparison of three treatment strategies for esophageal cancer within a single institution
Richmond J, Seydec H, Bae Y, et al
Int. J. Radiat. Oncol. Biol. Phys. 1987;13:1617

60. Radical radiation therapy with 5-Fluorouracil infusion and mitomycin C for oesophageal squamous carcinoma
Keane T, Harwood A, Elhakim T, et al
Radiotherapy and Oncol. 1985;4:205

61. Multimodality therapy of esophageal carcinoma: Still an experimental approach
Kelsen D
J. Clin. Oncol. 1987;5(#4):530

62. Determining sample sizes for clinical trials
Ellenberg S
Oncology 1989;3:39

63. Palliative dilation for dysphagia in esophageal carcinoma
Heit H, Johnson L, Seigel S, Boyce H
Ann. Int. Med. 1978;89(1):629

64. Palliative intubation of oesophagogastric neoplasms at fiberoptic endoscopy
Ogilvie A, Dronfield M, Ferguson R, Atkinson M
Gut 1982;23:1060

65. Endoscopic laser therapy for esophageal cancer: Present status with emphasis on past and future
Fleischer D
Lasers in Surgery and Medicine 1989;9:6

66. Palliative laser therapy of advanced esophgeal carcinoma: An alternative perspective
Murray F, Bowers G, Birkett D, Cave D
Am. J. Gastro. 1988;83:818

67. Palliation of obstructing esophageal cancer with BICAP tumor probe
Jensen D, Brunetaud J, Machicado G, et al
Gastroenterology 1989;96(Part 5, No. 2):A238