1 Esophageal Squamous Cell Carcinoma

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Key Points

- Esophageal squamous cell carcinoma (ESCC) is still more prevalent than adenocarcinoma worldwide. In western countries, high-risk individuals include smokers, patients with head and neck squamous cell carcinoma, tylosis, achalasia, lichen planus, scleroderma, Plummer–Vinson syndrome, and prior radiation of neck and chest.
- Esophagogastroduodenoscopy (EGD) with Lugol spray is currently considered as the most effective noninvasive way to identify squamous cell dysplasia and ESCC. Newer modalities such as narrow band imaging (NBI), confocal laser endomicroscopy (CLE), and autofluorescence imaging (AFI) are promising.
- Treatment for ESCC is based on the stage of the disease. Currently, ESCC that is limited in the mucosa can be managed by endoscopic mucosal resection. Patients with more advanced disease are candidates for surgery with or without neoadjuvant/adjuvant chemotherapy if it is resectable. Otherwise, for unresectable lesions, standard supportive care with or without chemotherapy is reasonable.
- The best strategies to reduce the incidence and mortality of ESCC are primary prevention and early diagnosis.

Key Web Links

http://seer.cancer.gov
US National Cancer Institute—a comprehensive database assessable to the public for various types of cancers

http://www.cancercare.on.ca
Cancer Care Ontario, Canada—updated practice guidelines for prevention and treatment of ESCC

http://www.nccn.org
US National Comprehensive Cancer Network—guidelines, education programs for heal care providers and patients

Handbook of Gastrointestinal Cancer, First Edition. Edited by Janusz Jankowski and Ernest Hawk.

http://www.asco.org/
American Society of Clinical Oncology—practice guidelines, research resources, education and training, public policy

http://www.asge.org/publications
The Role of Endoscopy in the Assessment and Treatment of Esophageal Cancer

Potential Pitfalls

- Physicians should be vigilant in diagnosing ESCC particularly among the high-risk subgroups.
- Endoscopic mucosal resection (EMR) is the treatment of choice for ESCC that is T1a (limited to the mucosa) or less. Avoid excessive deep biopsies of these lesions so that EMR can be safely performed for diagnosis and potential cure.
- For more advanced ESCC lesions, coordinated care involving gastroenterologists, medical oncologists, and thoracic surgeons is essential to achieve the best clinical outcomes.

Epidemiology

On a global basis, esophageal squamous cell carcinoma (ESCC) is the leading cancer of the esophagus, and it has been ranked as eighth in incidence and sixth in mortality among tumors of all sites.[1] However, its incidence varies significantly among different geographic and ethnic subgroups (Table 1.1).[2–6] The Asian Esophageal Cancer Belt, including western and northern China, Mongolia, southern parts of the former Soviet Union, Iran, Iraq, and eastern Turkey are considered the highest risk areas. The highest rate of incidence, 700 per 100,000, was reported in Linxian, China.[3] The factors associated with esophageal cancer in these high-risk areas vary as to the population. It is interesting to note that protective factors that have been identified include increased consumption of fresh fruit and vegetables, eggs, meat, and central water supply. The risk factors for this high incidence are still to be further elucidated, but they likely include cigarette smoking, pipe smoking, excessive alcohol use, dietary habits (vitamin deficiency, etc.), differences in cooking, and environmental exposure. In Linxian, China, for example, high levels of polycyclic aromatic hydrocarbons have been found in the food that implicates cooking fuels as a potential source of this carcinogen in this high-risk area. It is important to note that risk factors such as human papilloma virus present in head and neck cancers do not seem to be a factor in squamous cell cancer in the esophagus.

The incidence of ESCC in the United States has been declining since 1973. This is in line with decrease of adult cigarette smoking rate from

Table 1.1 Incidence of esophageal squamous cancer in selected regions of the world.

Region	Locality	Incidence (per 100,000) Male	Female
Asian esophageal cancer belt		>100	>100
China	Yangcheng	135.2	84.4
	Tianjin	16.6	8
India	Kashmir	42.6	27.9
	Bombay	11.4	8.9
	Bangalore	6.6	5.3
Europe			
Northern Europe		<4.0	<2.0
Eastern Europe		<4.0	<2.0
France	Calvados	26.5	–
UK	East Scotland	8.5	4.3
	England and Wales	6.5	3.2
South America			
Uruguay		40	–
Brazil	Porto Alegre	26.3	7.8
North America			
USA	Los Angeles	16.4	4.9
	Washington, DC		
Black		16.9	4.5
White		4.1	1.7
Africa			
Transkei		37.2	21.1

Source: Ribeiro, U.Jr., Posner, M.C., Safatle-Ribeiro, A.V. *et al.* (1996) Risk factors for squamous cell carcinoma of the oesophagus. *Br J Surg*, **83**(9), 1174–1185.

about 42% in 1960s to about 20% currently according to Centers for Disease Control and Prevention (CDC) reports. However, this decline of cigarette smoking has been stalled and caused significant public health concerns as the U.S. failed to drop below 12%, a goal set by *Healthy People 2010*. In addition, there appears to be an increase in younger smokers that may lead to a recurrence in the rate of cancer. Primary prevention of cancer is thought to be the most effective strategy in this disease in which the risk factors have been well established.

Although esophageal adenocarcinoma has surpassed ESCC since early 1990s in the United States, a high incidence is still seen among urban population and African Americans,[1] and patients with certain comorbidities such as achalasia, head and neck cancer, and tylosis (Table 1.4). The incidence among African Americans men (16.8 per 100,000) was five times higher than Caucasians (3.0 per 100,000).[4] And mortality was three times higher. In western countries, consumption of tobacco and alcohol could explain more than 90% of ESCC cases.[4] The higher ESCC rate among African Americans parallels the adult cigarette smoking rates. According to Surveillance, Epidemiology, and End Results (SEER) cancer registry data from 1992 to 1998, ESCC incidence rates for Native American and white Hispanics were not higher than general population, although select Native

American populations in specific regions of the country may have a higher incidence. Data from this group is influenced by the diversity of social and economic situations around the country.

Diagnosis

Patients with ESCC may present with dysphagia, weight loss, cough, and GI bleeding (hematemesis and/or melena). But there is no specific physical finding for ESCC, and rarely lymph nodes in the periphery could be appreciated. For cases with metastatic lesions, hepatomegaly could be present.

