Chapter

Squamous Cell Carcinoma: Esophagus

K.V. Veerendra Kumar, Ramesh Sagar and Joseph Mathew

Abstract

Esophageal cancer, according to GLOBOCAN 2018 data, ranks seventh in terms of incidence and sixth in mortality among all cancers worldwide. In India, it is considered the fourth most common cause of cancer-related deaths. Influenced by lifestyle, socioeconomic and environmental factors, striking geographic variations in incidence exist. With regard to histopathology, esophageal cancers are unique among malignancies of the gastrointestinal tract in that they principally comprise two variants: squamous cell carcinoma (SCC) and adenocarcinoma, with the former accounting for up to 80% of cases. Etiological factors for SCC show marked variations worldwide, with tobacco consumption, alcohol, hot beverages, and poor nutrition constituting the predominant predisposing factors. Although present day therapeutic interventions have begun to positively influence disease prognosis, with significant improvements in survival noted over the last 3 decades, cancer of the esophagus remains a highly lethal disease with a case fatality rate approaching 90%. Management of this disease includes all three primary modalities of treatment; surgery, chemotherapy and radiotherapy. Surgical resection, the only curative modality of treatment, remains a challenge even with advances like minimal access surgery and is feasible only in early stage disease. Early diagnosis and accurate staging are paramount for optimizing treatment and hence, prognosis.

Keywords: esophageal cancer, squamous cell carcinoma, adenocarcinoma

1. Introduction

Despite a better understanding of the biology of disease and a number of advances in diagnostic and therapeutic interventions, cancer of the esophagus remains a highly aggressive and lethal malignancy.

According to GLOBOCAN 2018 data, this disease ranks seventh in terms of cancer incidence (572,000 new cases) and sixth in overall cancer-related mortality (509,000 deaths), signifying that esophageal cancer was accountable for an estimated 1 in every 20 cancer-related deaths in 2018 [1]. In India, esophageal cancer is the fourth most common cause of cancer-related deaths.

Although advances in therapeutic interventions have begun to have a positive impact on survival evident over the past 3 decades, esophageal cancer remains a formidable disease with a case fatality rate of 90% [2].

Histopathologically, cancers of the esophagus are primarily of two types, squamous cell carcinoma (SCC) and adenocarcinoma. Marked geographic variation in incidence and cancer type has been known to occur and is influenced by life style, socioeconomic and environmental factors [3].

Alcohol consumption and smoking and the synergistic effects thereof are major risk factors for the development of SCC in the West. The incidence of esophageal adenocarcinoma in the West has seen a steep rise in the past 20 years, surpassing SCC as the most common type of esophageal cancer [4].

In India, squamous cell carcinoma accounts for up to 80% of all cases of esophageal cancers. Data from Kidwai Cancer Institute and Tata Memorial Hospital show that SCC of the esophagus is the second most common cancer among men and the fourth leading cause of cancer mortality. Although etiological factors implicated in SCCs show marked regional variation in different parts of India, tobacco consumption in various forms, alcohol, hot beverages, and poor nutrition remain the predominant predisposing factors in the subcontinent.

Despite the two pathological subtypes having different etiologic factors, biology and prognostic profiles, they have often been managed as a single entity. Today, management of esophageal cancer includes all three modalities of treatment, i.e., surgery, chemotherapy and radiotherapy. Considering that the esophagus spans three anatomic compartments: the neck, the thorax and the abdomen and its proximity to vital structures, surgery of this organ remains a challenge even with present -day therapeutic advances such as minimal access surgery. Surgery is the only curative therapeutic modality. However, its applicability is restricted to the early stages of the disease [5–7].

Most patients with esophageal cancer, on account of late onset of symptoms and a consequential delay in the final diagnosis, present with advanced disease which precludes definitive surgical intervention. Hence, the prognosis in general remains poor [5, 8]. Early diagnosis and accurate staging are considered vital for the optimal management of esophageal cancer.

2. Anatomy

The esophagus is a muscular tube beginning from the cricopharyngeal sphincter at the cricoid cartilage at the level of the sixth cervical vertebra and terminating at the gastroesophageal junction at the level of the 11th thoracic vertebra. It travels through the neck, chest and upper abdomen, and is anatomically divided into the cervical, the thoracic, and the abdominal segments [9] (**Table 1**). From its origin at the cricoid cartilage to the gastroesophageal junction, the length of the adult esophagus varies from 22 to 28 cm with the distal 3 cm lying intra-abdominally [10].

The cervical esophagus lies just left of the midline and is closely related to the trachea anteriorly and the prevertebral fascia posteriorly. Only a minimal amount of loose areolar tissue separates the trachea from the esophagus and malignancies are known to spread from the esophagus to the trachea and vice versa [11]. The upper

Part of esophagus	Extent	Distance from upper incisor (cm)
Cervical esophagus	Pharyngoesophageal junction to thoracic inlet	18
Upper thoracic	Thoracic inlet to the lower border of T6 vertebra	26
Mid thoracic	Lower border of T6 to lower border of T8 vertebra	31
Lower esophagus	Lower border of T8 to cardiac orifice	40

Table 1.
Parts of the esophagus according to UICC (1978).

portion of the thoracic esophagus curves slightly to the right and passes behind the tracheal bifurcation and the left main-stem bronchus. On either side of the thoracic esophagus are the lungs with their pleural linings. Additionally, the azygos vein, arching over the right main bronchus to drain into the superior vena cava, and the subclavian artery are important relations on the right. On the left are the aortic arch and the aorta which assumes a posterior course in relation to the esophagus. The lower portion of thoracic esophagus runs behind the pericardium and the left atrium, where it bends to the left to enter the abdomen through the esophageal hiatus. The left lobe of the liver bears an anterior relation to the abdominal esophagus [12].

