

Practice guidelines

Esophageal Cancer

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PREAMBLE

These guidelines are developed under the auspices of the American College of Gastroenterology (ACG) and its Practice Parameters Committee and approved by the Board of Trustees. They have been intensely reviewed and revised by the Committee, other experts in the field, physicians who will use them, and specialists in the science of decision analysis. When approved by the ACG, they are submitted to the other major gastrointestinal societies (American Gastroenterological Association and the American Society for Gastrointestinal Endoscopy) for their approval.

To develop the guidelines, the world literature is searched, then all appropriate studies are reviewed and evaluated by the authors. In the literature review, evidence is evaluated along a hierarchy, with randomized, controlled trials given the greatest weight. Abstracts presented at national and international meetings are only used in special circumstances in which unique data from ongoing trials were presented. When scientific data is lacking, recommendations are based on expert consensus.

These guidelines are intended to be applicable to all physicians who address the subject without regard to specialty training or interests, and are intended to indicate the preferable, but not the only acceptable, approach to this problem. Given the wide range of specifics in any health care problem, the physician must always choose the course best suited to the individual patient and the variables in existence at the moment of decision.

INTRODUCTION

The management of esophageal cancer presents some of the greatest challenges in the current practice of gastroenterology. Highly curable in its earliest stages, esophageal cancer is treatable but is usually fatal when more advanced (1–3). There is, therefore, an intense interest in methods for prevention and early diagnosis. Because outcome is so strongly associated with stage (4, 5), a new emphasis has been placed on the clinical staging of esophageal cancer

before considering the application of treatment options with an intent to cure, to prolong survival, or to palliate symptoms. In the United States, most patients currently present with advanced stage disease.

There is remarkable geographic variation in the incidence of esophageal cancer. For example, in Linxian, China new cases occur at an annual rate of 130 per 100,000 population (6). On the other hand, the United States represents overall a relatively low incidence area with an annual rate of <10 per 100,000 (7). The annual United States mortality of 11,200 approaches the incidence rate, emphasizing the continuing high lethality of the disease (8).

Another striking epidemiological phenomenon involving subtypes of esophageal cancer has taken place in the United States and other Western countries during the past two decades. Into the 1970s, about 90% of esophageal cancers were squamous cell type on pathological examination. Since then, adenocarcinomas have increased dramatically, currently accounting for about 50% of new cases (9, 10). Adenocarcinomas of the gastric cardia have increased in parallel to adenocarcinomas of the distal esophagus, indicating that this phenomenon cannot be explained by differences in classification or ascertainment (11, 12). Squamous cell esophageal cancer and adenocarcinoma of the distal stomach have remained stable in incidence or even decreased during this time. It is estimated that about 1/3 of the 23,500 new cases of gastric cancer in the United States in 1996 originated in the cardia. These are alarming trends. In a recent appraisal, adenocarcinoma of the esophagus was found to be rising with a rate of acceleration greater than that of any other cancer in the United States (9, 10). Inasmuch as adenocarcinoma of the distal esophagus and adenocarcinoma of the gastric cardia often cannot be clearly separated pathologically, probably share a common etiology, and present almost identical management issues, they will be discussed together in these guidelines.

RISK FACTORS

The US incidence of esophageal cancer varies with gender and ethnicity. Both squamous cell cancer and adenocar-

cinomas affect men more frequently than women (6, 7). The ratio for squamous cell cancer is in the range of 3:1 and for adenocarcinomas 7:1. Squamous cell cancers predominate in American blacks over whites by 6:1, and adenocarcinomas have the opposite preponderance, occurring in whites over blacks at a ratio of 4:1 (13). Both squamous cell cancers and adenocarcinomas are diseases of adults, rarely occurring before age 25. Mortality rates increase steadily with age with a median in the sixth decade of life. On the other hand, the incidence of esophageal cancer in blacks is higher than in whites at younger ages. Esophageal cancer is one of the most common malignancies among black men under age 55 (13).