The following modalities are commonly used to establish the diagnosis of ESCC:

1. Esophagogastroduodenoscopy (EGD) with Lugol sprays

   Lugol solution has been used in medicine since 1985. During EGD exam, Lugol solution, approximately 10–20 mL of 1.5% Lugol iodine solution (but the concentration may vary), is applied through a catheter over the entire esophagus. Since Lugol solution contains potassium and iodine, it should be avoided in patients with hyperthyroidism, iodine allergy, and renal insufficiency. Some authors believe that patients with hypopharyngeal tumors are not candidates for Lugol's unless under endotracheal intubation due to concerns of possible laryngeal edema caused by iodine.

   The Lugol staining pattern is associated with the degree of glycogen within the squamous epithelium, and squamous cell carcinoma does not include glycogen; hence, it is not stained and a clear identification is feasible. This enables endoscopist to visualize the dysplastic areas as Lugol-voiding lesions (LVLs). Biopsies could then target these LVLs to increase the yield. The overall sensitivity is 96–100% and specificity varies from 40% to 95%. It could also be used for intraoperative determination of tumor margins to assist surgical resection.

   LVLs could also be of prognostic value. In a study of 227 patients with head and neck squamous cell carcinoma (HNSCC), those with no LVLs did not have metachronous ESCC during median follow-up of 28 months; however, 15% of those with numerous irregular LVLs lesions developed ESCC.[7] One study examined nondysplasia epithelium (NDE) from LVLs, and it found 20% of them had a *p53* hotspot mutation, and 40% among dysplasia epithelium in contrast to no *p53* mutations in 103 paired NDE samples with normal Lugol staining. It was also suggested that the chance of finding dysplasia was much higher from a patient with more LVLs than those with fewer ones.

   EGD with Lugol spray is currently considered as the most effective noninvasive way to diagnose squamous cell dysplasia and ESCC. Other newer methods such as narrow band imaging (NBI) or autofluorescence imaging (AFI) have been compared with Lugol spray to assess their accuracy. It is important to note that not all squamous cell cancers are Lugol voiding.

2. Narrow band imaging (NBI)

   NBI is a novel noninvasive endoscopic approach to visualize the microvasculature on tissue surface. Compared with white light endoscope (WLE), NBI imaging uses blue light at 415 nm and green light at 540 nm, which gives hemoglobin special absorption characteristics. Thus, it provides better visualization of superficial and subsurface vessels that helps ESCC detection. Often times, the ESCC lesion appears reddish, likely due to microvascular proliferation and/or dilation.

   In one nonrandomized study of HNSCC patients, NBI endoscope with magnification was proved to have very high sensitivity, specificity, accuracy, positive predictive value, and negative predictive value (100%, 97.5%, 97.8%, 83.3%, and 100%, respectively).[8] In another multicenter, prospective, randomized controlled trial with 320 patients, NBI was shown to have 97% sensitivity for superficial ESCC.

   As to high-grade dysplasia (HGD), one study showed the intraepithelial papillary capillary loop (IPCL) patterns were very helpful. But sensitivity and specificity were not satisfactory in contrast to a recent meta-analysis that demonstrated NBI was very sensitive (96%) and specific (94%) in detecting HGD and intramucosal adenocarcinoma for Barrett's esophagus. It is noteworthy that all studies in this meta-analysis used NBI from a GIFQ240Z scope, an instrument that maintains the capabilities of a standard video endoscope and also affords a continuous range of image magnification adjustment up to X80.

   However, NBI is not for detecting the depth of esophageal lesions based on current studies.

3. Autofluorescence imaging (AFI) videoendoscopy

   When white light from a xenon lamp travels through a special optical filter, only the blue excitation light at 390–470 nm and green reflected light at 540–560 nm penetrate through. Interestingly, the blue excitation light can cause living tissue to emit autofluorescence, which passes through another filter and then captured by the charged coupled device at the end of scope. AFI system works by combining autofluorescence (from blue light) and reflectance (from green light) to differentiate the neoplastic lesions (appears purple or magenta) from normal background (green). For the EGD scope that is equipped with AFI, the endoscopist can simply press the AFI button to switch from regular WLE to AFI. However, the flat or depressed ESCC lesions appear to be dark green, which makes it very difficult to distinguish the green color from normal squamous cell background.[9] Because of this, AFI was considered not as sensitive as NBI for these flat or depressed lesions, making it a less attractive method despite that AFI had higher ESCC detection rate (79%) compared with WLE (51%). A multicenter randomized trial showed that in detecting dysplasia and early cancer from Barrett's mucosa, the sensitivity, specificity, positive predictive value, and negative predictive value for AFI were 42%, 92%, 12%, 98.5%, respectively. Thus, at current time, AFI is best used

as a complimentary method and not a screening test due to the low sensitivity.

AFI has also been used in bronchoscopy and colonoscopy for squamous cell carcinoma of lungs and dysplasia among ulcerative colitis patients in some studies with various results.

4. Confocal laser endomicroscopy (CLE)

CLE is a new technology that allows in vivo examination of histopathology at the cellular and subcellular levels by using cellular and vascular criteria. The term "confocal" refers to the alignment of both illumination and collection systems in the same focal plane. The laser light could be focused at the different layers of the tissue of interest. Then the reflected light from this layer is refocused and allowed to pass back to the lens in endoscope and to be processed and presented on the monitor. Thus, different depths of tissue can be examined in vivo, the so-called optical biopsy. Fluorescent contrasts, either intravenously or sprayed topically, can enhance the quality of CLE imaging.[10]

In a recent study, CLE provided an in vivo diagnosis in 21 patients who had known ESCC, and the sensitivity and specificity using histology as gold standard were 100% and 95%, respectively. It holds promise for determination of the depth of squamous cell esophageal cancer.[11] Another CLE study after Lugol spray and intravenous fluorescein sodium showed that the overall accuracy was 95%, and sensitivity and specificity were 100% and 87%, respectively. Intraobserver agreement was almost perfect (kappa, 0.95) and interobserver agreement was substantial (kappa, 0.79).[12]

CLE would potentially enable the endoscopist to proceed directly to endoscopic therapy, saving time and avoiding expensive and unnecessary further endoscopies. However, due to the limited tissue infiltration from the blue laser light, CLE may not be the right choice for submucosal lesions.