There are three areas of physiological/normal narrowing of the esophageal lumen: at the cricoid cartilage, at the point where it crosses the left main bronchus and the aortic arch and at the diaphragmatic hiatus.

2.1 Supports of the esophagus.

The outer longitudinal muscular layer of the esophagus inserts into the posterior ridge of the cricoid cartilage via the cricoesophageal tendon. The inner circular muscle layer is in continuity with the inferior laryngeal constrictor which inserts on the sphenoid. Bronchoesophageal and pleuroesophageal strands are fibromuscular bands which connect the esophagus with the trachea and bronchi and pleura, respectively. Inferiorly, the posterior gastric ligaments and the lesser omentum are the main anchors of the distal esophagus, the phrenoesophageal membrane serving as a weaker support [12].

The peritoneal reflections associated with the esophagus are the hepatogastric ligament and the gastrosplenic ligament. The former encloses the left gastric vessels, the hepatic division of the left vagal trunk and lymph nodes. The hepatogastric ligament continues to the left of the abdominal esophagus as the gastrosplenic ligament. The lesser sac lies posterior to these ligaments [10, 12].

2.2 Blood supply of esophagus

The esophagus has a segmental blood supply. The cervical esophagus is predominantly supplied by the inferior thyroid artery, the upper and mid thoracic esophagus by branches from the bronchial arteries and the descending thoracic aorta and the lower thoracic and intra-abdominal esophagus by branches from the left gastric and inferior phrenic arteries [13].

An extensive submucosal venous plexus communicates with the longitudinally oriented periesophageal veins through the muscularis. In the cervical esophagus, these veins drain principally into the inferior thyroid veins, in the thoracic esophagus into the azygos vein and in the abdominal esophagus, into the azygos and left gastric veins. Hence, in the distal esophagus, the caval and portal venous system are connected through the submucosal plexus. A rise in portal venous pressure can transform these submucosal veins into varices as is seen in portal hypertension [14].

Lymphatics form a dense submucosal plexus which runs along the long axis of the esophagus. Lymph flows primarily along the long axis of the esophagus the direction of which is cephalad in the proximal two thirds of the esophagus and caudad in the distal third. Nevertheless, a definitive watershed line for the demarcation of lymphatic drainage is not evident: lymph can course freely along the entire length of the esophagus via the esophageal plexus before draining into the regional nodes. This lymphatic network serves as a means for the spread of cancer intramurally. Consequently, cancers of the upper esophagus can metastasize to the superior gastric nodes or cancers of the lower esophagus to the superior mediastinal nodes. The submucosal plexus gives off branches which communicate with the peri-oesophageal

lymph plexus which then drains into the posterior mediastinal nodes. Again, these nodes can drain into both the supraclavicular and the left gastric nodes [12].

In general, lymph from the upper esophagus drains mostly into the cervical and paratracheal nodes and that from the lower thoracic and abdominal esophagus into the retrocardiac and celiac nodes.

3. Histology

The mucosal lining of the esophagus comprises a thick layer of stratified squamous non-keratinizing epithelium. Proximally, it is continuous with the mucosa of the oropharynx. Histologically, the gastroesophageal junction is delineated by an irregular line (the "Z line") between the stratified squamous epithelium proximally and the simple columnar epithelium distally. However, patches of gastric epithelium can be found proximal to the squamocolumnar junction. Deep to the mucosal lining are the lamina propria and the muscularis mucosa. The submucosa is a layer of connective tissue layer that lies deep to the mucosa. It contains small vessels, lymphatics, nerves and mucous glands. The submucosa is widely considered the strongest layer of the esophageal wall. Meissner's nerve plexus is found in the submucosa [10, 15].

The tunica muscularis comprises two layers; the external or longitudinal muscle layer and the inner circular muscle layer both beginning at the level of the cricoid cartilage. Auerbach's plexus lies in the connective tissue between the circular and longitudinal muscular layers.

The musculature of the pharynx and proximal esophagus is striated and is gradually replaced by involuntary smooth muscle in the distal esophagus reflecting the embryonic development of the esophagus. The lower esophageal sphincter although not an anatomically defined sphincter is a high pressure zone which serves to prevent acid reflux into the esophagus. The tunica adventitia is the outermost thin layer of loose areolar tissue. It contains small vessels, lymphatics and nerves. The esophagus lacks a serosal lining; anastomotic dehiscence following esophageal resection and anastomosis has been attributed to this absence of this outermost layer [15].

4. Embryology

The esophagus develops from the foregut of the primitive endodermal tube which is embryological precursor of the gastrointestinal tract. The foregut starts to divide into the laryngotracheal and the oesophageal tubes in the fourth week of gestation. Failure of division may result in congenital anomalies ranging from esophageal atresia to tracheo-oesophageal fistulae. Distal to the oesophageal tube, the foregut dilates to form the stomach [10].

Cephalad to the aortic arch, the esophageal musculature is derived from the branchial arches whereas caudal to the aortic arch, the embryonic esophagus is suspended in a mesentery, similar to the rest of the foregut [10]. Hence, the tunica muscularis of the upper third of the esophagus comprises skeletal muscle whereas that of the middle and lower third is predominantly smooth muscle.

5. Physiology

The esophagus primarily serves as a conduit to convey food through the thoracic cage.

Swallowing may be divided into three phases. The oral phase is voluntary and results in the food bolus entering the pharynx. The pharyngeal phase is involuntary and initiates a peristaltic wave propelling food through the upper oesophageal sphincter.