There is a clear-cut relationship of squamous cell cancer of the esophagus to the use of tobacco and alcohol. There is also a definite association with head and neck cancer, and multiple cancers of the upper aerodigestive tract, probably because these cancers are also related to heavy use of tobacco and alcohol (14). There are long-term risks associated with chronic inflammation and stasis, as occurs in strictures after caustic injury (15). The risk in achalasia is inconclusive (16, 17). The highest risk is in tylosis, a rare dominantly inherited disease (18). The only confirmed risk factor for adenocarcinoma is Barrett's esophagus (9–12). Studies have been divided over whether smoking, alcohol consumption, or obesity increases the risk for esophageal adenocarcinoma (12, 14, 19–21).

DIAGNOSIS

Endoscopy with biopsy is the primary method for the diagnosis of esophageal carcinoma.

Early cancers of the esophagus generally are asymptomatic, although ulcerated lesions may sometimes present with evidence of gastrointestinal bleeding, such as melena, or be found during workup for occult gastrointestinal bleeding or iron deficiency anemia. Advanced cancers can also cause bleeding, but most commonly present with dysphagia. Cancers usually become quite large before compromising the lumen sufficiently to cause the sensation of blockage or "sticking" of a swallowed food bolus. Difficulty ingesting solid foods occurs before liquids. Symptoms commonly have a very gradual onset. Weight loss is usually present. Odynophagia, the sensation of pain with swallowing is less common (22–24).

The diagnosis of esophageal cancer is made with endoscopy and biopsy, or by barium contrast radiography followed by endoscopy and biopsy (22, 25–27). Many physicians continue to order x-ray studies initially to evaluate patients with dysphagia. The rationale is that barium contrast radiographs can document contour and motility abnormalities, such as strictures and achalasia, and the presence of unexpected airway fistula. On the other hand, flexible endoscopes are now thin and easily passed under direct vision, and a radiological "road map" is rarely needed. Most fistulas are evident on clinical grounds with persistent cough made

worse by swallowing (28). Thus, there is an increasing trend toward using endoscopy as the primary examination for the diagnosis of esophageal cancer, saving barium contrast radiography for selected cases.

Endoscopy is also the preferred method for the diagnosis of early cancer, because small areas of abnormality can be directly biopsied for tissue diagnosis (29–33). Air-contrast barium radiography can detect some small lesions, but these always require further evaluation with endoscopy and biopsy (22). In malignant stricture, the combination of endoscopic biopsies and brush cytology has an accuracy of virtually 100% in obtaining a tissue diagnosis of esophageal cancer (25, 26). Cytology is particularly useful in malignant strictures in which the endoscope cannot be inserted beyond the top of the lesion, but the brush usually is easily passed into the main area of abnormality (34).

SCREENING AND SURVEILLANCE

There is no currently acceptable screening method for esophageal cancer in the United States. Individual patients at increased risk for esophageal cancer are candidates for endoscopic surveillance.

Screening involves the testing of large population groups, asymptomatic but at high risk of developing a disease. In the US, although carcinoma of the esophagus and gastric cardia are increasing in incidence, the absolute number of cases remains too small to consider screening the general public. This is not true in high risk areas such as northern China, where populations have been screened for esophageal cancer using the technique of abrasive balloon cytology (35, 36). With this method, a deflated balloon covered with a mesh is swallowed, the balloon inflated, and then withdrawn. Cytological material retained on the mesh is smeared on slides, stained, and examined by light microscopy for evidence of dysplastic or malignant cells. Positive tests lead to endoscopy and biopsy (37).

Screening directed at high risk groups for esophageal cancer has been carried out in the US, but has not yet shown proven value. Abrasive balloon cytology has been applied to patients with a history of high alcohol and tobacco consumption, but resulted in many false-negative and false-positive cases (38). Endoscopy combined with Lugol's iodine staining of the esophageal mucosa has been used in such patient groups to aid in the detection of areas of dysplasia and early cancer. Lugol's iodine, when sprayed on the esophageal mucosa during endoscopy, stains the glycogen in normal squamous epithelium a dark brownish color. Abnormal areas are left unstained, and are easily targeted for biopsy (39, 40). The procedure is quick and inexpensive, and has been effective in detecting dysplasia and early squamous cell cancer not evident on standard examination. Further testing of this relatively simple method in high risk patients seems reasonable.