5. Endoscopic ultrasound (EUS)

After systematic metastatic lesions are ruled out for ESCC patients, EUS could be performed by using either conventional EUS scope or miniprobe sonography (MPS) through the regular endoscope channel. It is considered as the most accurate noninvasive method for T staging and evaluation of lymph nodes around esophagus. It could also evaluate other organs such as adrenal glands, pancreas, liver, bile ducts, and mediastinal structures. Fine needle biopsy of lymph nodes can be done if necessary. However, it is difficult to distinguish T1a and T1b lesions sometime even with MPS. When a patient has scarring from previous radiation therapy (RT), endoscopic resection, or significant ongoing inflammation, it is also very challenging to provide accurate information. Despite of all these, the overall T staging accuracy of EUS is 85–90% as compared with 50–80% for CT; the accuracy of regional lymph nodes staging is 70–80% for EUS and 50–70% for CT. However, a recent review showed that T-stage from EUS had concordance of only 65% when compared with pathology specimens obtained by endoscopic mucosal resection (EMR) or surgery.

MPS is a small probe that could safely pass through a tight stricture or narrowing, and it could achieve higher resolution by using higher frequency. The use of MPS can also represent an improvement in the comfort and safety and is highly cost-effective.[13] The drawbacks for MPS are (1) unable to perform real-time ultrasound-controlled fine needle aspiration and (2) lower penetration depth due to higher frequency used, which means less satisfaction in assessing structures (lymph nodes, etc.) that are further away from GI tract.

6. Radiology: esophagraphy/CT/PET/MRI

An esophagram with barium may identify a mass lesion. However, this role has been largely supplanted by EGD exam, which could in addition provide biopsy of suspected tissues. Once HGD or mucosal ESCC are identified, chest CT with or without PET scan should be used to assess systemic involvement. This global evaluation of a patient's metastatic status (M and N staging) should be carried out before EUS.

For T staging, EUS is certainly superior to PET scan, which can only be considered when EUS or CT is inadequate. For N staging, EUS could more reliably distinguish the primary tumor from periesophageal lymph nodes based on a review in 2007. In centers with adequate experience, EUS should be the first choice unless it can not be performed due to stenosis. For M staging, PET scan has clear advantage for detection of disease beyond the celiac axis; however, it is challenging to differentiate the regional node, N1 node, and the celiac axis M1a node. As to the overall impact on the management, PET scan changed 17% of patients from curative to palliative, 4% from palliative to curative, and another 17% changed in treatment modality or delivery based on the results from a study with 68 esophageal cancer patients.

United States Preventive Services Task Force (USPSTF) recommends PET scan to improve the accuracy of M staging for patients who are potential candidates for curative therapy; however, no adequate research examined the value to predict response to neoadjuvant therapy or recurrence.

Recently, the accuracy of diffusion-weighted MR imaging for postoperative nodal recurrence of ESCC was found comparable with FDG-PET. The role of MRI certainly needs more studies to be further defined.

7. Thoracoscopy and laparoscopy

Some surgical centers use these methods for esophageal cancer staging because of the superiority over noninvasive methods. Indeed, an intergroup trial of 107 patients reported that thoracoscopy and laparoscopy could increase the detection rate of positive lymph node from 41% when using noninvasive staging tests (e.g., CT, MRI, EUS) to 56% by thoracoscopy and laparoscopy, and no major complications or deaths were reported. A more recent study in 2002 examined 111 esophageal cancer patients and compared thoracoscopy and laparoscopy versus noninvasive methods such as CT, MRI, and/or EUS, and it showed very low concordance ranging from 14% to 25% for TMN staging. This study pointed out that when compared with the final

surgical pathology, a 100% specificity and positive predictive value was achieved by thoracoscopy and laparoscopy staging in diagnosis of lymph node metastasis. Although the sensitivity was about 75% (vs. 45% from noninvasive tests), the accuracy of thoracoscopy and laparoscopy could reach 90.8% and 96.4% in chest and abdomen metastases, respectively; these values were significantly higher than noninvasive staging methods (58% and 68%, respectively, for chest and abdomen).

Staging

The typical workup includes CT scan of chest (and abdomen if advanced lesions are suspected), PET (integrated PET–CT is preferred), and EUS if no metastatic lesions are found, and then surgical consult should be offered if it is resectable. The American Joint Committee on Cancer (AJCC) recently released its 7th edition of cancer staging manual (Table 1.2; Figure 1.1).

Table 1.2 TNM staging of esophageal squamous cell carcinoma (ESCC).

Part 1	
Primary tumor (T)[a]	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia[b]
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading adjacent structures, such as aorta, vertebral body, and trachea
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to two regional lymph nodes
N2	Metastasis in three to six regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Part 2	
Histologic grade (G)	
GX	Grade cannot be assessed—stage grouping as G1
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated—stage grouping as G3 squamous

Table 1.2 *Continued*

Anatomic stage/prognostic groups Squamous cell carcinoma[c]					
Stage	T	N	M	Grade	Tumor location[d]
0	Tis (HGD)	N0	M0	1, X	Any
IA	T1	N0	M0	1, X	Any
IB	T1	N0	M0	2–3	Any
	T2–3	N0	M0	1, X	Lower, X
IIA	T2–3	N0	M0	1, X	Upper, middle
	T2–3	N0	M0	2–3	Lower, X
IIB	T2–3	N0	M0	2–3	Upper, middle
	T1–2	N1	M0	Any	Any
IIIA	T1–2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1-2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

Source: The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer New York, Inc.
Note: cTNM is the clinical classification, pTNM is the pathologic classification.
[a]At least maximal dimension of the tumor must be recorded and multiple tumors require the T(m) suffix.
[b]High-grade dysplasia (HGD) includes all noninvasive neoplastic epithelia that was formerly called carcinoma in situ, a diagnosis that is no longer used for columnar mucosae anywhere in the gastrointestinal tract. Number must be recorded for total number of regional nodes sampled and total number of reported nodes with metastasis.
[c]Or mixed histology including a squamous component or NOS.
[d]Location of the primary cancer site is defined by the position of the upper (proximal) edge of the tumor in the esophagus.

Prognostication

The most significant prognostic factor is TMN staging, although emerging biomarkers could also explain some of the variations in survival:

1. TMN staging

An early study in 1990s showed that early ESCC lesions that did not invade through muscularis mucosa had low lymph node metastasis rate (2–4%) or vascular invasion (8%).[14,15] And resection of such lesions yielded excellent prognosis with 5-year survival of 90–100%. It was also reported that tumor budding, that is, the isolated cancer cells or microscopic clusters of undifferentiated cancer cells (usually less than five cancer cells) outside the tumor margin, was associated with significantly lower 5-year survival rates.