The esophageal phase is a continuation of the peristaltic wave initiated by the superior constrictor in the pharynx into the esophagus allowing the bolus to reach the stomach. Failure to do so results in esophageal distension which triggers secondary peristalses.

The lower esophageal sphincter is primarily a physiologic sphincter. The high pressure (15–25 mmHg) in this region serves to prevent the reflux of gastric juices into the esophagus. Other factors contributing to the functionality of the LES are the diaphragmatic crura, the gastric sling fibers, the valvular effect of the gastroesophageal angle and the positive intra-abdominal pressure. Gastroesophageal reflux disease is considered a predisposing factor for the development of adenocarcinoma of the esophagus [16–18].

6. Biology of esophageal cancer

Esophageal cancer shows marked variations in incidence, histopathological type of malignancy according to gender, ethnicity and geographic location. Environmental and socioeconomic factors also play a key role in carcinogenesis [3].

The two main histopathologic types of esophageal cancer are squamous cell carcinoma and adenocarcinoma. Other uncommon variants include squamous cell carcinoma with sarcomatous features, mesenchymal tumors, adenoid cystic carcinoma, mucoepidermoid carcinoma, neuroendocrine cancer and benign tumors.

The incidence of esophageal adenocarcinoma in Europe and in the United States has seen a steep rise in the past 2 decades, surpassing SCC as the most common type of esophageal cancer [4]. The rate of SCC of the esophagus has remained relatively stable or has seen a declining trend in Western countries [19–21]. Predisposing factors include gastroesophageal reflux disease and the ensuing Barrett's esophagus, obesity and smoking [20].

Nevertheless, squamous cell carcinoma remains the most common variety of esophageal cancer worldwide, arising as a result of long standing irritation of esophageal lining most commonly due to smoking and alcohol abuse, and occupational exposure. Tobacco and alcohol are strong, synergistic risk factors for the development of SCC [22]. Other notable predisposing factors are caustic injury, Plummer Vinson syndrome and achalasia cardia [20]. Squamous cell carcinomas of the esophagus are most likely to arise in the upper and middle thirds of the esophagus whereas esophageal adenocarcinomas are most common in the distal aspect of the esophagus.

7. Etiology of SCC

7.1 Environmental promoters of carcinogenesis

7.1.1 Alcohol

Alcohol abuse is a known risk factor for the development of esophageal. SCC more so when ingestion exceeds 170 g/week. This risk increases in a linear fashion with increasing consumption [23]. Key mechanisms in carcinogenesis include metabolic activation and decreased detoxification of potential

carcinogens, and increased cellular exposure to oxidants, a critical determinant of DNA damage. Also, production of acetaldehyde is increased, leading to diminished methyl transferase activity. The risk is compounded by synchronous exposure of tobacco [24].

7.1.2 Tobacco

Tobacco smoke contains polycyclic aromatic hydrocarbons, N-nitroso compounds, epoxides, lactones and tar, all of which are known carcinogens. They are irritant to the squamous epithelial lining of the esophagus and can give rise to metaplasia, a precursor of malignancy, on chronic exposure. Smoking is considered a risk factor for the development of both esophageal adenocarcinoma and SCC. Smoking was shown to contribute to a 12-fold greater incidence of atypical nuclei and a two-fold increase in incidence of in situ carcinoma within the basal layer of esophagus. Smokers have a nine-fold higher risk of developing SCC when compared to nonsmokers (hazard ratio 9.3; 95% CI: 4.0–21.3) [25, 26].

7.1.3 Nitrosamines

The human body is constantly exposed to N-nitrosamines at levels of 20–200 mcg/day. Nitrates and nitrites are precursors to N-nitroso compounds. These compounds are transformed in vivo into alkylating electrophiles that form adducts with DNA, by alkylating the N7 and O6 positions of guanine in the DNA helix.

7.1.4 Vitamin and mineral deficiency

Deficiencies of vitamins A, C, E and the B complex vitamins such as cyanocobalamine, riboflavin and folic acid may predispose to the development of squamous cell carcinoma of the esophagus. Among the micronutrients, zinc deficiency can induce carcinogenesis by the formation of O6-methylguanine DNA adducts by microsomal activation of N-nitrosomethyl-benzylamine. The trace element molybdenum is considered protective against the development of esophageal cancer by inhibiting the formation of nitrate reductases.

Selenium as an antioxidant plays a role in the inhibition of cell membrane lipid peroxidation. Deficiencies in these micronutrients have been linked to an increased risk of developing SCC of the esophagus [27–29].

7.1.5 Food and water contaminants

Fungi such as Fusarium, Alternaria, Geotrichium, Aspergillus, Cladosporium, and Penicillium have been associated with the development of esophageal cancer either by a direct mutagenic effect or through the formation of nitrosamines.

Other rarer causes of esophageal SCC are Helicobacter pylori infection, Plummer Vinson syndrome, caustic injury, achalasia cardia and human papillomavirus infection. HPV infection may account for as much as a third of all cases of esophageal cancer in high incidence areas as seen in Asia and South Africa [30, 31].

Barrett's esophagus, longstanding GERD and obesity are considered exclusive risk factors for the development of esophageal adenocarcinoma apart from other factors such as smoking, socioeconomic status, deficiency in dietary micronutrients which are also associated with SCC of the esophagus. Chronic gastroesophageal reflux leads to columnar metaplasia of the distal esophagus (Barrett's esophagus) which is associated with a 30- to 40-fold increased risk of progressing to esophageal adenocarcinoma [25].

