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Cancer Concepts: A Guidebook for the Non-Oncologist

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Cancer of the Esophagus

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Summary and Key Points

1. Esophageal cancer is classified histologically as squamous cell carcinoma or adenocarcinoma.¹
2. Worldwide, squamous cell carcinoma is the more common type of cancer of the esophagus.
3. The incidence of esophageal adenocarcinoma has been rising in the developed nations, apparently due to its association with gastroesophageal reflux disease, obesity and Barrett's esophagus.
4. Squamous cell carcinoma is more common in a setting of tobacco and alcohol use.
5. The tissue diagnosis of esophageal carcinoma is made by endoscopy with biopsy.
6. Staging workup is classically performed using endoscopy and/or barium swallow under fluoroscopy, CT and PET/CT.
7. The American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) classification system is used to stage esophageal cancer.
8. Multimodality treatment for local control and palliation is almost always indicated if the patient is able to tolerate it. Most esophageal carcinomas present at a fairly advanced stage because symptoms occur late in many patients, but early diagnosis improves outcomes.¹
9. The prognosis for most patients with esophageal cancer remains poor. Treatment is often focused on symptom relief.



Case Presentations

1. A 50-year-old woman with a long history of heartburn presented to her primary care physician complaining of progressive difficulty swallowing solids, occasionally having to cough up food, and 10-kilogram weight loss over the last 2 months.

She is referred for upper endoscopy, which reveals a circumferential ulcerated and fungating mass at 35 cm from the incisors (Figure 1a). The endoscope cannot be advanced through the lesion. Ultrasound demonstrates the mass extends through the esophageal wall's deep muscular layer (T3 lesion, Figure 1b) and one round, hypo echoic para-esophageal lymph node (N1) (Figure 1c) Biopsy from the lesion is read as demonstrating grade 2 adenocarcinoma with Barrett's esophagus (Figure 1d).

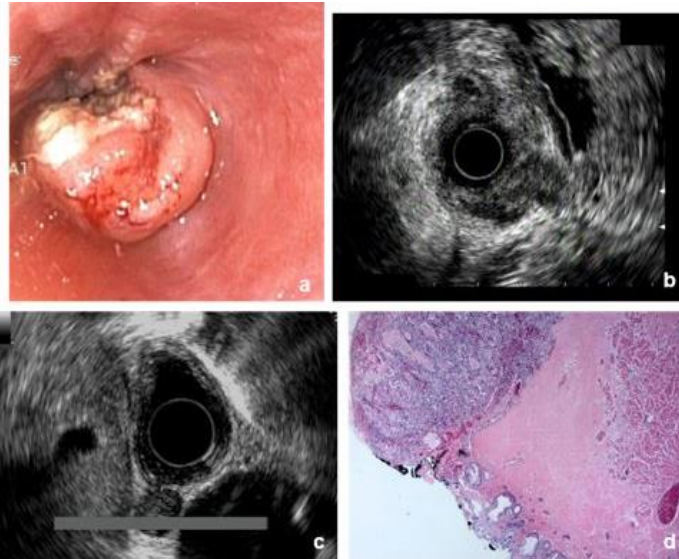


Figure 1. a) Endoscopic photograph of mass in lumen of esophagus. University of Massachusetts Medical School, Department of Medicine, Gastroenterology Division; b) Endoscopic ultrasound of mass in lumen of esophagus. University of Massachusetts Medical School, Department of Medicine, Gastroenterology Division; c) Endoscopic ultrasound of lumen of esophagus superior to mass. University of Massachusetts Department of Medicine, Gastroenterology Division; d) Invasive adenocarcinoma of the esophagus. Image courtesy of the University of Massachusetts Medical School, Department of Pathology.

2. A 65-year-old man with 2 pack per day smoking history and consumption of 2-6 **boilermakers** per day over the last 45 years complains of severe sore throat, new onset cough on swallowing and difficulty getting bread to go down.

Endoscopy demonstrates a mass at 20 cm from the incisors. The endoscope passes easily, and endoscopic ultrasound shows the lesion is confined to the esophageal wall, and no lymph nodes are visible (Figure 2a). Biopsy reveals well differentiated squamous cell carcinoma (Figure 2b).



Figure 2a. Endoscopic ultrasound of mass in lumen of esophagus. Image courtesy of the University of Massachusetts Medical School, Department of Medicine, Gastroenterology Division.

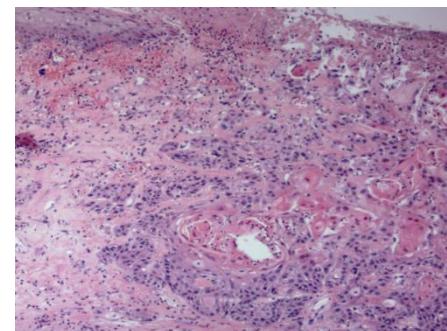


Figure 2b. Well differentiated squamous cell carcinoma. Image courtesy of the University of Massachusetts Medical School, Department of Pathology.



Introduction

Esophageal cancer is one of the leading causes of cancer death worldwide, ranking eighth in incidence and sixth in mortality.² It should be thought of as two distinct diseases, adenocarcinoma (AC), which usually occurs in the distal esophagus, and squamous cell carcinoma (SCC), which can occur anywhere in the esophagus, but more commonly involves the upper 2/3 of the organ. Cancers in the gastroesophageal junction are almost always adenocarcinomas and are treated and reported as esophageal cancers.³

Epidemiology

The American Cancer Society projects that approximately 16,940 new cases will be diagnosed in 2017 with approximately 12,720 male and 2970 female deaths.⁴ Worldwide, esophageal cancer is the 6th most common cause of cancer death, and the 8th most common cancer.⁵ Risk increases with age. Incidence varies geographically with high prevalence in Asia, southern and eastern Africa and parts of France as compared to North America and the rest of Africa and Europe. SCC is more common than AC worldwide and continues to increase, especially in the esophageal cancer belt, across central Asia.⁶ The incidence of esophageal AC has been increasing in developed nations.⁷ The increasing incidence of AC in the United States is the reason that cancer of the esophagus is the only relatively common malignancy that is increasing in incidence, despite declining SCC.