The number of lymph node metastases was found to impact the survival. In a retrospective study of 1149 ESCC patients, the overall 5-year survival rates for the patients with 0, 1, and ≥2 positive nodes were 59.8%, 33.4%, and 9.4%, respectively. And the stage-specific

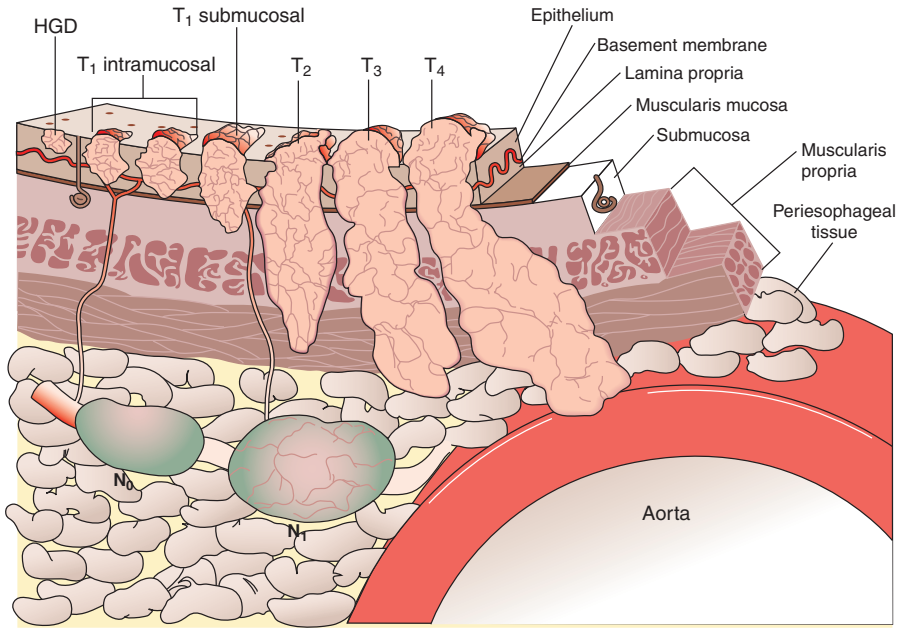

Figure 1.1 Layers of esophagus and stages of esophageal cancer. (Reproduced from Rice, W.R. (2002) Diagnosis and staging of esophageal carcinoma. In: Pearson, F.G., Cooper, J.D., Deslauriers, J. *et al.* (eds), *Esophageal Surgery*, 2nd ed, p. 687. Churchill Livingstone, New York.)

5-year survival for T2N1M0 and T3N1M0 was significantly higher in group with one positive lymph node than the group with ≥2 positive nodes (T2N1M0: 41.5% vs. 24.1%; T3N1M0: 31.2% vs. 6.8%).

Among ESCC patients with negative lymph nodes who generally have good 5-year survival, the finding of positive lymphatic invasion was linked to higher risk for hematogenous dissemination. This is from a study of 88 consecutive ESCC patients who underwent three-field lymph node dissection and no positive lymph nodes were found initially. Among those patients who eventually had lymph node invasion, the incidence of lymphatic invasion was higher than vascular invasion (79% vs. 38%), suggesting that lymphatic invasion was more commonly seen than vascular invasion. Both lymphatic and vascular invasion were independently associated with poor survival (relative risk of 4.9 and 3.5, respectively).

2. Biomarkers

CIAPIN1 is a downstream effector of the receptor tyrosine kinase–Ras signaling pathway in animal cell lines. The decreased expression of CIAPIN1 was statistically correlated with lower degree of differentiation, more depth of invasion, and lymph node metastasis among ESCC patients. Consistently, the survival rates of patients with CIAPIN1-negative tumors tended to be statistically lower than those with CIAPIN1-positive tumors.

Higher tumor-specific expression of survivin, a member of the inhibitors of apoptosis gene family, has been found to be a significant marker for poorer survival for ESCC but not esophageal adenocarcinoma. The disease-specific 5-year survival rate of patients with low survivin mRNA expression was greater than those with high survivin (43% vs. 12%).

Serum squamous cell carcinoma antigen positivity, which indicates the circulating esophageal squamous cancer cells in peripheral blood, was found more often among advanced ESCCs, but its prognostic value is limited.

Overexpression of cyclin D1, an amino acids frequently expressed in G1 phase of cell cycle, was thought to play an important role in cell growth and cancer progression. On the contrary, E-Cadherin, the most essential one of Cadherin family, which is the backbone of cell-to-cell adhesion, is also a key molecule in the initial step of cancer cell invasion. Increased cyclin D1 expression and reduced E-cadherin expression were significant prognostic factors in ESCC patients.

Prevention

1. Reduce exposure to risk factors

Carcinogenesis of ESCC is a complex process and no single risk factor can explain the variations of incidence rates among different groups. These potential factors may also exert synergic impact on each other during this multistep carcinogenesis (Table 1.3).

(a) Tobacco and alcohol

It is undisputable that tobacco and alcohol, acting alone or synergistically, are the significant risks for ESCC. In one study, the significant synergistic impact of cigarette smoking and alcohol drinking on the risk of ESCC was staggering (odds ratio, 50). Population attributable risk (PAR), the difference in rate of a condition between an exposed population and an unexposed population, for the ever-smokers who consumed more than 30 alcoholic drinks per week were 56.9% and 44.9%, respectively. Tobacco and alcohol use was also associated with higher number of

Table 1.3 Risks associated with ESCC.

Environmental/dietary/behavior factors	Host factors
Tobacco	Ethnicity (African American)
Alcohol	Head and neck squamous cell carcinoma
Nitrosamines/its precursors (Barbecue)	Tylosis
Hot liquid	Achalasia
Nutritional deficiency	Lichen planus
Caustic injury (lye)	Scleroderma
Radiation	Plummer–Vinson syndrome
Agent orange (case reports)	

dysplasia lesions, and *p53* and *p21* gene mutations were also linked to ESCC during the evolving process of early stage neoplasia.

The risk varies among different types of smoking (pipe and cigar smoking have higher risk) and alcohol beverage. Interestingly, the polymorphism in acetaldehyde dehydrogenase 2 (ALDH2), which could cause flushing after alcohol use, was found to be a useful sign identifying individuals susceptible to ESCC development.

(b) Achalasia

In Greek, achalasia means "do not relax." It is a condition that causes no peristalsis in the distal segment of esophagus where the musculature is mainly smooth muscle, and inability to relax LES (lower esophageal sphincter). This is likely the result of neuron degeneration in myenteric plexuses from many reasons such as inflammation, infection, infiltration. The annual incidence is approximately 1 case per 100,000, and both genders are equally affected. The features of achalasia include dysphagia for solids and liquid, excessive belching, etc. The diagnosis can be established by symptoms, barium swallow, esophageal manometry, and EGD exam. The relationship between achalasia and esophageal carcinoma was first reported by Fagge in 1872.