7.2 Molecular oncogenesis

Epidermal growth factor (EGF) is an autocrine growth factor whose DNA is amplified in esophageal SCC. Overexpression of mRNA and the protein product appears to decrease survival. EGF receptor gene is the homolog of erb-B oncogene. The overexpression of the epidermal growth factor correlates with an increased frequency of lymph node metastasis [32].

Transforming growth factor-alpha is another autocrine growth factor that is co expressed with EGF and EGF receptor gene. They code for proteins that are homologous to EGF. The co-amplification correlates with advancing clinical stage and a worse prognosis in esophageal SCC [32, 33].

Ras encodes a protein product, p21, and has homology to G-proteins; a critical aspect of the signal transduction cascade. Over expression of p21 has been observed in esophageal SCC.

Tumor suppressor genes inhibit uncontrolled growth. They are necessary for repair to take place before damaged DNA is replicated. Gene inactivation in chromosome 17p is detected in at least half of esophageal cancers. PCR amplification and direct sequencing may detect p53 mutation in one third of specimens.

Human papilloma virus has been associated with the development of esophageal cancer. Low risk HPV genotypes are HPV 6 and 11.high risk genotypes are HPV 16, 18, and 33 [31].

Geographic distribution of esophageal squamous cell carcinoma SCC of the esophagus is the most common histologic type of esophageal cancer outside Western countries, where adenocarcinoma predominates. Incidence rates in China and some parts of Africa are estimated to be as high as 140 per 100,000 population [34]. Men and women are affected equally in these high-incidence areas [25]. However, in the United States and Europe, the incidence is much lower, estimated to be around 3 cases per 100,000 population with a declining trend [34].

8. Screening and early detection

Despite several potential preventive measures, none have been proven to decrease the risk of esophageal carcinoma in prospective well-designed trials [23]. The relatively low incidence of disease, absence of symptoms in the early stage, and the rarity of hereditary forms make population-based screening untenable except in certain high-risk areas of the world [35].

9. Diagnosis

The management of esophageal cancer remains a challenge even today because of the late stage at presentation of the majority and the overall poor prognosis of disease. It is estimated that only one in eight esophageal cancers are identified at an early stage (T1). These include cancers diagnosed incidentally during a gastroscopy performed for other reasons or during the course of surveillance programs. However, most esophageal cancers are diagnosed after symptoms develop. Typical symptoms which prompt patients to seek medical attention include dysphagia (which signifies a 50% reduction in the esophageal lumen) [36], vomiting, loss of body weight, and gastrointestinal bleeding. In general, these are manifested in tumors that are locally advanced and hence, inoperable. Moreover, unlike esophageal adenocarcinoma, which evolves from premalignant conditions such as Barrett's

esophagus in the background of gastroesophageal reflux disease, SCC lacks a premalignant stage. Hence, they tend to present at an advanced stage.

Gastroscopy remains the investigation of choice for the diagnosis of esophageal cancer as it permits the visualization of mucosal abnormalities and enables retrieval of tissue for histopathological examination. If erosions, ulcers, or strictures are found, the endoscopist decides whether these changes are neoplastic or not and whether they necessitate a biopsy. Dysplastic signs are discolorations, fine granulated surfaces (orange peel effect), as well as small elevations and troughs.

The sensitivity of endoscopy in detecting early-stage carcinoma may be improved by adjunctive techniques such as chromoendoscopy (using 1.5–3% acetic acid for adenocarcinoma and 0.5–1% Lugol's solution for SCC) or virtual chromoendoscopy which serves to highlight foci that are suspicious for malignancy.

A 'targeted' biopsy may be obtained from these areas for confirmation [37]. The current recommendation with respect to diagnostic tissue sampling in esophageal cancer is that a minimum of eight samples be taken from the lesion specifically from the margins and center; sensitivity for biopsies in detecting esophageal cancer has been shown to be 96% when multiple samples are taken from the lesion in question [37]. Alternatively, a diagnostic endoscopic mucosal resection may be performed [38].

Preoperative assessment and staging of esophageal SCC As in any malignancy, accurate staging is crucial for optimizing treatment in esophageal cancer. The depth of the tumor determines the feasibility of endoscopic management.

Several imaging techniques have been employed in the preoperative staging of these patients [39–45]. These include endoscopic ultrasonography (EUS), computed tomography (CT) and magnetic resonance imaging (MRI) among others. However, all these modalities have their limitations.

Numerous studies have demonstrated the superiority of EUS in both local tumor (T) and nodal (N) staging over CT [46]. EUS is the ideal modality for assessing the depth of invasion of the primary tumour with accuracy for T staging approaching 90% in superficial and partially obstructing esophageal cancers [47]. However, accuracy declines in cases of completely obstructing tumors wherein the luminal compromise associated with disease cannot be negotiated by the echo-endoscope [47–50]. This is considered the major limitation of this technique and precludes accurate staging in 16–50% of esophageal cancer patients [49–50]. Also, its ability to discriminate between subtle differences in T1 disease, that is, T1a versus T1b, is less exact [51]. For assessing regional lymph node metastases, EUS is reported to be more sensitive but less specific than CT and hence carries a risk of over-staging [48, 49]. Endosonographic characteristics of a malignant lymph node include size >10 mm, round and smooth features, proximity to the primary tumor, and hypoechogenicity. The accuracy of EUS for nodal staging based solely on these criteria approaches 80% [52, 53]. Accuracy of nodal staging can be increased to 92–98% when FNA of the lymph node is performed concurrently with EUS [53, 54]. However, false positive results, as a result of contamination by exfoliated cancer cells from the primary tumor site, are a possibility when EUS guided FNAC of suspicious nodes is performed [55].