Worldwide, there is a male predominance of both AC⁸ and SCC⁹. In the United States, AC is concentrated in white males, while SCC remains more common in white females and black individuals of both sexes.

Regional variation in incidence of both types strongly suggests a large environmental or lifestyle component to the etiology of these malignancies.

Screening

Screening may be useful in areas of the world where esophageal cancer is very common – northern China, for example- as early detection and treatment have been documented to improve survival statistics. But where the disease is rare, the chance of finding an early case is so low that the cost of finding an early case far exceeds the potential benefit, so screening is not indicated for the general population in the United States. Even for patients with Barrett's esophagus (discussed below), screening may not

be cost effective, except perhaps for patients found to have dysplasia, particularly high grade dysplasia, on initial endoscopy.

Etiology

Adenocarcinoma

AC, which tends to occur in the lower third of the esophagus and gastroesophageal junction, is thought to be related to gastroesophageal reflux disease (GERD), obesity and Barrett's esophagus.

Obesity has been linked to an increase in the risk for esophageal AC, likely due to increased acid reflux related to elevated levels of abdominal adipose tissue (central obesity), or perhaps inflammatory substances secreted by fat cells. Physical activity appears to be protective.

Barrett's esophagus is a condition in which the normal squamous epithelial lining of the esophagus is replaced with columnar, glandular metaplastic cells apparently caused by chronic GERD (Figure 3). GERD is more common in obese patients, and so is Barrett's esophagus.

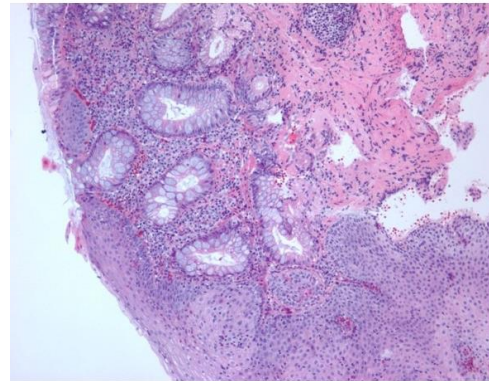


Figure 3. Barrett's esophagus 100X: Biopsy of the gastroesophageal junction showing intestinal metaplasia that has crypts typically found in the intestine, and numerous Goblet cells in these glands that also are characteristic of intestinal epithelium. Image courtesy of the University of Massachusetts Medical School, Department of Pathology.

The exact pathogenesis of Barrett's is unclear; however it is thought to be due to repeated exposure to acid that results in inflammation with mucosal injury which may lead to intestinal metaplasia and ultimately dysplasia of



the epithelial lining. Patients diagnosed with Barrett's have a 1-in-8 to 1-in-14 risk of being diagnosed with AC of the esophagus.¹⁰

Tobacco abuse is a moderate risk factor for developing AC; alcohol does not appear to be.⁹ There is some evidence of a small genetic contribution.

There may be a genetic component to development of both Barrett's and AC, since familial clusters have been seen.¹¹

Squamous cell carcinoma

In contrast, both tobacco and alcohol are strongly associated with SCC of the esophagus, and when usage is combined they increase risk dramatically. Dietary and nutritional factors are also implicated in the development of SCC, especially diets rich in carbohydrates and fats and deficient in vitamins and minerals, consumption of very hot liquids ([mate](#)), betel nut chewing, especially when mixed with tobacco.¹²

There are also genetic risks for SCC, including tylosis, an autosomal dominant disease that causes hyperkeratosis of palms and soles and is associated with SCC. Chinese studies suggest a genetic component increasing risk for heavy alcohol and tobacco use in some people.

Protective Effects

Overall esophageal cancer risk was 29% lower in the most physically active. AC risk was 32% lower, in the most physically active, independent of body mass index. A simple lifestyle intervention of increased physical activity may decrease the rate of esophagus AC. In one study, the risk of AC was 32% lower in the most active people, with an intermediate risk in people less active compared to sedentary people.¹³ Exercise appears to be protective against AC, partially by decreasing obesity, and partially by decreasing the inflammatory substances or by lowering fasting insulin levels and insulin resistance.^{14,15}

Interestingly, *Helicobacter pylori* (*H. pylori*) infection appears to be protective as well, perhaps because it ultimately decreases acid production. Consumption of high fiber diet, with vegetables and fruits, decreases the risk of both types of esophageal cancer.¹⁶

Clinical Presentation

Patients with any esophageal neoplasm are usually asymptomatic. But as tumor bulk increases, patients complain of dysphasia and report weight loss. The dysphagia usually begins with solid foods and is progressive, whereas dysphagia for liquids is a very late occurrence. This distinction helps differentiate (benign) motility disorders of the esophagus from obstructing neoplasms.

Late symptoms include drooling from complete obstruction and inability to swallow the patient's own oral secretions. Cough, hoarseness, back pain and retrosternal pain suggest locally advanced disease with possible invasion into the recurrent laryngeal nerve or the trachea. Tumors that bleed can cause [hematemesis](#), fecal occult or manifest blood loss, and sometimes frank [melena](#).

The patient history is very important in esophageal diseases including cancer and must explore smoking and alcohol history, symptoms of reflux, and Barrett's. Patients should be asked about prior endoscopy and often they will remember what the findings were, particularly if Barrett's was discovered, as this would typically lead to subsequent and repeat endoscopic examinations. Problems with reflux over many years can be surmised from the use of antacids, calcium-containing over-the-counter tablets, and prescription drugs that reduce acid. As in all patients, family health history should be explored.

On physical exam early esophageal cancer provides few clues to its presence. In advanced cases weight loss, cachexia, palpable lymph nodes in the supraclavicular fossae or abdominal masses are likely to be found. The patient's nutritional status should be assessed, as this invariably will influence tolerance of therapy.