Because achalasia patients often have difficulty in swallowing as baseline, clinicians should have low threshold to initiate a new workup plan for ESCC among these patients. Studies have shown that these cases were often diagnosed late and the prognosis was very dismal. However, close endoscopy surveillance does not seem cost-effective, and other modalities such as blind brush cytology still warrant research. Even so the surveillance should be carried out among those who are fit enough to undergo surgical resection if tumors are found.

One report showed 8.6% of achalasia patients could have ESCC in 15–20 years after the onset of symptoms. In another study of 1062 achalasia patients (9864 person-year follow-up), 2.3% had ESCC, a 16-fold increase of cancer risk compared with general population. It is very difficult to determine the true prevalence of ESCC among achalasia patients, and it varies from 1.7% to even 20%. Likely this variation is due to different referral base and length of follow-up. One study showed the mean interval between the diagnosis of achalasia and carcinoma was 5.7 years.

(c) Tylosis

Tylosis (focal nonepidermolytic palmoplantar keratoderma), an autosomal dominant skin disorder with thickening of the skin in the palms and soles, was associated with a high risk of squamous cell carcinoma. It was first described in 1958 in two large Liverpool families. The causative locus, the tylosis esophageal cancer (TOC) gene, has been localized to a small region on chromosome 17q25. Studies on loss of heterozygosity have indicated a role for the TOC gene in sporadic squamous cell esophageal cancer and Barrett's

adenocarcinoma. About half of tylosis patients may develop ESCC by 45 years old or 95% by the age of 65.

(d) Scleroderma

Scleroderma is skin thickening and hardening associated with many different medical conditions, and it is called systemic sclerosis when other organs are also involved. Most of these patients have manifestations in GI tract and half of them may be asymptomatic. In the esophagus, it predominantly causes distal esophageal hypomotility and weak LES tone, although the upper sphincter pressure and proximal esophageal motility is normal. Clinically, it can present as heartburn and dysphagia, and it is associated with esophagitis, ulceration, strictures, Barrett's esophagus, spontaneous esophageal rupture, esophageal adenocarcinoma, or ESCC. On esophageal manometry, it has distinctive features of low contractility and weak LES.

Both ESCC and adenocarcinoma of the esophagus were found among up to 70% of scleroderma patients in an early study in 1979. However, a more recent review of seven studies showed that the link between scleroderma and cancer was not overwhelming with probably a modest increase in lung cancer. This cancer risk might be much lower among localized scleroderma (morphea) patients.

(e) Head and neck squamous cell carcinoma

It is well known that some patients with HNSCC could have either synchronous (found around the time of HNSCC diagnosis) or metachronous ESCC (diagnosed during follow-up). SEER data from 1973 to 1987 showed that the incidence of esophageal cancer was about 1.6% among 21,371 HNSCC patients, a 23 × increase of risk compared with general population. One study showed that 5% of 389 patients were found to have synchronous ESCCs within 1 year after the diagnosis of HNSCC.[16] It also revealed that metachronous ESCC was found more often among hypopharyngeal cancer patients (about 16%) than in laryngeal, oropharyngeal, or oral cancer patients. By combining seven studies with total of 25,834 HNSCC patients, the rough estimate of esophageal cancer is about 1.6%.

Although no societal guideline is available, some authors recommended panendoscopic examination (bronchoscopy, pharyngoesophagoscopy, and laryngoscopy) in patients with early-stage head and neck cancer at the time of diagnosis and then every 6 months for 5 years.

(f) Human papillomavirus (HPV)

The relationship between HPV infection and ESCC remains controversial. It was demonstrated in a high-risk population in China but not in low-risk patients in Europe.

2. Preventive measures

(a) Screening

Considerable efforts have been made in searching for optimal screening methods. The cytologic detection of ESCC or precursor

Table 1.4 Recommendations regarding endoscopy surveillance for ESCC for high-risk patients (American Society for Gastrointestinal Endoscopy).

Risk factors	EGD surveillance	
	Starting time	Intervals
Achalasia	Insufficient data for surveillance. If considered, could initiate 15 years after onset of symptoms	Undefined
Tylosis	Age 30 years old	Requires more studies; no more than every 1–3 years
Caustic ingestion	15–20 years after caustic ingestion	No more than every 1–3 years. Low threshold to evaluate swallowing problems with endoscopy

Source: This table is based on American Society for Gastrointestinal Endoscopy. (2006) *Gastrointestinal Endoscopy*, **63**, 570–580.[17]

lesions by using balloon and sponge samplers yielded very low sensitivity, although a recent study showed greater than 90% sensitivity in detecting Barrett's esophagus by cytosponge. However, the latter study also utilized trefoil factor 3, an immunostain diagnostic marker for Barrett's esophagus based on the systematic gene expression profiling, which may have enhanced the sensitivity significantly.

(b) Chemoprevention

Isotretinoin is a synthetic retinoid with chemopreventive effects that induces a differentiated state. It could potentially reduce the ESCC rate from 24% to 4% among HNSCC patients in a placebo-controlled study.

Although providing a protective effect on patients with mild esophageal squamous dysplasia after 10-month use, selenomethionine failed to inhibit esophageal squamous carcinogenesis for high-risk subjects based on a randomized, placebo-controlled study, which also demonstrated that celecoxib had no detectable protective benefit.

(c) Surveillance

The American Society for Gastrointestinal Endoscopy (ASGE) recommended surveillance on three high-risk populations: achalasia, caustic ingestion, and tylosis Table 1.4).[17]

Cancer management

In general, ESCC patients seek for medical attention when significant symptoms emerge, such as unexplained weight loss and dysphagia, at which time it is highly likely that the disease has spread to the degree that only palliative care could be provided. About 75% of patients present with stage III or IV disease. The National Comprehensive Cancer

Network (NCCN) provides a very detailed guideline in esophageal cancer management on their Web site. Based on this guideline and other publications, the current consensus can be summarized as follows:

1. Early ESCC

Early ESCC means intramucosal lesion (T1a or less). We now have much more experience in treating them with noninvasive procedures.