With the increasing incidence of adenocarcinoma, some gastroenterologists have suggested screening patients at

TABLE 1
Staging Classification of Esophageal Cancer

Primary Tumor (T)	Regional Lymph Nodes (N)*	Distant Metastasis (M)	Stage Groupings
TX: Primary tumor cannot be assessed.	NX: Regional lymph nodes cannot be assessed	MX: Presence of distant metastasis cannot be assessed	Stage 0: TisN0M0
T0: No evidence of primary tumor	N0: No regional lymph nodes metastasis	M0: No distant metastasis	Stage 1: T1N0M0
Tis: Carcinoma <i>in situ</i>	N1: Regional lymph node metastasis	M1: Distant metastasis	Stage IIA: T2N0M0; T3N0M0
T1: Tumor invades lamina propria or submucosa [†]			Stage IIB: T1N1M0; T2N1M0
T2: Tumor invades muscularis propria			Stage III: T3N1M0; T4, any N, M0
T3: Tumor invades adventitia			
T4: Tumor invades adjacent structures			Stage IV: Any T, any N, M1

* 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.

[†] T1 has been further subdivided into T1_m, cancer confined to the mucosa, and T1_{sm}, cancer invading the submucosa.

highest risk. Because Barrett's esophagus is secondary to chronic gastroesophageal reflux, some believe that patients with persistent symptoms, particularly middle-age white men with the highest risk, should be screened (41, 42). Endoscopy, the best way to make a diagnosis of Barrett's esophagus, has been advocated for such patients (43). However, millions of Americans complain of chronic gastroesophageal reflux. Such a strategy could prove worthwhile for individual patients, but because of the expense of endoscopy, might not prove cost-effective. The use of balloon cytology in patients with reflux has been tested, but has not yet proven effective (44).

Surveillance is the terminology used to describe the periodic testing of individual patients found to be at high risk for disease. The surveillance of patients with Barrett's esophagus for the development of dysplasia and adenocarcinoma using periodic endoscopy is widely practiced and recommended, but remains of unproven value (27, 45). This issue has been discussed in detail in a recently published Guideline (46). Flow cytometry, molecular biomarkers in biopsy material, laser-induced fluorescence spectroscopy, and optical coherence tomography all offer the possibility of improved accuracy in the future for endoscopic surveillance (47–50).

STAGING

To plan therapy for esophageal cancer, the anatomical extent of disease should be assessed using the TNM staging system. Computed tomography of the chest and abdomen should be the initial tests for staging. If there is no evidence of metastatic disease, endosonography should be performed to achieve the most accurate regional staging.

The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) have established essentially identical staging classifications for esoph-

ageal cancer (51, 52). Staging is based solely on the TNM system, which defines the anatomical extent of disease (Table 1).

"T" indicates the depth of primary tumor invasion. Squamous cell carcinoma and adenocarcinoma of the esophagus are staged similarly. These cancers originate in the mucosa and invade progressively deeper layers of the gastrointestinal tract wall as they advance.

"N" indicates the spread of cancer to specified regional lymph nodes. In esophageal cancer any regional lymph node metastasis is considered N1. There is no longer an N2 category, and more distant nodal spread is considered to represent distant metastasis (M1). For example, lymph node metastases at the celiac axis are considered to be not regional, but rather distant metastases.

"M" indicates distant metastases to lymph nodes outside specified regional nodes, or to organs such as liver, lung, and adrenal glands not involved by direct extension from the primary esophageal cancer.

In the AJCC/UICC staging classifications, it is important to note that clinical, surgical, and pathological stages are based on the same TNM anatomic criteria. Symptoms such as dysphagia, laboratory tests, and biomarkers, have no role in the classifications. T stage is based specifically on the depth of invasion of the primary cancer. The length of the cancer, the extent of involved circumference, or the degree of luminal compromise are not factors in staging.