Cancer of the esophagus irrespective of its type is among the most catabolic of human diseases, and weight loss beyond that expected from difficulty swallowing and alcohol abuse is common. A search for other causes of dysphagia is essential when first seeing these patients, with motility disorders such as achalasia and scleroderma high on the list of possibilities. Foreign body dysphagia rarely is longstanding enough to be confused with esophageal cancer, but esophageal strictures or esophageal rings often complicate longstanding reflux and could present in a similar fashion.



Pathology

Squamous cell carcinoma is the most common histology seen in the esophagus (Figure 4).

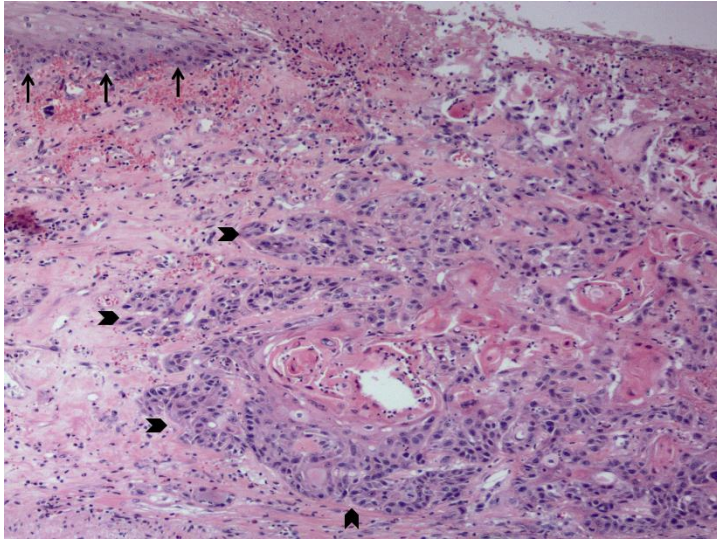


Figure 4. Invasive SCC of the esophagus showing normal squamous mucosa in the left upper corner of the picture (arrows). Nests of malignant cells with hyperchromatic and enlarged nuclei and forming keratin pearls are seen infiltrating into the lamina propria and muscularis in the middle and right side of the picture (arrowheads). Image courtesy of the University of Massachusetts Medical School, Department of Pathology.

Adenocarcinoma (Figure 5a and 5b) is next most common, but incidence is rising rapidly in the developed world.

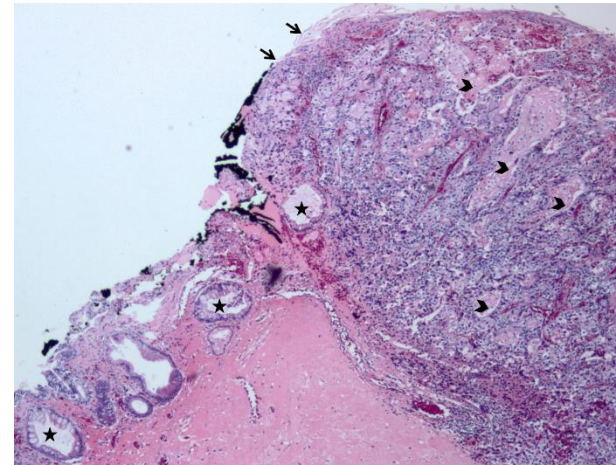


Figure 5a. Invasive adenocarcinoma of the esophagus showing intestinal metaplasia (stars) in the left side of the picture, normal esophagus mucosa in the upper side of the picture (arrows). There are infiltrating malignant cells forming glands or ducts below normal squamous epithelium in the lamina propria (arrowheads). Image courtesy of the University of Massachusetts Medical School, Department of Pathology.

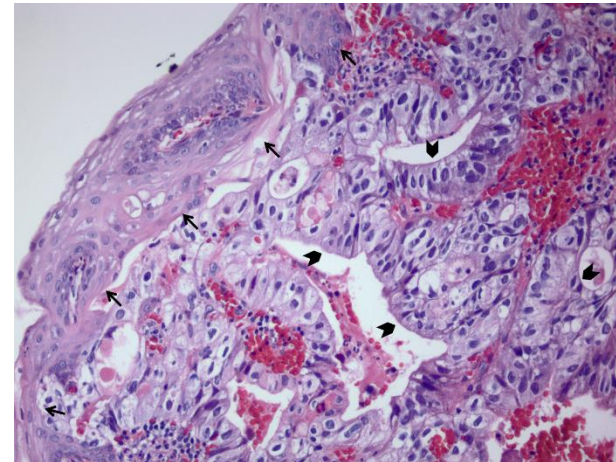


Figure 5b. On high magnification, normal esophagus mucosa in the left upper side of the picture (arrows) and infiltrating malignant cells with hyperchromatic and enlarged nuclei and forming glands or ducts below normal squamous epithelium in the lamina propria (arrowheads). Image courtesy of the University of Massachusetts Medical School, Department of Pathology.



Much less common are [gastrointestinal stromal tumor \(GIST\)](#), [leiomyosarcoma](#), lymphoma, carcinoid and melanoma of the esophagus are rare; melanomas may be metastatic from other sites.

Diagnostic Workup

When esophageal pathology is suspected on history and physical exam, searching for the cause usually involves upper endoscopy or barium swallow GI series, or both. While endoscopy is often recommended as a first test, a barium swallow can suggest a motility disorder, exclude esophageal diverticula as responsible for the symptoms, and reveal tumors, strictures, and other problems. When a probable cancer is seen on barium swallow (Figure 6), upper endoscopy is essential to confirm radiologic findings, obtain anatomic information such as tumor location, relationship to the gastroesophageal junction (GEJ), ulceration and luminal obstruction, and for possible stent placement. Biopsy is often performed at the time of endoscopy (Figure 7).