(a) EMR

EMR is a minimally invasive endoscopic procedure to remove mucosal lesions that are less than 2 cm, or piecemeal removal of larger size lesions. Techniques can be subdivided as injection-, cap-, and ligation-assisted EMR. Specifically, EMR techniques include injection-assisted EMR, EMRC (cap with suction and then snare mucosectomy), and duette multiband mucosectomy Kit.[18] An alternative for en bloc resection of a large lesion is ESD (endoscopic submucosal dissection), but its utility in the esophagus is still under investigation as it takes much longer to perform and has higher complication rates.

About 2–4% of mucosal ESCC (Tis or T1a) patients have lymph nodes invasion, and a few studies had shown that EMR is preferred for this population. EUS is performed first before EMR to ensure there are no lymph nodes involved. EMR could be performed for diagnostic and therapeutic purpose. In experienced hands, it has very low complications, although it can cause minor complications such as short-lived chest discomfort and pain, or minor bleeding (<2 g/dL of hemoglobin drop). Other major but fortunately rare complications include significant bleeding, perforation, and stenosis. The recurrence after EMR varies and it largely depends on the patient selection, whether or not other ablation modalities are performed. One study of 142 mucosal ESCC patients who underwent EMR showed no recurrence of diseases in 9 years of follow-up.

The Mayo clinic researchers in the Barrett's esophagus unit conducted a study and found that antiplatelet agents can be continued after procedures to minimize cardiovascular complications among high thromboembolic risk patients. Based on the American Society of Gastroendoscopy (ASGE), patients who need to continue anticoagulation can be bridged with low-molecular-weight heparin.

(b) Photodynamic therapy (PDT)

Since the 1980s, PDT has been used for various medical conditions such as cancers (skin cancer, cholangiocarcinoma, and esophageal neoplasia) and wet macular degeneration. PDT uses a special agent such as sodium porfimer (approved in North America) and 5-aminolevulinic acid (5-ALA, used in Europe), either orally or intravenously to sensitize the tumor about 4 hours (oral agent) or 24 hours (intravenous agent) before photoradiation. Then laser light at 630–635 nm wavelength from a very small fiber

through the endoscope channel is applied. This can activate the drug, which in turn interacts with oxygen molecule to generate a singlet oxygen state causing cell death.[19]

The response rate varies from 50% to 100% based on different studies. Severe dysplasia and superficial mucosal cancer (<2 mm in depth) can be completely ablated by PDT. However, it may not be able to eradicate the early carcinoma thicker than 2 mm in depth. A large retrospective study of 123 patients (104 ESCC, 19 adenocarcinomas) showed no difference in complete response rate and survival rate between[1] PDT alone and PDT plus multimodal treatment groups (with chemoradiation),[2] the adenocarcinoma and squamous cell carcinoma groups. PDT-related complications include stenosis (35%) and cutaneous photosensitization (13%). Other side effects may include stricture, fistula, chest pain, nausea, and vomiting; however, the perforation rate was about 1% that is lower than EMR.

However, although it is simple to perform, the role of PDT in treatment of esophageal diseases has been limited when other newer and safer methods such as EMR and radiofrequency ablation (RFA) are gaining more popularity.

(c) Other modalities

Although RFA has been used widely among Barrett's esophagus patients, the experience is still limited for ESCC. Only one case of ESCC with RFA treatment was reported in 2008. Very scarce experience with cryotherapy or argon plasma coagulation (APC) for ESCC has been reported.

2. Locally advanced ESCC

Locally advanced ESCC is defined as any T stages with local lymph nodes but no evidence of distant disease. The chemotherapy regimen should be individualized based on tumor stage and patients' performance status. Unfortunately, most of these regimens have low-to-median response rates with significant toxic profiles.

In reviewing the studies on chemoradiation and surgery, it is worth noting that (1) most clinical studies recruited not only ESCC but also esophageal adenocarcinoma, and some even stomach cancers; (2) some studies were criticized because of overall design (e.g., not randomized), small sample size, enrollment bias, uncontrolled crossover between study arms, underperformance of control arm (thus type I error), etc., so one should interpret the results with precautions; (3) these different regimens may prolong the median survival but usually no more than 12 months (most of them had benefits of 3–9 months compared with best supportive care) at the price of very serious adverse effects; (4) multimodality therapy has better response but more adverse effects; (5) surgery alone or surgery combined with other modalities, but not chemotherapy or RT alone, could be potentially curative for early-stage cancer.

(a) Chemotherapy

The most frequently investigated and clinically used regimen includes infusion of cisplatin and 5-fluorouracil (5-FU) at the first

and fourth week of RT. Its response rate varies from 20% to 50%. A randomized phase II study of cisplatin and 5-FU versus cisplatin alone in advanced squamous cell esophageal cancer revealed that combined therapy failed to provide more survival benefits but had significantly more adverse effects such as grade 4 aplasia and septicemia, meningeal hemorrhage, cerebrovascular accident, and ischemia. Actually, cisplatin seems to be the most active agent (response rate of approximately 20%). But in practice, cisplatin and 5-FU are most commonly used in combination.

Other choices are ECF regimen (epirubicin, cisplatin, and 5-FU), DCF (docetaxel, cisplatin, and 5-FU), MCF (mitomycin, cisplatin, and 5-FU), irinotecan and cisplatin, and gemcitabine and cisplatin. The REAL-2 study revealed that capecitabine, an oral agent that converts into 5-FU at tumor tissue, was as effective as 5-FU, and that oxaliplatin was similar to cisplatin but with significantly less grade 3 or 4 neutropenia, alopecia, kidney toxicity, and thromboembolism, but slightly more grade 3 or 4 diarrhea and neuropathy.

(b) Radiation therapy

External plus intraluminal radiotherapy was superior to external alone in both local control and long-term survival; however, the complications such as bleeding, fistula, ulcerations, and complication-related mortality were much higher in the combined group. Up to 70–80% patients with dysphagia from the tumor could improve their symptoms.

Among postoperative ESCC patients, one retrospective study demonstrated that higher total radiation dose (>50 Gy) after surgery was associated with fewer locoregional recurrences and better diseases-free survival without more serious acute and late complications, but no improvement of overall mortality.

However, by randomizing nonsurgical patients with T1 to T4, N0/1, M0 squamous cell carcinoma, or adenocarcinoma to receive higher dose RT (64.8 Gy) or standard dose RT (50.4 Gy) while receiving the same 5-FU and cisplatin therapy, INT 0123 study showed that higher dose RT (64.8 Gy) treatment did not yield statistically significant improvement in median survival when compared with 50.4 Gy group (18.1 vs. 13.0 months), and that the locoregional failure was about the same (56% vs. 52%). More treatment-related mortality was observed in the higher dose RT group. Thus, RT with 50.4 Gy is currently considered as standard dose when combined with chemotherapy.

