Management of oesophageal cancer

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Abstract Oesophageal cancer is a disease of dismal prognosis. There are variations of epidemiology among different ethnic groups and geographic regions. India is a country with high incidence. This can be attributed to the interplay between environmental, dietary factors and life-style of the population of the country. Optimal therapeutic strategy for patients with oesophageal cancer demands individual consideration.

Majority of oesophageal cancer patients present at an advanced stage of disease. Screening programmes or strategies aiming at early diagnosis can improve the prognosis; unfortunately this is not cost-effective except in very high incidence areas. Accurate staging can help select the most appropriate treatments, such as excluding those patients with metastatic disease who are unlikely to benefit from surgery, and treating very early lesions with endoscopic means. When surgery is indicated, treating patient in a high-volume centre can improve the outcome and minimise complications. Although surgical resection remains the main treatment modality, long-term prognosis after surgical resection alone has been suboptimal except in those with early disease. Multidisciplinary approaches including chemotherapy and radiotherapy with or without surgery are increasingly employed for patients with advanced disease. Collaboration among surgeons, clinical oncologists, radiologists and physicians is of utmost importance to achieve the best results. Treatment for patients should be individualised to enhance outcome.

Keywords Oesophageal cancer · Oesophagectomy · Multimodality treatment

Epidemiology

There have been tremendous improvements in the management of oesophageal cancer in the recent three decades. However, the prognosis of the disease remains poor. Oesophageal cancer is the sixth most common cause of death from cancer worldwide [1]. The overall 5-year survival rate in most countries is only 10–20% after diagnosis. In India, for instance, an average 5-year survival of <12% was reported [2]. Late presentation and early spread of disease are the major factors responsible.

The divergence of epidemiology between East and West also poses additional challenges. For the last three decades, the incidence of oesophageal and gastrooesophageal junction adenocarcinoma has increased dramatically in western countries, and it has surpassed that of squamous cell carcinoma. This latter cell type remains the predominant histological type of oesophageal cancer in the East [3, 4]. This phenomenon of a rising epidemic in adenocarcinoma can be attributed to increase in obesity, gastrooesophageal reflux disease and Barrett's oesophagus [5]. In Asia, the prevalence of obesity and gastrooesophageal reflux disease is much less. It has also been postulated that the high prevalence of *Helicobacter pylori* infection in Eastern populations may offer some degree of protection against reflux and the development of Barrett's oesophagus, thus accounting for the difference in cancer cell type [6]. In India, there has been no convincing epidemiological data to show a significant change of cell type of cancer in the recent two decades [7]. Squamous cell carcinoma remains the predominant histology in India.

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There is great variation in the incidence of oesophageal cancer in different ethnic groups and geographic locations. In China, oesophageal cancer is the fourth most common cancer and the most common cause of cancer death with an age-adjusted mortality of up to 140 per 100,000 [8, 9]. The age-standardised incidence rate of esophageal cancer in China is 27.4 per 10⁵ individual per year [1]. Central and northern parts of China such as Henan and Shanxi provinces have a particular higher incidence [10, 11]. Similar to China, North-East India has a higher incidence compared to other regions of the country [12]. Kashmir valley, for instance, has reported age-adjusted incidence rates of 43.6 and 27.9 per 10⁵ individual per year in men and women, respectively [13]. Other regions in the world that have high incidences include the Caspian littoral of Iran, Normandy in France and Transkei province of South Africa.

The pathogenesis of oesophageal cancer is multifactorial and includes environmental carcinogens, life-style, dietary habits and genetic factors. Poor nutrition, tobacco smoking, betel quid chewing, alcohol consumption are major known risk factors [14]. The dietary risk factors, specifically identified in North-East India are hot salty soda tea, red chillies and high-nitrate diet especially locally grown Brassica leaves [15]. Hot salty soda tea induces chronic irritation of the oesophageal epithelium and predisposes carcinogenic substance to initiate tissue-specific malignant transformation. People who use red chilli pepper in the region have a higher risk [13]. The average daily dietary intake of nitrate in Kashmir valley is 237 mg which is much higher than that reported from most Western countries (Germany 75 mg/day; Britain 95 mg/day) [13]. Reports from southern India suggest that more than 80% of oesophageal squamous cell carcinoma patients are chronic tobacco smokers. This risk-related to smoking is further potentiated by heavy consumption of alcohol and other additional risk factors such as nutritional and vitamin deficiencies [16].