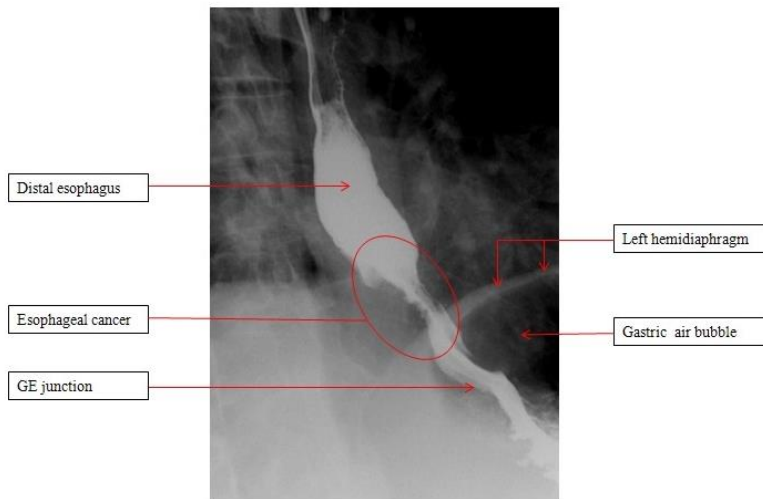


Figure 6. 60-year-old male presented with progressive dysphasia. Spot radiograph from upper GI series demonstrates a circumferential narrowing (apple core lesion) in the distal esophagus, just proximal to the gastroesophageal (GE) junction. Note the irregular contour at the level of the esophageal narrowing secondary to mucosal ulceration and nodularity. Endoscopic biopsy revealed a poorly differentiated esophageal adenocarcinoma. Image courtesy of the University of Massachusetts Medical School, Department of Radiology.

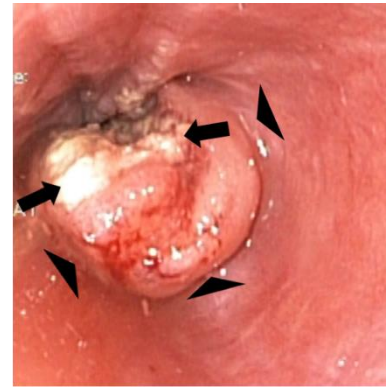


Figure 7. Circumferential large esophageal mass (arrow heads) obliterating the lumen of the esophagus. An ulcer (arrows) is noted on the mass. Image courtesy of the University of Massachusetts Medical School, Department of Medicine, Division of Gastroenterology.

Once the diagnosis has been made, additional diagnostic studies are important for staging. Endoscopic ultrasound (EUS) has the capability to accurately evaluate the depth of esophageal lesions and whether there is invasion of surrounding structures (Figures 8, 9 and 10).

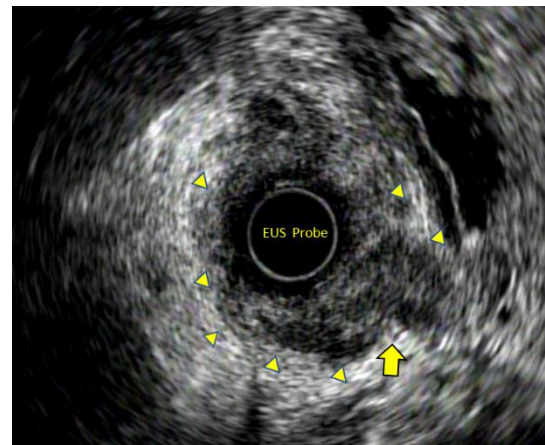


Figure 8. Endoscopic Ultrasound image showing circumferential hypoechoic mass with loss of normal wall architecture (arrow heads) invading the adventitia (arrow). Image courtesy of the University of Massachusetts Medical School, Department of Medicine, Division of Gastroenterology.

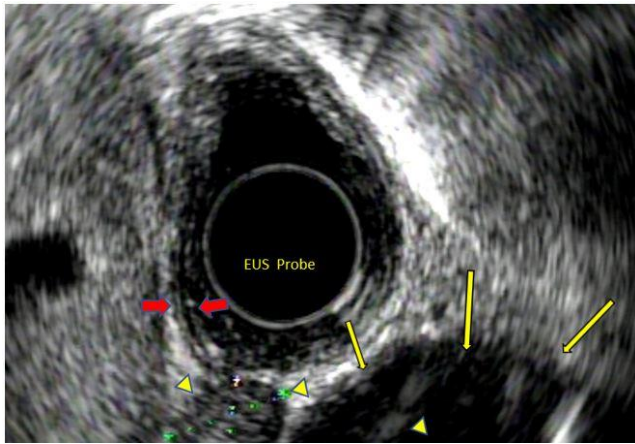


Figure 9. Endoscopic Ultrasound image showing a well-defined hypoechoic 8.7 mm X 8.3 mm round “plump” lymph node (arrowheads) next to the esophageal wall (red arrows) and adjacent to the aorta (yellow arrows). Image courtesy of the University of Massachusetts Medical School, Department of Medicine, Division of Gastroenterology.

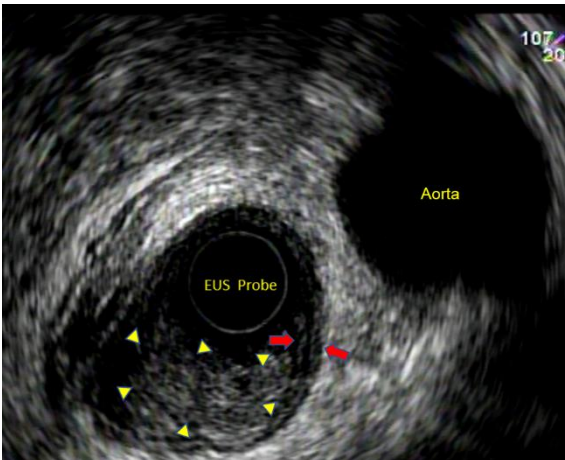


Figure 10. Endoscopic Ultrasound image showing non-circumferential hypoechoic esophageal mass (yellow arrowheads) confined to the mucosa with a well-preserved esophageal wall architecture (in between the red arrows). Image courtesy of the University of Massachusetts Medical School, Department of Medicine, Division of Gastroenterology.