In a summary, the current recommendation is to use 50.4 Gy radiation together with chemotherapy.

(c) Chemoradiation therapy

Chemoradiation therapy is considered more efficacious than either chemotherapy or radiation therapy alone. For patients with significant cardiopulmonary issues who are not surgical candidates, this could be a potential cure.

A prospective trial in 1992 randomized patients to either the group with combined 5-FU and cisplatin plus 50.0 Gy of RT or to RT alone group (64.0 Gy). The results showed that combined therapy prolonged the median survival from 9 to 12.5 months, and the survival rates at 12 and 24 months were 50% and 38% in combined group versus 33% and 10% in RT alone group.

In another prospective study, 196 ESCC and adenocarcinoma patients with T1-T3, N0-N1, and M0 staging, Karnofsky score of at least 50, were randomized to chemotherapy (cisplatin and 5-FU) plus RT (50.0 Gy) versus RT (64.0 Gy) alone. It showed the 5-year survival for combined therapy was 26% compared with 0% from the RT-only group. However, due to the serious or even life-threatening adverse effects from the combined treatment, only 68% patients completed the whole chemoradiation therapy.

For potentially resectable ESCC of the mid or lower esophagus, the two- or three-stage esophagectomy with two-field dissection or chemoradiotherapy offered similar survival based on results from the prospective randomized trial—CURE study (the Chinese University Research Group for Esophageal Cancer (CURE)). The regimen they used was 5-FU 200 mg/m^2/day infusion from days 1 to 42, cisplatin 60 mg/m^2 on days 1 and 22, and total RT of 50–60 Gy.

In a summary, chemoradiation therapy is more efficacious than either chemotherapy or radiation therapy alone. For resectable patients, surgery could provide similar benefit as chemoradiotherapy.

(d) Surgery

Cervical and cervicothoracic esophageal carcinoma located at <5 cm from the cricopharyngeus should be treated with definitive chemoradiation rather than surgery. For other appropriate candidates, surgical options include transhiatal esophagectomy or Ivor-Lewis procedure (needs thoracotomy and laparotomy) (Table 1.5).

Table 1.5 Resectability of the esophageal cancer.

Staging of esophageal cancer	Methods for resection
Tis and T1a tumors (within the mucosa)	Endoscopic mucosal resection or submucosal dissection
T1b (submucosa)	Esophagectomy
T1–T3 with regional nodal metastases (N1)	Esophagectomy
T4 with involvement in pericardium, pleural, or diaphragm	Esophagectomy
Stage IVa, distal cancer with resectable celiac nodes, but sparing the celiac artery, aorta, or other organs	Esophagectomy
Stage IVa, distal cancer with unresectable celiac nodes; involvement of celiac artery, aorta, or other organs	Unresectable
Stage IVb, unresectable tumor invading other adjacent structures, such as aorta, vertebral body, and trachea	Unresectable

The acceptable surgical options include the following[20]:

- Standard Ivor Lewis esophagogastrectomy (laparotomy and right thoracotomy) or minimally invasive Ivor Lewis (laparotomy and limited right thoracotomy).
- Standard McKeown esophagogastrectomy (laparotomy, right thoracotomy, and cervical anastomosis) or minimally invasive McKeown (limited laparotomy, right thoracotomy, and cervical anastomosis).
- Transhiatal esophagogastrectomy (laparotomy and cervical anastomosis).
- Robotic minimally invasive esophagogastrectomy.
- Left transthoracic or thoracoabdominal incision with anastomosis in the chest or neck.
- Options for reconstruction after esophagectomy include gastric pull-up, colon interposition, or jejunal interposition.

(e) Surgery with or without preoperative therapy (neoadjuvant)

A recent review (2007) of neoadjuvant therapy with chemoradiation showed better curative resection rates and lower locoregional recurrence than surgery alone, but the overall benefit for survival was not clearly demonstrated although some studies revealed such a trend. However, as eluded earlier, many of these studies were not optimally designed; study groups were mixed (gastric cancer, esophageal adenocarcinoma, and ESCC); sample size was small and under powered; and some yielded conflicting results. The multicenter, randomized trial to compare preoperative chemoradiotherapy followed by surgery with surgery alone in patients with stage I and stage II squamous cell cancer of the esophagus failed to show difference in the overall survival although it did prolong disease-free survival.

The CROSS trial is a multicenter, randomized, phase III clinical trial that compares neoadjuvant chemoradiotherapy followed by surgery with surgery alone in patients with potentially curable esophageal adenomas and ESCC with inclusion of 175 patients per arm. The results of this study are still pending.

The practice guideline from Cancer Care Ontario (http://www.cancercare.on.ca/) provided the following recommendations:

- *Bimodal regimen*: A published abstract of an individual patient data-based meta-analysis of nine randomized trials (2102 patients) comparing preoperative chemotherapy followed by surgery (CT + S) to surgery alone demonstrated a 4% (from 16% to 20%) absolute overall survival advantage for chemotherapy at 5 years. Based on seven trials (1849 patients), the disease-free survival was 10% in CT + S group versus 6% in surgery-alone group. No difference was seen in postoperative death.
- *Trimodal regimen*: A meta-analysis of 10 randomized trials comparing esophageal adenocarcinoma patients who received preoperative chemoradiotherapy followed by surgery to surgery

alone showed a 13% absolute benefit in survival at 2 years for preoperative chemoradiotherapy.

- Thus, trimodal is preferred to bimodal regimen if preoperative therapy is considered.
- Randomized trials demonstrated no survival benefit for RT given alone, either preoperatively or postoperatively, compared with surgery alone.
- Randomized trials demonstrated no survival benefit for postoperative chemotherapy compared with surgery alone.

In a summary, based on less-than-optimal studies, neoadjuvant therapy before surgery could provide small benefit in overall survival and is currently recommended.

(f) Surgery with or without postoperative therapy (adjuvant therapy)

Compared with neoadjuvant therapy, fewer studies addressed the issue of adjuvant therapy. In 2000, a study randomized 556 patients with either resectable gastric and gastroesophageal junction adenocarcinoma, to postoperative chemoradiotherapy or surgery alone. Patients in the postoperative chemoradiation arm had a median survival of 36 months and patients in the surgery alone arm had a median survival of 27 months ($p = 0.005$).