EUS is not indicated for the evaluation of distant lymph node metastases, where CT is preferred [49]. Other limitations associated with EUS are its limited availability and operator dependence for accurate staging. With respect to its ability to provide accurate staging information after neoadjuvant therapy, EUS is not considered reliable due to the presence of post-treatment adherence and fibrosis [56].

To date, MRI has not gained widespread acceptance for the locoregional staging of cancers of the esophagus. Despite initial data [57] suggesting inferiority of MRI when compared to CT with respect to accuracy in staging esophageal malignancies,

subsequent literature [58] reported that the two modalities were comparable when assessing resectability of carcinomas of the esophagus. Nevertheless, CT remains the most widely used imaging modality on account of its utility in detecting metastatic disease and greater availability. Moreover, a CT scan also provides useful information regarding extension of the tumor especially with regard to involvement of the trachea or the aorta (T4b disease). Suspicion of direct invasion of the thoracic aorta or the tracheobronchial tree should be confirmed with MRI and bronchoscopy, respectively.

An abdominal ultrasound or preferably, a multi-slice CT scan of the thorax and abdomen are required for metastatic evaluation of the tumour before definitive therapy is initiated.

FDG-PET scan provides the most accurate information regarding potential metastatic disease, increasing the accuracy of detecting occult metastasis by as much as 20% over CT alone [59]. Also, FDG-PET is considered a reliable imaging modality for post-treatment reassessment and to assess the response to neoadjuvant therapy [60]. However, its specific indication and role in this scenario is yet to be defined [61].

AJCC 8th Edition [62]

TNM clinical classification—squamous cell carcinoma and adenocarcinoma

T—primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	High-grade dysplasia, defined as malignant cells confined to the epithelium by the basement membrane
T1	Tumour invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumour invades lamina propria or muscularis mucosae
T1b	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades adventitia
T4	Tumour invades adjacent structures
T4a	Tumour invades pleura, pericardium, azygos vein, diaphragm, or
T4b	peritoneum Tumour invades other adjacent structures such as aorta, vertebral body or trachea
N—regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
M—distant metastasis	
M0	No distant metastasis
M1	Distant metastasis
Definition of histologic grade (G)—squamous cell carcinoma and adenocarcinoma	
GX	Grade cannot be assessed
G 1	Well differentiated
G2	Moderately differentiated

G3	Poorly differentiated, undifferentiated		
Stage and prognostic group			
Clinical stage			
Stage 0	Tis	N0	M0
Stage I	T1	N0, N1	M0
Stage II	T2	N0, N1	M0
	T3	N0	M0
Stage III	T1,T2	N2	M0
	T3	N1, N2	M0
Stage IVA	T4a,T4b	N0, N1, N2	M0
Stage IVA	Any T	N3	M0
Stage IVB	Any T	Any N	M1

10. Treatment

10.1 Early stage cancer

Early esophageal cancer as an entity, according to the AJCC seventh edition, comprises all high grade dysplastic lesions and T1 malignancies [62]. Presence of intraepithelial malignant cells without a breach in the basement membrane is termed high grade dysplasia. T1 lesions include malignancies involving the mucosa (T1a) and submucosa (T1b) but not invading the muscularis propria.

In order to facilitate greater precision in staging and to further optimise stage-specific treatment in early esophageal cancer, T1a and T1b lesions have been further categorized into three subtypes (M1–M3 and SM1–SM3, respectively) according to the depth of invasion. Endoscopic mucosal resection is considered feasible in cancers involving the upper third of the submucosa (SM1 lesions) [63–66].

10.1.1 High grade dysplasia and T1a lesions

In cancers confined to the mucosal layer, the risk of lymph nodal disease correlates with the depth of tumour invasion and the histological type. For HGD or for intramucosal cancer, a systematic review of surgical literature, has reported that the rates of occult invasive cancer in patients undergoing esophagectomy for the treatment of HGD was 12.7% (pooled average in 441 patients from 23 studies) [67]. The rate of node positivity in high grade dysplasia and T1a cancers was estimated to be 0–2%. A retrospective review of 126 patients with T1 tumors of adenocarcinoma histology reported the rate of nodal involvement in T1a and T1b as 1.3–22%, respectively [64]. Data in early esophageal cancer has shown that M3 cancer (disease extending to the muscularis mucosa) has at least 6% risk of lymph metastases [63]. Additional characteristics which impact the risk of nodal involvement include vascular invasion, tumor size, and the degree of tumor differentiation. Given the low risk of node positivity in early stage esophageal cancer confined to the mucosa, there is general consensus that endoscopic management is adequate and reliable for the treatment of mucosal disease (T1a). Endoscopic resection is, therefore, curative in such lesions. Initially, options included argon beam coagulation, laser, and photodynamic therapy. More recently, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), radio-frequency ablation (RFA), cryotherapy, and free-hand mucosal resection have

increasingly been applied [68]. However, data on these modalities of treatment are limited at present, and efficacy of one technique over another has not been established [69].

However, all visible lesions should ideally be removed by EMR for definitive histopathological staging and to ensure adequacy of resection margins. This recommendation is based on the poor accuracy of EUS to discriminate between T1a and T1b lesions. In this regard, EMR remains the sole technique able to stage the degree of invasion into the esophageal wall. For intramucosal cancer associated with Barrett's esophagus, eradication of the metaplastic mucosa is essential to prevent the development of potentially malignant lesions. For segments that measure ≤5 cm and harbor HGD or intramucosal cancer, an EMR approach is used. For patients with segments >5 cm, all focal lesions are resected with EMR or ESD and the residual base of the Barrett's lesion radiofrequency ablated which reduces the incidence of stricture formation [68].