Additionally, the size, shape, and borders of involved lymph nodes can be assessed with sensitivity and specificity of 92% and 93% respectively. Coupled with fine needle aspiration (FNA) (Figures 11 and 12) EUS-FNA is highly sensitive in staging nodal disease.

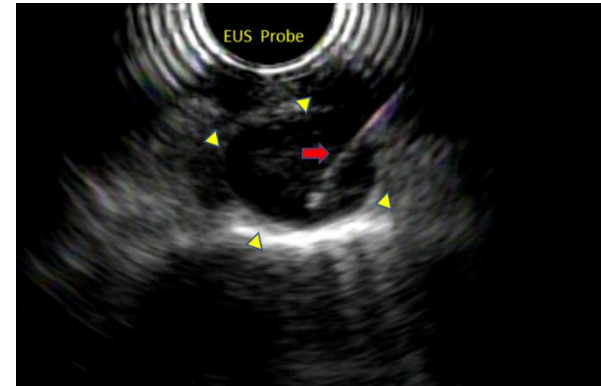


Figure 11. Endoscopic Ultrasound image showing FNA (Fine Needle Aspiration) (red arrow) of a para-esophageal lymph node (yellow arrow heads). Image courtesy of the University of Massachusetts Medical School, Department of Medicine, Division of Gastroenterology.

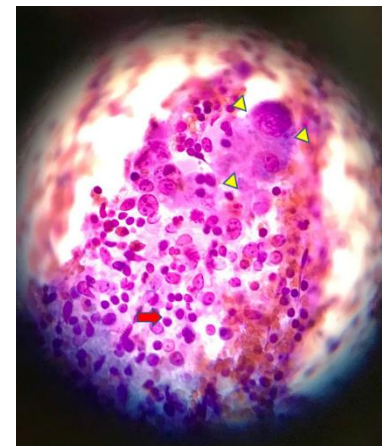


Figure 12. Cytology of the lymph node showing normal lymphocytes (red arrow) and malignant cells characterized by enlarged and variably shaped nuclei. Image courtesy of the University of Massachusetts Medical School, Department of Medicine, Division of Gastroenterology and Department of Pathology.



Computed tomography (CT) is often performed at diagnosis for local staging and to detect other sites of metastatic disease. It is also helpful for superior anatomic detail in surgical planning. Additionally, PET/CT is frequently performed as it provides superior sensitivity of nodal involvement and detects sites of disease that are otherwise not identified on conventional imaging techniques. PET/CT has been shown to upstage or downstage disease in approximately 24% of patients (Figure 13).

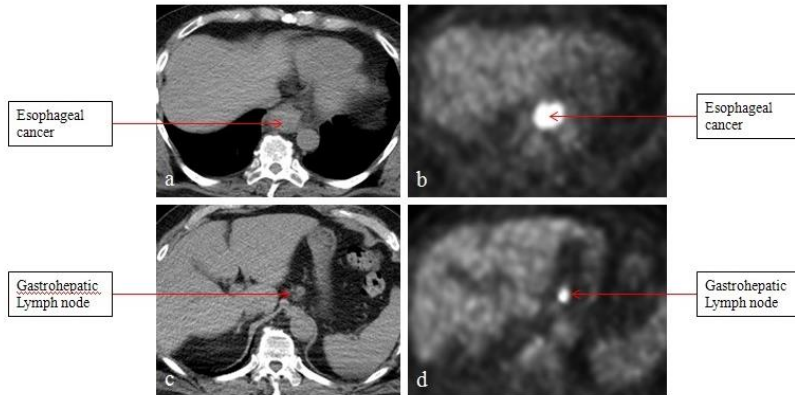


Figure 13. PET/CT scan demonstrates a distal esophageal ¹⁸-FDG avid thickening that corresponds to the patient's esophageal cancer (a,b). An ¹⁸-FDG avid metastatic gastrohepatic lymph node was also noted (c,d). CT scan (a,c); PET scan (b,d). Image courtesy of the UMass Memorial Hospital, Department of Diagnostic Radiology.

Staging

Staging of esophageal carcinoma is performed via the tumor (T), node (N) and distant metastasis (M) system, revised by the American Joint Committee on Cancer (AJCC) in 2016, effective January 2018, and available [here](#). For esophageal cancer, T stage refers to the depth of tumor invasion as portrayed in Figure 14. Clinical staging uses all information available before surgery, including particularly endoscopic ultrasound, which can define depth of tumor penetration and local lymph node involvement, as well as PET/CT for regional and distant disease assessment.