Clinical staging begins with a thorough physical examination that focuses on sites prone to metastases, including the supraclavicular lymph nodes, the liver, and the lungs. Blood tests can provide a clue to possible liver metastases, and chest x-rays will help to identify pulmonary and mediastinal disease. However, the most critical clinical staging tests involve modern imaging methods, primarily computed

TABLE 2
Depth of Invasion (T) Compared With EUS Wall-Layer Abnormality at
Frequencies of 7.5–12 MHz

Depth of Invasion (T)	EUS Wall-Layer Abnormality
T1m, mucosa	1 and 2
T1sm, submucosa	3
T2, muscularis propria	4
T3, adventitia	5
T4, adjacent organ	Adjacent organ

tomography (CT) and endoscopic ultrasonography (EUS) (4, 5).

EUS uses high frequency ultrasound transducers inside the esophageal lumen to produce detailed images of the esophageal wall and structures close to the esophagus. At the usual ultrasound frequencies of 7.5 MHz, structures up to about 5 cm from the esophagus can be imaged (53). Higher frequencies produce more detailed images, but with even a more limited field. The great advantage of EUS for staging is the ability to image distinct wall layers with histological correlates. EUS at 7.5 MHz or 12 MHz produces a five-layer image of the esophageal wall: the first layer corresponds to the boundary echo and superficial mucosa, the second layer to the mucosa (including the muscularis mucosae), the third layer to the submucosa, the fourth layer to the muscularis propria, and the fifth layer to the adventitia (54). Primary esophageal cancer is usually imaged as a hypoechoic disruption of the wall layers. The compatibility of the AJCC/UICC classification for T, depth of cancer invasion, with the EUS wall image is shown in Table 2.

EUS has consistently outperformed CT for regional staging of esophageal cancer (55). Even the new faster scanners and helical CT do not image the esophageal wall as a series of layers (56). MRI currently does not seem to add much to advanced CT in staging esophageal cancer (57). It has become clear that staging the depth of tumor invasion (T) on the basis of wall thickness and contour is open to frequent error (58, 59). The thickness of the normal esophageal wall is variable because of its distensibility. Usually 200 ml of an oral contrast agent, such as diluted diatrizoate meglumine (Gastrografin) is administered orally to minimize contrast interface artifacts. A wall thickness of 5 mm is often used as the upper limit of normal. T1 cancer cannot be distinguished from T2. T1 and T2 disease are diagnosed if the wall measures between 5 mm and 15 mm in thickness, and T3 if the wall is >15 mm with an irregular outer contour. T4 disease, invasion of adjacent structures, is based on loss of fat planes and mass effect (5, 56, 58).

Lymph nodes >10 mm in diameter on CT are generally considered to be metastatic (58). Similar measurements have been used to assess lymph nodes on EUS, but additional criteria for malignancy are nodes that are uniformly hypoechoic, sharply demarcated from surrounding fat, and

rounded (60). Benign nodes, particularly in the mediastinum, may be >10 mm, but are often elongated with distinct cortical and medullary areas, and more hyperechoic with less distinct borders. These are subjective criteria and prone to greater diagnostic error than the depth of tumor invasion (55). EUS-guided needle aspiration for cytology may help to improve specificity in this regard (61).

Based on accumulated data, the accuracy of EUS for staging depth of tumor invasion (T) is 85% compared with surgical pathology, and for staging regional lymph node metastases (N), the accuracy is 75% (55). The lower accuracy for N relates to the difficulty in distinguishing benign from malignant nodes.

Endoscopic ultrasound generally is not useful for staging distant metastases (M) except for celiac axis lymph nodes. Inasmuch as regional staging has little importance if distant metastases are present, it is recommended that CT scan should be the initial staging test. If CT is negative for metastases, EUS should then be carried out. The combination of CT and EUS has an overall stage accuracy in the range of 85%, significantly more accurate compared with surgical pathology than CT alone (55, 58).

A caveat for regional staging is that for greatest accuracy it should be done before any preoperative radiation therapy or chemotherapy (4). Fibrosis and inflammation resulting from successful neoadjuvant therapy may be indistinguishable from residual primary tumor or nodal metastases. It is recognized that EUS is operator-dependent and not widely available. On the other hand, EUS is consistently more accurate for regional assessment of esophageal cancer than CT alone (55). In patients with no evidence of metastatic disease, EUS should be performed whenever possible for staging the regional extent of esophageal cancer.