One randomized study in 2003 showed that cisplatin and 5-FU adjuvant therapy did improve the 5-year disease-free survival from 45% to 55% ($p = 0.037$) for ESCC patients with stage IIA, IIB, III, or IV with distant node involvement (M1 lymph node) after surgery.

A more recent study in 2009 prospectively randomized 151 ESCC patients (stage II–III) to surgery and adjuvant therapy versus surgery alone, and it showed significant better 5- and 10-year survival rates of 42.3% and 24.4%, respectively, for the group with adjuvant therapy versus 33.8% and 12.5%, respectively, for the surgery alone group. The local recurrence rates in the combined group and surgery alone group were 14.9% and 36.4%, respectively ($p < 0.05$).

In a summary, based on limited data, adjuvant therapy with chemoradiation may provide some survival benefit when compared with surgery alone.

(g) Target therapy

Since the current therapy has limited response for esophageal cancer patients, target therapy aiming toward certain molecules such as HER-2, VEGFR, is an area with active investigation.

The Trastuzumab for Gastric Cancer (ToGA) trial that included HER-2 positive patients with gastroesophageal and gastric adenocarcinoma demonstrated that 5-FU/cisplatin/trastuzumab was superior to 5-FU/cisplatin with median survival of 13.5 versus 11.1 months. Besides trastuzumab, other agents used in the targeted therapy include cetuximab, erlotinib, matuzumab, gefitinib (anti-HER2 antibodies), and bevacizumab (an anti-VEGFR antibody) that are also under investigations.

(h) Herbal agents

A recent Cochrane review was unable to identify a true randomized control trial among 43 articles regarding herbal use as an adjunct therapy to chemoradiation for esophageal cancer patients. The herbals in these studies were from large variety of plants and no specific brands or names were listed. This review concluded that we had no solid evidence to support or against the use of herbal agents among esophageal cancer patients.

3. Metastatic diseases and palliative care

Patients with Eastern Cooperative Oncology Group (ECOG) performance score of ≥3 could be supported by best care; if ECOG score is ≤2, chemotherapy can be considered. No regimen is considered as standard.

For space-occupying lesions, esophageal stents could be placed to restore esophageal patency, but ESCC within 2 cm of upper esophageal sphincter is a contraindication. Sometimes dilation with balloon or Savary dilators may be necessary before stent placement. Self-expanding metal stents (SEMS) have been improved continuously over the last decade in its diameter, shape, distal and proximal flanges, and types of coatings, and they are preferred over plastic one for palliative purpose. SEMS could be placed via endoscopy with or without fluoroscopy by gastroenterologists or under fluoroscopy by radiologists. The complications of stents include migration, bleeding, perforation, tumor overgrowth, pressure necrosis, etc., and the rates vary by types of stents and anatomic location of placement. The placement successful rate could be 90–97%.

Percutaneous endoscopic gastrostomy (PEG) can be considered if a patient has dysphagia. If jejunum access is needed, percutaneous endoscopic jejunostomy or PEG tube with jejunum extension can be placed.

If patients have bleeding from tumor surface, then endoscopy treatment with APC (APC) or electrocoagulation might be helpful. However, if severe bleeding is from fistulization between tumor and aorta, endoscopy intervention is insufficient and patients suffer from high mortality.

Family screening

There is no specific recommendation for family screening. However, if the family is exposed to similar environments or has similar life style as in the index case, screening seems appropriate although no formal recommendation is available.

Case Study

A 67-year-old Caucasian female has 22 years history of achalasia and underwent Heller's myotomy 12 years ago. She has had progressively worsening heartburn symptoms despite of PPI therapy. For a few years, she has intermittent vomiting especially when she lies flat. The

vomitus may include undigested food from previous meal. This time she presented in your clinic with progressive dysphagia to solids, and she mainly takes liquid nutrition supplement and some mechanically soft food. She also has about 25 lb weight loss that she attributed to poor appetite. She is ambulatory and capable of all self-care but unable to carry out any work activities.

Q1. What are the possible underlying etiologies for her dysphasia?

In a different scenario, if this lady presented a few days after her Heller's myotomy, it is still possible that her symptoms are due to tissue swelling from the surgery, or possible scar formation if it is a few weeks after her operation.

However, in her current situation, she is suffering from reflux of food retained in her distal esophagus. It is possible that her achalasia had recurred. Another possible etiology for her dysphagia (the worst case scenario) is squamous cell carcinoma of esophagus, or esophageal adenocarcinoma, which could be the reason for her solid food dysphagia and significant weight loss.

Q2. What is the next step in her medical care?

One could start with esophagram, but definite diagnostic modality is EGD exam with biopsy. If cancer is found, then PET/CT scans are the next step in this investigation. If negative, then EUS can be performed for T staging.

Q3. What are the treatment options?

It certainly depends on TNM staging and her performance status. If she has metastatic diseases and space-occupying mass that caused her dysphagia, then SEMS could provide palliation. Chemotherapy or RT is also an option to reduce the tumor size.

If it is locally advanced disease, then neoadjuvant chemotherapy with ECF regimen (epirubicin, cisplatin, and 5-FU) with RT followed by esophagectomy could be offered. If it is only a mucosal lesion (which is highly unlikely given her dysphagia), series of EMR could be a potential cure and she should be under close surveillance to monitor recurrence.

Key Patient Consent Issues

Consent for EGD/EUS/EMR/Stent

Mr. (or Mrs.) X, we will perform upper endoscopy exam under sedation with ultrasonic view of your esophageal lesion and surrounding lymph nodes. If it is a shallow lesion, we may perform a procedure to resect it. It may cause some bleeding where the resection takes place, but the vast majority of patients will stop the oozing spontaneously without intervention; otherwise, cautery, coagulation, hemoclip, etc., can be utilized to stop the bleeding. Other significant, but fortunately very rare, complications are major bleeding or perforation, which may be treated with surgery or esophageal stenting.

If your lesion in esophagus is occupying the lumen, we could place a metal stent over it to relieve the trouble with swallowing. The risks include bleeding, stent migration, tumor tissue growth into the stent causing obstruction, or necrosis and even perforation.

Discussion for some chemotherapy regimens

The adverse effects could be serious for some of the agents. For example, Oxaliplatin plus capecitabine regimen could cause leukopenia (50.0%), nausea and vomiting (51.6%), diarrhea (50.0%), stomatitis (39.1%), polyneuropathy (37.5%), and hand–foot syndrome (37.5%).[21] We will closely monitor you and terminate your treatment if you are not able to tolerate it.

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