10.1.2 T1B and T2 tumors

As mentioned above, lymphatic invasion and hence, nodal involvement in T1a lesions is uncommon. However, once the muscularis mucosa is breached, dissemination of cancer cells can occur via the submucosal lymphatic plexus. Thus, T1b and T2 cancers have a disproportionately higher incidence of node positivity when compared to T1a cancers [64]. The depth of invasion beyond which an endoscopic resection is considered inadequate treatment remains controversial. In one clinical series, it was demonstrated that EMR could be performed in low grade submucosal SM1 lesions (considered 'low risk' tumors) [70]. At a mean follow-up of 5 years, no tumor related deaths were reported. However, according to other series, rate of node positivity in SM1 tumors is in the range of 16.5–21% [64, 71–73]. For tumors invading beyond SM1, existing literature suggests that the incidence of nodal involvement in patients with T1b cancer ranges from 21 to 50% [59, 74].

Also, in a review of outcomes for T2 lesions, the current approach to clinical staging correlated with the pathological stage in just 13% of patients of those inaccurately staged, 63% were overstaged and the rest, understaged. Based on these results, the recommendation for treatment of T2 lesions is to proceed with definitive surgery as it is considered optimal in both patients who are overstaged and accurately staged.

With regard to T1b and T2 cancers, the general consensus is to proceed to surgical resection without neoadjuvant therapy [75]. Patients who are discovered to be understaged after esophagectomy can be considered for adjuvant therapy [76]. Indications for esophagectomy in early stage esophageal cancer include failures of endoscopic therapy and all incomplete endoscopic mucosal resections.

Invasion of tumour into the submucosa is now considered an indication for esophagectomy, although invasion into the superficial third of the submucosa does not carry the same risk of nodal metastasis as the deeper two thirds, and could be potentially treated endoscopically [77, 78]. Apart from tumor characteristics, the treatment modality chosen may also be tailored according to the patient preferences and characteristics and the surgical or endoscopic expertise available. A vagal sparing esophagectomy has also been proposed recently as an alternative to conventional esophagectomy. This procedure, which involves resection of the esophagus from the mediastinum using a stripping device leaving the vagi and the nodes intact, has been reported to offer several advantages in carefully selected patients including the preservation of meal size, gastric emptying and BMI [74, 79]. However, prospective data in support of this technique is not available.

10.1.3 Indication of neoadjuvant therapy in early stage cancer

Surgery alone in the form of an esophagectomy remains the standard treatment for early stage cancer. Data promoting the benefits of neoadjuvant treatment for localized esophageal cancer is scant. The Fédération Francophone de la Cancérologie Digestive (FFCD) 9901 assessed whether preoperative chemoradiotherapy (CRT) improved outcomes in patients with localized (stages I or II) esophageal cancer [75]. From 2000 to 2009, 195 patients were randomized and assigned either to the surgery only group (n = 98) or to the neoadjuvant CRT group (n = 97). Although postoperative morbidity rates were not statistically significant between the two groups, 30 day-mortality rates were 1.1% in the surgery alone group compared to 7.3% in the CRT group (p = 0.054). At a median follow-up of 5.7 years, the median survival was 43.8 months in the surgery group compared to 31.8 months in the CRT group (HR 0.92; 95% confidence interval 0.63–1.34; p = 0.66). The trial concluded that neoadjuvant CRT with cisplatin and fluorouracil does not improve overall survival but increases postoperative mortality in patients with stage I and II esophageal cancer compared with surgery alone.

10.2 Locally advanced esophageal cancer

The vast majority of esophageal cancers are found to be locally advanced at presentation. Traditionally, both locally advanced esophageal SCC and adenocarcinoma have been managed with surgical resection. In this regard, esophagectomy with radical lymphadenectomy was considered to be the ideal treatment in terms of achieving local control. However, many patients developed locoregional recurrence or metastatic disease after surgery and survival was poor. Analyses of disease recurrence patterns and the dismal outcomes following surgery alone in this subset of patients of prompted the introduction of adjuvant treatment as a means of achieving locoregional control. However, esophagectomy being a major procedure with high morbidity, adjuvant therapy may not always be feasible and hence, management strategies have now adopted neoadjuvant therapy. In some cases of carcinoma esophagus and more so in esophageal SCC, definitive CRT has been advocated as the first line treatment, taking into consideration the excellent response achievable by this modality. In these cases, surgery is reserved as a second line therapeutic option for patients in whom definitive CRT has failed (termed a "salvage" esophagectomy).

10.2.1 Neoadjuvant chemotherapy or chemoradiotherapy

Both neoadjuvant chemotherapy and radiotherapy are known to improve overall and disease free survival. They improve locoregional disease control by downstaging the cancer and improving resectability rates. Moreover, chemotherapy eradicates systemic micrometatstic disease by impeding the dissemination of cancer cells. Ameta-analysis by Gebski et al. evaluated outcomes associated with neoadjuvant chemotherapy and chemoradiotherapy followed by surgery compared to surgery alone in patients with locally resectable esophageal cancer regardless of the histological type [80]. The analysis included pooled data from 10 randomized controlled trials comparing surgery alone with neoadjuvant CRT and 8 randomized controlled trials comparing neoadjuvant chemotherapy with surgery. In the neoadjuvant chemotherapy group, the hazard ratio (HR) for all-cause mortality was 0.90 (95% CI, 0.81–1.00; p = 0.05), indicating a 2-year absolute survival benefit of 7%. Survival benefit associated with neoadjuvant chemotherapy differed with the cancer histology: patients with SCC did not experience a survival benefit with neoadjuvant chemotherapy [HR for mortality 0.88 (0.75–1.03); p = 0.12] whereas

in the adenocarcinoma group, survival benefit was significant [HR for mortality 0.78 (0.64–0.95); $p = 0.014$]. In the neoadjuvant chemoradiotherapy group, the HR for all-cause mortality was 0.81 (95% CI, 0.70–0.93; $p = 0.002$), corresponding to a 13% absolute difference in survival at 2 years when compared to surgery alone. With respect to tumour histology, neoadjuvant CRT was associated with a significant benefit over surgery in both esophageal adenocarcinoma and squamous cell carcinoma [HR of 0.84 (0.71–0.99; $p = 0.04$) for SCC and 0.75 (0.59–0.95; $p = 0.02$) for adenocarcinoma].