Laparoscopic exploration is advocated by some groups to document small liver and intraperitoneal metastases, usually before aggressive surgical therapy is undertaken (62). Thoracoscopic examination is also advocated by some surgical investigators to achieve the greatest accuracy for lymph node staging in the mediastinum (63). In expert hands, both of these invasive procedures seem to add accuracy to the staging of esophageal cancer, albeit at some increased morbidity and cost. Bronchoscopy should be performed to exclude airway invasion by advanced cancers in the proximal esophagus (22).

TREATMENT

The treatment of esophageal cancer will depend on selecting the best risk/benefit ratio, modified by the patient's preferences and available professional expertise. Stage-directed therapy offers a rational approach to attempt cure, prolongation of survival, or palliation. Patients with early disease (stages 0, I, and IIA) are usually cured with surgery alone. Endoscopic resection or ablation may be curative in stages 0 and I. In advanced esophageal cancer (stages IIB and III), surgery, radiation, and chemotherapy in combina-

tion are associated with modest prolongation of survival, but with high morbidity and low cure rates. In patients with metastatic disease (stage IV), surgery usually should be deferred. Radiation and chemotherapy may provide palliation. For most patients with advanced regional cancer or metastatic disease, a variety of endoscopic methods can provide palliation of malignant dysphagia. Patients should be encouraged to enter clinical trials designed to improve the treatment of esophageal cancer.

The primary treatments for esophageal cancer are surgery, radiation therapy, and chemotherapy. *Per oral* endoscopic methods include dilation, stents, cauterization, laser, injection, and photodynamic therapy. The application of these treatments is dependent on the stage of the disease at diagnosis, and the treatment objective: cure, prolongation of survival, or palliation of symptoms. These objectives are not mutually exclusive, but must take into consideration the risks and morbidity of the treatments, and the age and concurrent medical status of the patient.

An individualized approach is essential, including detailed discussion with the patient and family of risks, benefits, and areas of uncertainty. The acceptance of a range of probable outcomes will vary among individuals. For example, some may be willing to accept a low likelihood of benefit and a high risk of morbidity from a potentially curative treatment plan, which would be totally unacceptable to others. Based on their prior experience, some patients may have a particular desire for, or distaste for, a specific type of treatment. Finally, local expertise will also play a major role in determining which treatments will be more readily available. A further reality in choosing treatments is that the specific methods or techniques for applying surgery, radiation, and chemotherapy remain controversial and under development.

Surgery

Surgery has long been a mainstay in the treatment of esophageal cancer (64). Surgical methods vary from a combined laparotomy and thoracotomy technique with intrathoracic anastomosis of the esophagus and stomach to an extrathoracic method involving the anastomosis of the stomach and the cervical esophagus (65–67). Interposition of intestine, usually the colon, to replace the resected esophagus has also been advocated (68). The degree of lymph node dissection has also been controversial. Extensive *en bloc* resection has been advocated, with distinctions between level 2 and level 3 dissections (69, 70). It has been argued that extensive dissections seem best suited to earlier stage disease than later stages, where systemic metastases may make such extensive dissection with attendant increased morbidity less useful.

Radiation therapy

The delivery of radiation therapy has been improved in recent years with more precise delivery methods, but the ideal amount of radiation and the timing of delivery are not

yet fully established (71–74). The benefits of adding intraluminal radiation therapy (brachytherapy) to external beam radiation remain unproven (75). A majority of patients will have some response to radiation therapy given in “curative” doses, but the response tends to be brief, averaging about 3 months, and 3-yr survival in clinically localized disease is <10% (74).

Chemotherapy

Because esophageal cancer is associated with such early systemic spread, effective chemotherapy would be a great addition to management. There has been progress in recent years, but the benefits of chemotherapy remain modest. Although a wide variety of single agents (most recently paclitaxel) has shown activity against esophageal cancer, combinations of chemotherapeutic agents have produced the best results (22, 76, 77). The most widely used combination, cisplatin and 5-fluorouracil, has shown objective response in 20–40% of cases, but has had no impact on survival (77).