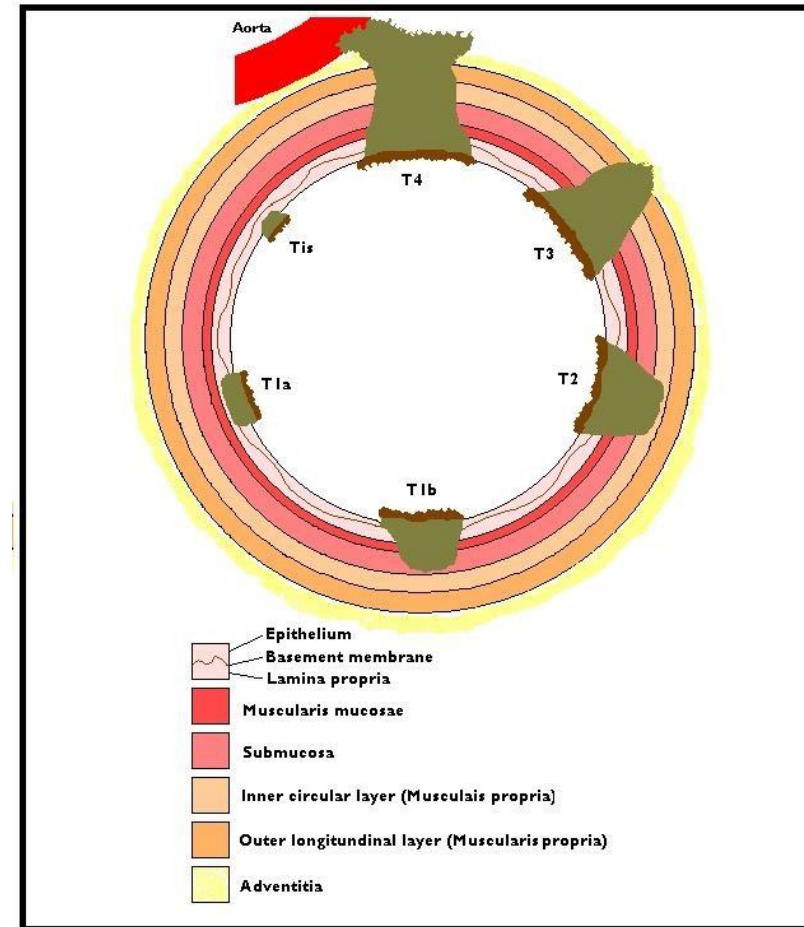


Figure 14. Cross section of esophageal wall depicting T stage according to depth of invasion through the various layers. Drawing by Rebecca M. Kwait, MD.

Principles of Treatment

Management of esophageal cancer requires a multidisciplinary approach, and all patients should be presented at a Tumor Board, with surgical, medical, radiation oncologists, diagnostic radiologist, pathologist and patient navigator present. Patients also benefit from early referral to a nutritionist and a palliative care team.



Surgery

Surgical treatment of esophageal cancer may involve endoscopic mucosal resection, radical resection (**esophagectomy**), palliative resection (also esophagectomy) or placement of a stent. Esophagectomy is a complex operation. Historically high morbidity and mortality rates have improved with improvements in pre-operative staging modalities, surgical techniques and appropriate patient selection.

For lesions 2 cm or smaller in size, endoscopic mucosal resection (EMR) may provide both diagnosis and cure.

Although esophageal cancer typically presents at relatively advanced stages, surgical resection continues to be the mainstay of treatment for patients with more invasive disease (Stage Ib, II, IIIa). There are multiple surgical approaches to the resection of invasive (non-superficial) but potentially “curable” esophageal cancers. Discussion of surgical details is beyond the scope of this book, but removal of the esophagus requires re-anastomosis of the gastrointestinal tract, with pull up of a more distal portion of the tract, often the stomach, into the chest. Figure 15 is the preoperative situation and Figure 16 is a postoperative gastric pull-up for reconstruction.

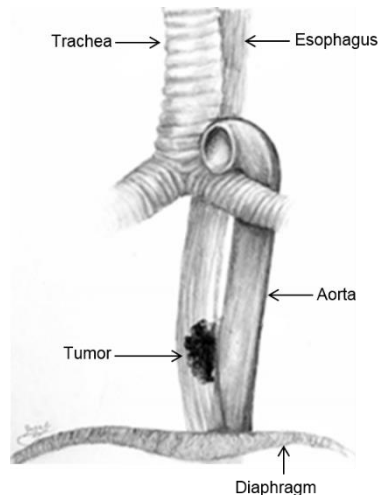


Figure 15. Preoperative images of esophageal cancer in distal esophagus 1a. Tumor has extended to edge of esophagus, and not touched aorta. **R0 resection** is likely. Drawn by Sarah Alyssa Uy.

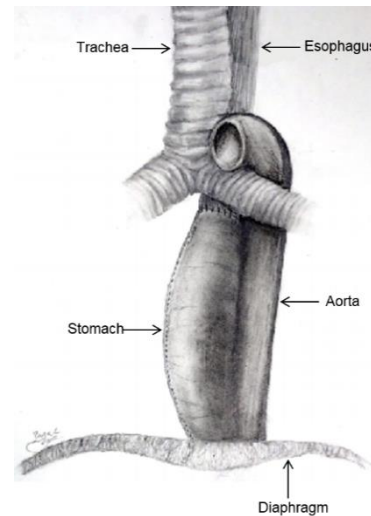


Figure 16. Reconstruction of the gastrointestinal tract. Stomach has been mobilized and pulled up into the chest, then anastomosed to the proximal stump of the esophagus. Drawn by Sarah Alyssa Uy.

To achieve an **R0 resection**, margins of normal esophagus must be obtained both proximally and distally; current recommendations are for 5 cm margins.

Patients with stage I tumors have high cure rates with surgery alone and do not generally require chemotherapy or radiation. If regional lymph node metastasis has occurred (stage IIb and III), the rate of cure with surgery alone is reduced to less than 20%. A meta-analysis of trials comparing neoadjuvant therapy followed by surgery with surgery alone suggests a 13% absolute improvement in 2-year survival with combined therapy.¹⁷

Chemotherapy and Radiation Therapy

Preoperative chemoradiation is therefore recommended for Stages IIa, IIb and III in patients who are able to tolerate it. The preferred regimen is weekly carboplatin plus paclitaxel, based on the 2012 randomized phase III CROSS trial that demonstrated improvement in median survival from 24 months with surgery alone to 49.4 months with neoadjuvant chemoradiation ($p=0.003$).¹³ As an alternative, a combination of cisplatin



plus 5-fluorouracil may be used along with radiation. Perioperative chemotherapy without radiation is also appropriate for tumors of the gastroesophageal junction based on the randomized, multicenter, phase III MAGIC trial.¹⁹

Combined treatment with chemotherapy and radiation is superior to either chemotherapy or radiation alone and has achieved long term survival rates in up to 25% of patients. In patients who are poor surgical candidates due to serious medical comorbidities or poor functional status ([Eastern Cooperative Oncology Group](#) score>2), chemoradiation alone should be considered for localized disease (stage II or IIIa). Chemoradiation as definitive, nonsurgical therapy is more likely to achieve long term disease survival in patients with squamous cell carcinoma than in patients with adenocarcinoma.