The updated meta-analysis published by Sjoquist et al in 2011 included 4,188 patients from the 17 studies evaluated in the previous meta-analysis with an additional seven more recent studies [81]. The inter-group analysis demonstrated strong arguments for CRT compared to CT in patients with SCC or adenocarcinoma. The HR for all-cause mortality for neoadjuvant chemotherapy was 0.87 (0.79–0.96; $p = 0.005$). When comparing the histological subtypes, the HR for SCC only was 0.92 (0.81–1.04; $p = 0.18$) whereas that for adenocarcinoma was 0.83 (0.71–0.95; $p = 0.01$). The HR for all-cause mortality for neoadjuvant CRT was 0.78 (95% CI, 0.70–0.88; $p < 0.0001$); that for SCC only was 0.80 (0.68–0.93; $p = 0.004$) and for adenocarcinoma, 0.75 (0.59–0.95; $p = 0.02$). When comparing all-cause mortality for neoadjuvant CRT versus neoadjuvant chemotherapy, the HR for the overall indirect comparison was 0.88 (0.76–1.01; $p = 0.07$).

However, the above meta-analysis did not include data from the recent phase III 'CROSS' trial which compared the outcomes associated with concurrent CRT (involving carboplatine and plaxitaxel with 41 Gy) followed by surgery and surgery alone [82]. A pathological complete response was noted in 47 of 161 patients (29%) who received neoadjuvant CRT followed by surgery. Despite the rate of postoperative complications and in-hospital mortality being similar in both groups, the overall survival was significantly better in the CRT group [HR 0.657 (0.495–0.871; $p = 0.003$)]. Median OS was 49.4 months in the CRT followed by surgery group as against 24 months in the surgery alone group.

In conclusion, neoadjuvant CRT is strongly recommended and may be considered the standard of care in patients with locally advanced esophageal cancer compared to neoadjuvant chemotherapy alone. However, the optimal neoadjuvant treatment regimen has not been established yet, as the various trials conducted have employed different drugs, doses, and schedules of chemotherapy and radiotherapy.

10.2.2 CRT: sequential or concomitant?

Gebski et al, in their meta-analysis, concluded that there was no survival benefit of sequential CRT for patients with SCC [HR for mortality 0.9 (0.72–1.03); $p = 0.18$]; the results obtained in the sequential CRT group were similar to that of the neoadjuvant chemotherapy group [80]. Concomitant CRT in patients with SCC had a significant benefit [HR for mortality 0.76 (0.59–0.98); $p = 0.04$]. On this basis, concomitant CRT has been recommended in patients with locally advanced cancer of the esophagus planned for neoadjuvant therapy.

10.2.3 Neoadjuvant or adjuvant treatment?

This issue was addressed by the Japan Clinical Oncology Group which conducted two randomized controlled trials to assess potential benefits of adding adjuvant therapy to surgery in patients with SCC. The JCOG 9204 sought to identify the benefit associated with adjuvant cisplatin plus 5-FU when compared to surgery alone in patients with resectable stage I and II esophageal cancer [83]. Although overall survival was not significantly different between the two groups (5-year

survival rate 52 vs. 61%; $p = 0.13$), disease-free survival was significantly better in those receiving postoperative CT, especially in node positive disease. In the JCOG 9907 study, neoadjuvant cisplatin and 5-FU was compared with adjuvant cisplatin plus 5-FU in patients with clinical stage II or III esophageal cancer [84]. In terms of overall survival, neoadjuvant CT was found to be superior with a 5-year survival rate of 60% compared to 38% in the adjuvant group ($p = 0.013$). Based on the results of these studies, neoadjuvant chemotherapy followed by radical surgery is currently recommended as the standard in locally advanced SCC.

10.2.4 Neoadjuvant CRT followed by surgery or definitive CRT?

Definitive CRT as a treatment modality in the management of esophageal cancer was introduced following the Radiation Therapy Oncology Group (RTOG) 8,501 study [85]. This trial, which included both esophageal SCC and adenocarcinoma, compared outcomes after RT alone (64 Gy) with concurrent CRT (cisplatin, 5- FU, and radiotherapy 50 Gy). This study demonstrated the strong sensitivity of SCC to concomitant CRT which resulted in better overall survival and decreased local failure rates when compared to RT alone. Subsequently, a Japanese phase II trial analyzed the efficacy of definitive CRT (cisplatin and 5-FU with classic portal radiation 60 Gy) in squamous cell carcinoma of the esophagus [86]. Although a complete response was obtained in 68% with a 3-year survival rate of 46%, these results were not superior to those obtained with conventional surgical resection with or without chemotherapy. Among the trials conducted comparing definitive CRT with neoadjuvant CRT in esophageal SCC, the study performed by the German Esophageal Cancer Study Group reported that the 2-year overall survival was similar in the neoadjuvant CRT followed by surgery group (39.9%) and the definitive CRT treatment group (35.4%) [87]. The neoadjuvant therapy group was complicated by a higher rate of early postoperative mortality, while definitive CRT was associated with a higher incidence of local relapses. These results were reproduced in another large randomized study, the FFCD-9102, where surgery was proposed in responders to CRT. Although surgery was reported to improve local control, it did not translate to an improvement in survival as neoadjuvant therapy was associated with increased early mortality [88].