Combined modality therapy

Combined modality or multimodality therapy, usually combining radiation therapy with combination chemotherapy, has been a recent advance. The chemotherapy seems to potentiate the radiation therapy to achieve improved local control. Systemic failure remains a problem because of the inherent weakness of even the best combinations of chemotherapeutic agents. The best doses and timing of radiation therapy and chemotherapy are still not established. Methods have included both concurrent and sequential administration of radiation and drugs. Morbidity increases with higher doses of either radiation or chemotherapy, and can be substantial. Severe side effects have been reported in 10–44% of patients, life-threatening in 3–20% with some mortality (77–83). Several studies in both squamous cell cancer and adenocarcinoma of the esophagus have now shown benefit of combination radiation therapy and chemotherapy, *versus* radiation therapy alone, in terms of survival or prolongation of the disease-free interval before recurrence (77–83).

Combined therapy with surgery

Both radiation therapy alone and chemotherapy alone have been used before and after surgical resection of esophageal cancer. After some initial enthusiasm, larger studies could not document benefits from these approaches (84–91). On the other hand, a recent randomized trial has shown a survival benefit of preoperative (neoadjuvant) multimodality therapy in patients undergoing resection for esophageal adenocarcinoma (92). This and other studies of multimodality therapy before surgery have confirmed a complete pathological response with no evidence of tumor in the resected specimen in the range of 20–25% (93–99). The patients who have achieved this level of local success are most likely to have prolonged survival. The need for additional local control by surgical resection in patients who have had a clinical complete response to multimodality

TABLE 3
Summary of Therapeutic Options for Esophageal Cancer

Treatment	Advantages	Disadvantages
Surgery*	Potentially curative, best in early stages	High morbidity and expense; low overall cure rate
Radiation therapy	Modest response rate	Multiple treatments; moderate morbidity and expense; rarely curative
Chemotherapy	Treats metastatic disease	Low response rate; minimal survival impact
Multimodality therapy (chemotherapy + radiation therapy)	Improved survival associated with complete response	High morbidity and expense
Multimodality therapy followed by surgery†	May increase cure rate and prolong survival	Very high morbidity and expense
Dilation	Usually effective	Brief palliation
Stents	Ease of insertion of expandable metal stents; covered stents effective for airway fistulas	High rate of late complications; expandable metal stents are expensive
Electrocautery	Inexpensive	Difficult to control
Argon plasma coagulator	Noncontact method	Superficial treatment; gas distension
Nd:YAG laser	Powerful; deep penetration	Technically difficult; expensive
Injection of alcohol	Inexpensive, widely available	Difficult to control
Photodynamic therapy	Technically easy; selective tumor ablation; effective for complete obstruction	Expensive; skin photosensitivity

* Endoscopic mucosectomy, thermal ablation, or photodynamic therapy may be curative in selected patients with early cancer confined to the mucosa.

† Chemotherapy + radiation therapy followed by surgery.

therapy remains an important open question (100–104). However, at this time there is no clinically reliable way to detect locally residual microscopic cancer preoperatively.

Stage-directed therapy

After intensive clinical staging as described above, stage T1s, I, and IIA esophageal cancer have high cure rates with surgery alone, and are usually treated with curative intent by surgical resection (Table 3). Patients with carcinoma *in situ* or high grade dysplasia are almost all cured, whereas patients with early stage cancer who have no lymph node metastases (I and IIA) are likely to be cured in the 80% range by surgery (1–3). If lymph node metastases have occurred before surgery, the rate of surgical cure is markedly reduced. The likelihood of nodal metastases increases with the depth of penetration of the tumor. With cancer limited to the mucosa (T1m), the likelihood of nodal metastases is $\leq 10\%$ (105). However, with invasion of the submucosa (T1sm), the rate of nodal metastases increases to the range of 30–50% (stage IIB), and cure rates from surgery alone drop sharply to the range of 10% (1–3).