Radiation Therapy (RT)

Radiation therapy for esophageal cancer is most effective when administered with radio-sensitizing chemotherapy. Because of the lymphatic tracts of the esophagus, which run predominantly longitudinally, [skip metastases](#) in the esophagus are common, and therefore, a long margin of apparently uninvolved esophagus must be treated to ensure adequate coverage of disease. In addition nodal metastases are common, so it is important to treat the lymph nodes at greatest risk of spread. These are referred to as first echelon nodes. For the lower third and the GEJ, the first echelon nodes include the celiac and gastrohepatic ligament nodes. To treat these nodal groups, much of the stomach must be treated.

Because of the risk of tumor growing from the esophagus through the membranous posterior wall of the trachea, radiation oncologists usually require bronchoscopy prior to treatment, to know whether the tumor has grown through into the bronchial lumen.

Radiation of the stomach is highly [emetogenic](#). Inclusion of the stomach in the target volume can lead to significant mucosal irritation with profound nausea as an acute side effect. Modern anti-emetic medications have greatly decreased this problem.

However because long sections of the esophagus must be treated, radiation esophagitis remains an issue, sometimes associated with candidiasis. Combination medications including antifungals, coating agents and local anesthetic agents have proven beneficial. Sometimes

coating agents alone are sufficient, with the use of a bland, low acid, lukewarm, smooth diet or liquid supplements to permit adequate nutrition.

Often despite treatments, nutritional intake is poor and insertion of a feeding tube is necessary so this is often done before treatment starts. However, patients who completely stop swallowing may be unable to resume eating normally after treatment, so it is important to encourage some daily oral intake.

Patients who have had difficulty swallowing solids often experience improvement in swallowing ability after two to three weeks of radiation treatment, only to have the symptoms return as esophagitis develops. Medications can help in this situation to permit continued oral intake and avoidance of a feeding tube.

Cancer of the Cervical Esophagus

Cancer in the cervical esophagus is rare and is almost always of the squamous cell carcinoma type. Management has been controversial. In the pre-chemotherapy era, the results for surgery and radiation therapy were very similar, but given the rarity of this disease patient numbers are always very limited and most studies are retrospective case series. A randomized trial will probably never be feasible, as the annual number of cases is too small to conduct a study of this type in a reasonable time period.

The anatomy of the esophagus in the neck previously mandated pharyngo-laryngo-esophagectomy for resection. However more recently larynx preserving resection has been described as a treatment option.

Currently this disease is managed in the same fashion as other head and neck cancers, with resection or definitive concomitant chemoradiotherapy in an attempt to preserve the organs and cure the patient. Local failure after surgery is usually treated with radiotherapy with or without chemotherapy. Alternatively for more advanced tumors, local failure after radiotherapy alone may become amenable to surgical resection but operating on radiated tissue in the neck is fraught with high rates of anastomotic failure.²⁰

Supportive Care during Definitive Therapy

Patients with significant tumor obstruction may require local measures such as esophageal stent placement or percutaneous feeding tube insertion to maintain adequate hydration and nutrition during



chemoradiation or chemotherapy. Multidisciplinary consultation is required to determine the optimal procedure with consideration of risks including stent complications, and peritoneal seeding from endoscopic feeding tube placement. The need to preserve the distal stomach for future anastomosis and the possibility of performing diagnostic laparoscopy to evaluate for peritoneal disease must also be considered, so the standard of care is placement of a tube in the jejunum (J-tube), rather than the stomach (gastrostomy tube (G-tube) or percutaneous endoscopic gastrostomy tube (PEG)). Consultation with a nutritionist is also appropriate to optimize nutrition perioperatively.

Physical activity also enhances tolerance of treatment. A small randomized trial of weekly nutritional counselling plus supervised walking for 20 minutes three times a week found improved nutritional status, functional walking capacity, grip strength and implied quality of life compared to a usual care group.²¹

Therapy for Incurable Disease

More than half of patients present with either locally extensive tumor spread (T4) that is unresectable or distant metastases (M1) (stage IIIB or IV). Surgery is usually not warranted in these patients. Similarly, the majority of patients with Stages II and III esophageal cancer who are treated with chemoradiation and/or surgery will relapse with metastatic disease, most within three years of initial diagnosis. Since prolonged survival can be achieved in only a few patients, the primary goal of treatment of metastatic disease is to provide relief from dysphagia and pain, optimize quality of life and minimize treatment side effects. The optimal palliative approach depends on the presence or absence of metastatic disease, expected survival, patient preference and institutional experience. Many patients with advanced disease may prefer concerted efforts at pain relief and care directed at symptom management.

Chemotherapy and Chemoradiation

Combined radiation and chemotherapy may achieve palliation in two-thirds of patients with unresectable tumor, but is associated with significant side effects. It should be considered for all patients with locally advanced tumors without distant metastases (stage IIIB) who have good functional status with no significant medical problems. Improvement in dysphagia occurs within 2-4 weeks in almost 90% of patients, and is sometimes associated with long term survival.

Combination chemotherapy may also be considered in those patients with metastatic disease who still have good functional status and expected survival of at least several months. Three drug combinations commonly include a fluoropyrimidine (5-fluorouracil or capecitabine), a platinum drug (cisplatin or oxaliplatin), and either epirubicin or a taxane (docetaxel or paclitaxel). However, three drug regimens are also quite toxic. Only patients with a very good performance status should be offered a three-drug combination. Most patients with metastatic esophageal cancer will be best served with a two drug regimen.

Roughly 15%-20% of adenocarcinomas of the G-E junction overexpress HER-2 (human epidermal growth factor receptor 2). Patients with these cancers who have metastatic disease should be treated with the anti-HER2 monoclonal antibody trastuzumab in addition to a fluoropyrimidine and platinum agent.²²

Current initial chemotherapy will produce a meaningful response in only about 20%-30% of patients. The duration of tumor responses is usually around four to six months. Hence, almost all patients with metastatic esophageal cancer will either not respond to initial treatment, or develop progressive disease within the first year after starting treatment. At the time of progression, many patients will be best served with palliative treatments, including hospice care. A few patients may have a good enough functional status to warrant additional treatment. These patients will typically be treated with a single chemotherapy drug, rather than combination chemotherapy.