On the basis on these results, both definitive CRT and neoadjuvant CRT followed by surgery seem to have similar long-term results. Despite flaws in these studies, surgery appears to provide better local control of the tumor but without any impact on long-term survival outcomes. Cost of major surgery and the risk of postoperative mortality are important factors that should be considered in patients being planned for neoadjuvant therapy followed by esophagectomy.

10.3 Salvage esophagectomy

In Japan and in Western countries, medical and radiation oncologists have reported satisfactory outcomes with definitive CRT blurring the boundaries of traditional treatment strategies. Definitive CRT is now considered a treatment option even in potentially resectable patients. Another factor favoring definitive CRT is that a complete response has been noted in the resected specimen in 15–30% of patients undergoing neoadjuvant therapy followed by surgery [81]. However, persistent disease and risk of local failure after definitive CRT remains a concern. It should be noted that locoregional morbidity need not always be related to the neoplastic process; local toxicity secondary to CRT or mechanical complications such as stricture formation may also be associated. Locoregional recurrence is defined as tumor detected more than 3 months after CRT whereas persistent

disease is the detection of malignancy within 3 months of CRT at the same site [89]. Unfortunately, locoregional control is often quite poor with definitive CRT, and up to 40–60% of the patients have persistent or relapsed tumor at the primary site within 1 year [88]. Moreover, due to radiotherapy associated fibrosis, histological confirmation of the malignancy is achievable in less than 60% of cases [90]. The prognosis is dismal in 11–26% of patients who do not exhibit any morphologic tumor response following definitive CRT (median survival of 9 months) [91]. Salvage esophagectomy is considered the only curative option for a subset of carefully selected patient who have received up to 50 Gy of radiation and who are physiologically fit for surgery. A number of studies have demonstrated the utility of salvage esophagectomy as a therapeutic option in recurrent or persistent disease following definitive CRT [90–98] with a subset of patients being cured after salvage esophagectomy with acceptable long-term outcomes. However, the decision to proceed with salvage esophagectomy is seldom straightforward considering the high postoperative morbidity and mortality associated with this procedure; each case must be evaluated individually. Initial studies examining the utilization of 'salvage esophagectomy' indicated that the procedure was associated with a significantly higher incidence of post-operative mortality, anastomotic leak, pulmonary complications and an increased length of ICU and in-hospital stay [89–99]. Much of this concern originated from the historical impression that surgical resection 4–8 weeks following radiotherapy or CRT was technically more challenging and associated with increased postoperative morbidity and mortality. This opinion has recently been challenged [100] with several publications demonstrating that the selected utilization of salvage esophagectomy in patients who have failed definitive CRT for esophageal SCC resulted in acceptable morbidity and mortality rates [89, 90, 94]. Special attention should be paid to the dose of radiation given: salvage surgery is considered highly morbid when the volume dose of radiation exceeds 55 Gy [90]. A randomized clinical trial assessing long-term outcomes indicated that definitive CRT could potentially cause progressive deterioration in pulmonary function when compared to surgery alone [100].

10.4 Minimally invasive esophagectomy (MIE)

MIE includes total thoraco-laparoscopic esophagectomy, robot-assisted minimally invasive esophagectomy (RAMIE) and hybrid procedures. Over the last decades, MIE has expanded worldwide and is estimated that they account for 15–30% of all esophagectomies performed at present [101, 102]. It seems likely that importance of MIE will exceed that of hybrid techniques. There are now centers that are publishing consecutive series of over 1000 minimally invasive procedures [103]. The approach to esophagectomy varies from center to center, and any decision regarding the surgical approach should be tailored according to individual physiologic and tumor-related issues in each patient [104].

11. Conclusions

Management of esophageal cancer has been refined since the last decades. Surgery continues to play a pivotal role in the treatment of the disease, either alone or in combination with multimodal approach. Progress in anesthesia and in surgery has led to a significant decrease in the mortality rate. Mortality rates average 5% and are under 2% in some experienced and high volume centers. The progress made in the field of minimal access surgery has led surgeons to consider these techniques to reduce the morbidity and mortality that have traditionally been associated with

surgery of the esophagus. Qualified surgeons with a high-level of expertise in high-volume centers are essential in this context to ensure optimal outcomes.

12. Future perspective

Multimodality treatment involving the surgeon, gastroenterologist, oncologist (medical and radiotherapy), radiologist, pathologist, and palliative care physicians is fundamental in the management of esophageal cancer. This serves to individualize treatment, optimize outcomes and ensure the best possible quality of life for the patients. Minimally invasive techniques have been proven to be noninferior to open surgery in terms of oncological safety and will benefit the patient in terms of post-operative recovery. In future, advances in cancer genomics and gene testing can be expected identify key genetic and epigenetic alterations in cancers of the esophagus which initiate the growth and progression of disease. Identification of these genetic alterations may also result in the introduction of targeted therapies which may be individualized based on the molecular profile of the cancer.

Author details

K.V. Veerendra Kumar*, Ramesh Sagar and Joseph Mathew
Kidwai Cancer Institute, Bangalore, India

*Address all correspondence to: veerendra.prof@gmail.com

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