There is currently no indication to add radiation therapy or chemotherapy to the surgical management of early stage cancer (I, IIA) (106, 107). In patients with early stage cancer who are too ill to undergo surgery or who refuse an operation, there are numerous small series indicating that endoscopic-guided treatments can be curative. Endoscopic mucosectomy has an advantage in providing a histological specimen for evaluation of resection margins. Mucosectomy is usually accomplished with a cautery snare. Recent improvements include lifting the mucosa by the submucosal injection of saline or other fluid (“strip biopsy”), and lifting the mucosa with endoscopic suction using a variceal band ligator or a slotted overtube (105, 108, 109). Superficial

tumors have also been destroyed with thermal methods such as electrocautery, argon plasma coagulation, and Nd:YAG laser (110). Photodynamic therapy using porphyrin compounds to sensitize the tumor to low power laser light has been highly successful in ablating superficial esophageal cancer, and this is becoming a major indication for this novel treatment (111, 112). Radiation therapy or even combined radiation and chemotherapy have been used alone or with endoscopic therapy for superficial esophageal cancer, but there are scanty data in this area and significant side effects (83).

The most difficult therapeutic decisions occur in the management of more advanced regional disease, clinical stages IIB and III. Surgery alone will cure only about 10% of patients, and mortality rates are almost in the same range (about 7%) with significant long-term morbidity. Radiation therapy and chemotherapy have both been used as single surgical neoadjuvant treatments with no significant benefit. Despite involving major additional morbidity, neoadjuvant combined radiation therapy and chemotherapy can be added in patients who are physiologically able to withstand the rigors of this approach. At the present time this triple modality therapy seems to offer the greatest chance for prolonged disease-free survival in advanced esophageal cancer.

Balancing the low probability of cure against the considerable morbidity of triple modality treatment is the dilemma faced by patients with regional advanced disease but without evidence of macroscopic distant metastases. Based on personal preference, some patients confronted with these choices will elect to have surgery alone. If there is high surgical risk, combined radiation therapy and chemotherapy is reasonable. If the patient is too ill for either of these approaches, palliative treatments alone may be most appro-

priate. In malnourished patients planning aggressive therapy, placement of a percutaneous gastrostomy tube may be a reasonable approach to maintaining adequate nutrition during therapy. Percutaneous endoscopic gastrostomy (PEG) should generally be avoided if surgery is a treatment option, as PEG can complicate the use of the gastric pull-up to achieve an esophagogastric anastomosis.

Stage IV disease, documented distant metastasis, is currently incurable, and treatment is palliative (Table 3). Surgery is generally avoided in such patients. Radiation therapy and chemotherapy are often applied in this setting for palliation and for potential prolongation of survival. Palliation is achieved in 60–70% of patients treated with combined modality therapy (78–83). For patients too ill to undergo radiation therapy or chemotherapy and for those who decline these treatments, palliation but not prolongation of survival may still be offered through *per oral* therapies.

Palliative therapy

There are a variety of *per oral* palliative methods for alleviation of dysphagia in advanced esophageal cancer (Table 3). The choice of method will vary according to the anatomical features of the malignant obstruction, patient preferences, and available expertise. Methods can be broadly divided into those which are primarily mechanical, thermal, or chemical. Of the mechanical methods, dilation is the most frequently used, either with expandable through-the-scope balloons, or wire-guided polyvinyl bougies under fluoroscopic control (113). All but a small percentage of patients can be successfully dilated to the point where a standard 9–10-mm forward viewing endoscope can be passed through the tumor, which usually allows consumption of a soft diet. The benefits of dilation are usually brief, however, measured in days, and other methods are required for more prolonged relief (114, 115).

Hollow tubes or stents placed inside malignant strictures can maintain a patent lumen and alleviate dysphagia. The insertion of tubes made of plastic materials has been successful, but associated with a $\leq 15\%$ risk of acute complications during insertion, particularly esophageal perforation (113–115). Recently developed, expandable metal stents, although more expensive, are much easier to insert with a significantly lower rate of acute complications (116). There are four different types of stents currently available in the US, some partially or completely covered with plastic membranes to prevent tumor ingrowth, and all are relatively easy to insert compared with rigid plastic stents. On the other hand, the incidence of late complications (such as migration, hemorrhage, and fistulization) is high, with overall postinsertion complications reported with wide variation in the range of 20–40% (117). Patients who have had prior radiation and chemotherapy seem to be prone to more frequent and serious complications (118, 119).