Recently, the monoclonal antibody ramucirumab was approved either alone, or in combination with paclitaxel, as treatment for adenocarcinoma of the GE (gastroesophageal) junction in patients who relapsed after initial treatment with a platinum-based regimen. Ramucirumab targets the vascular endothelial growth factor receptor.²³

In light of the poor outcomes of patients with metastatic esophageal cancer after treatment with currently available therapies, referral of patients to an appropriate clinical trial is also a very reasonable option. Regardless of whether a patient enters an investigational study, is treated with standard therapy, or foregoes anti-cancer treatment, all patients with metastatic esophageal cancer should be referred for a palliative care consultation. Goals of care should be discussed frequently throughout the course of a patient's illness and hospice referral should be considered when appropriate.



Immunotherapy

Immunotherapy has, as yet, no clinical role in either esophageal cancer. It does remain under preclinical investigation, particular for AC.²⁴

Local Therapy for Esophageal Obstruction

Patients with advanced esophageal cancer often have poor functional and nutritional status. Radiation therapy alone to the area of esophageal obstruction may afford short term relief of pain and dysphagia. This can generally be performed in a short course over a few weeks but may be complicated by temporary worsening of dysphagia and odynophagia.

Rapid palliation of dysphagia may be achieved by peroral placement of permanent expandable wire stents (alone or followed by radiation to minimize tumor progression back into the stented lumen). Stents are most commonly used because of their relative ease of placement. Although dysphagia and quality of life are improved, patients seldom can eat normally after stent placement. Complications occur in 20-40% and include perforation, migration, and tumor ingrowth.

For a few medically appropriate patients, palliative resection may be considered because it may provide the most rapid palliation of obstruction.

Finally, after careful discussion with patient and family, Palliative feeding tube placement may be considered for hydration and nutrition in selected cases if the obstruction is not amenable or is refractory to stenting, radiation or other local therapies. However, patients must be aware that such feeding is unlikely to significantly prolong life.

Outcome

Depending on stage, neoadjuvant chemoradiation can be incorporated to reduce the bulk of disease and decrease surgical complications. While the evaluation of chemotherapeutic agents has been hampered by ambiguity in the definition of "response" and the debilitated physical condition of many treated patients, significant reductions in the size of tumor masses have been reported. In 15-25% of patients given single-agent treatment and in 30-60% of patients treated with drug combinations including cisplatin, there is partial regression of the tumor. As a result the use of neoadjuvant chemoradiation followed by resection appears to prolong survival as compared with resected controls in many small randomized trials and has become standard for invasive cancers.

Early diagnosis improves outcome.¹ Very small lesions are amenable to local resection with EMR. Regardless of preoperative stage, total resection of all gross tumor is feasible in only 45% of cases, with residual tumor cells frequently present at resection margins leading to anastomotic recurrences. Additionally, surgical complications such as anastomotic leaks, fistulas, subphrenic abscesses, mediastinitis and respiratory or cardiac complications also contribute to poor outcomes with a 5-year survival rate of 20% after a total resection.

Definitive concomitant chemoradiotherapy may provide comparable 5-year survival and is a reasonable option, especially for patients with squamous cell carcinoma or medical comorbidities.

Regardless of the histology, and despite treatment advances, even for patients with localized disease, the chance of long term survival is limited.

Because of the rich lymphatic network of the esophagus, cancers in this structure tend to metastasize early. Therefore the prognosis of patients, despite treatment advances, for patients with esophageal carcinoma is poor even for patients with localized disease of either histology. Fewer than 15% of patients survive five years after the diagnosis, so management often aims for symptom control rather than cure.

However, even for patients with metastatic disease there is now some hope of progress. Trials of checkpoint inhibitors with or without radiation therapy, vaccines and other modalities show promise and are ongoing.²⁵

Conclusion

Cancer of the esophagus should be thought of as two different diseases, with similar treatment at this time. As it tends to spread early and present with locally advanced disease, prognosis is poor, although a few patients are cured. Treatment requires a multidisciplinary team, and should include nutritional support and early palliative care referral.



Thought Questions

1. What is the relationship between obesity and incidence of esophageal cancer?

Your answer:

2. What makes the management of esophageal carcinoma so morbid?

Your answer:

Expert Answer

Expert Answer



3. Why is the prognosis of esophageal cancer, no matter the histology, so poor?

Your answer:

[Expert Answer](#)

4. What factors have influenced the changing prevalence of esophageal adenocarcinoma in the United States?

Your answer:

[Expert Answer](#)



5. Why is it important to document patient's use of histamine receptor antagonists or proton pump inhibitors?

Your answer:

Expert Answer

Glossary

18-FDG - 18-Fludeoxyglucose

Boilermaker – A drink combining a shot of whiskey and a glass of beer, consumed either as a mixture or sequentially.

Gastrointestinal stromal tumor (GIST) – Mesenchymal tumor of the GI tract

Leiomyosarcoma – Smooth muscle connective tissue tumor

Eastern Cooperative Oncology Group (ECOG) score – Performance status scale used to assess how a patient's disease is progressing. Scale 0-5, 0 being fully active and 5 being dead.

Emetogenic – Causing nausea and perhaps vomiting

Hematemesis - Vomiting blood

Mate – A tea from South America made from yerba mate leaves, often served very hot.

Melena – Black stool, due to iron in the stool, usually from digested blood

Pharyngo-laryngo-esophagectomy – Removal of the hypopharynx, larynx and esophagus with permanent tracheostomy

R0 resection – Complete removal of all gross disease

Skip metastases – Deposits of cancer cells (tumors) in the esophagus at a distance from the primary tumor. These are thought to arise from cells travelling in the longitudinal lymphatic channels in the esophageal wall.



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