Problem areas for stents are in the proximal esophagus, where there may be a foreign body sensation or airway compromise, and the esophagogastric junction, where stent-

ing may be associated with serious reflux and where stents are more prone to migration, ulceration, and food impaction. There is no doubt, however, that covered stents are the best treatment for tracheoesophageal fistulas. Successful palliation of this disastrous occurrence has been achieved in 70–80% of cases (117).

Thermal treatments for palliation include monopolar and bipolar electrocautery for tumor ablation, but these have proven difficult to control, and are infrequently used (120, 121). High power Nd:YAG laser can provide palliation of dysphagia by coagulating and vaporizing malignant tissue with endoscopic control (121–124). Noncontact and contact laser probes both have proponents (125). The lasers are expensive, but are widely available in the US. Palliation, with ingestion of a soft diet, can be achieved in a majority of patients for about 4–6 wk (121–125).

The least expensive endoscopic technique for esophageal cancer ablation is the chemical method of injecting a sclerosant during endoscopy in a method similar to the free-hand injection of esophageal varices (126, 127). Absolute alcohol has been the sclerosant most used. Experience is small, but problems relate to a lack of control as the sclerosant tracks along tissue planes, with damage to normal tissues and perforations reported (126, 127).

An expensive but more precise tumor ablation can be carried out using photodynamic therapy (PDT) (128). In this treatment, the currently available light-sensitive drug, porfimer sodium (Photofrin) is injected systemically and preferentially concentrates in tumor tissue (129–131). A second level of selectivity is achieved by endoscopically guiding a low power laser diffuser to expose the tumor area to red light. This initiates a photochemical reaction resulting in tumor necrosis. Red light is chosen for greatest penetration depth, about 5 mm. Palliation is comparable to that achieved with Nd:YAG laser, but procedures are significantly easier to carry out and more comfortable for patients (129). Areas technically difficult to treat with Nd:YAG laser, the cervical esophagus and the esophagogastric junction, are more effectively palliated. Because of more selective destruction of tumor tissue, PDT can be safely used to treat cancers completely obstructing the esophageal lumen (132). The major problem with PDT is retention of Photofrin in the skin for about 6 wk after injection, and the need to avoid direct sun exposure during this time or to risk severe sunburn (127–130). PDT can be carried out before or after radiation and chemotherapy, and has been used to treat tumor growing through or over the ends of esophageal stents (133).

Choosing among the methods for palliation should involve a detailed discussion of the risks and benefits of each. Tumor morphology and location, patient preferences, physician experience, expense, and local availability will all factor into the final choice. It is usually possible to attempt a second method if the first should prove a failure. Patients with advanced esophageal cancer are in general quite ill, with average survival of about 6–12 wk from diagnosis. In patients being treated primarily for palliation, it is usually

possible to maintain reasonable comfort while minimizing inpatient hospital care.

CONCLUSIONS

Every effort should be made to prevent esophageal cancer or to detect it at an early curable stage with appropriate treatment and surveillance of high risk patients. The rapid acceleration in the rate of adenocarcinoma of the distal esophagus in the US and other western countries justifies surveillance in patients with Barrett's metaplasia. Endoscopy with biopsy is the primary method for diagnosis of esophageal cancer. The most accurate anatomical staging of esophageal cancer is achieved with a combination of CT and endoscopic ultrasonography. Stage-directed therapy offers a rational approach to management of esophageal cancer. Progress has been made in surgery, radiation, and chemotherapy for advanced esophageal cancer, but overall results remain poor, with some prolongation of survival but with high morbidity and low cure rates. Several new endoscopic *per oral* methods for palliation of dysphagia in advanced esophageal cancer are currently available. Because of the many uncertainties and the generally unsatisfactory current management options, patients should be encouraged to enter clinical trials designed to improve the diagnosis, staging, and treatment of esophageal cancer.

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