Regardless of causation, the differences in epidemiology, tumour cell type and patient population characteristics have practical implications on treatment strategies. In the following sections, we shall discuss the management for patients with oesophageal cancer, with particular emphasis on stage-directed therapy, options of combined treatment modalities and lastly, the ways to achieve excellent outcome.

Diagnosis

The most common presenting symptom of oesophageal cancer patient is progressive dysphagia. In high-risk areas, elderly patient who complain of dysphagia should be assumed to have oesophageal cancer until proven otherwise. Majority of oesophageal cancer patients present with advanced stage disease because early cancer is asymptomatic and most patients do not seek medical advice until severe dysphagia and weight loss have occurred. The rich submucosal

lymphatics of the oesophagus also facilitate early spread of tumour cells. Patients with squamous cell carcinoma and adenocarcinoma have different demographics. The former group of patients are usually of lower socioeconomic class, are blue-collar workers, chronic smokers and consume much alcohol; while the latter group of patients are of higher socioeconomic class, and have obesity-related co-morbid conditions such as gastrooesophageal reflux disease and ischaemic heart disease.

Diagnosing oesophageal cancer at an asymptomatic or early stage is crucial in improving prognosis. Population screening is possible in high-incidence area like China. Abrasive cytology using inflatable balloon in China or encapsulated sponge in Japan were reported [17, 18]. A 5-year survival rate approaching 90% can be achieved when early cancers are identified with these methods [19]. Endoscopy and systematic biopsies remain the gold standard for diagnosis. Adjunctive techniques such as chromoendoscopy with Lugol's iodine, narrow band imaging and autofluorescence imaging can aid diagnosis of early cancers or even premalignant dysplastic lesions. The Barrett's oesophageal metaplasia-dysplasia-cancer sequence allows introduction of surveillance programmes. There is evidence that patients with Barrett's oesophagus who are recruited into surveillance programmes have a better prognosis than non-surveyed patients [20].

Pretreatment evaluation

When a patient has a diagnosis of oesophageal cancer confirmed, the next step is to stage the disease accurately and to assess the co-morbid conditions of the patient thoroughly. This is crucial in formulating optimal therapeutic strategy. With increasing choices and combinations of therapeutic options, the treatment for early and advanced cancer should be individualised.

Method of staging

The purpose of accurate staging is to plan stage-directed therapy. The staging system is based on the American Joint Committee on Cancer Staging (AJCC) or the International Union Against Cancer (UICC) TNM system. The systems are recently modified and shown in Table 1a, 1b and 1c [21]. The principle of investigation follows that of the staging system, namely, tumour status (T), nodal status (N) and presence of distant organ metastasis (M) [21]. The algorithm for staging oesophageal cancer patients at the authors' institution is shown in Fig. 1. Esophagogastroduodenoscopy, bronchoscopy, percutaneous ultrasound of cervical lymph nodes ± fine-needle aspiration (FNA) cytology and CT scan are routine methods. Bronchoscopy is specially indicated for mid and upper third tumours because of the anatomical proximity; airway involvement

Fig. 1 Investigation algorithm for oesophageal cancer at The University of Hong Kong

precludes surgical resection. Endoscopic ultrasonography (EUS) is readily available in specialised centres and it is regarded as the best staging modality for T and N stage. The accuracy of determining T stage ranges between 85 and 90% and N stage ranges 70 and 90% [22, 23]. 2- ^{18}F fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography (PET) scan is becoming more commonly utilised especially in detecting distant nodal or organ metastasis. Reported sensitivity, specificity and accuracy rates for identifying distant metastasis are 88%, 93% and 91%, respectively but the accuracy of detecting regional nodal disease is still inferior to EUS [24–27]. It has also been used to evaluate the response to neoadjuvant chemotherapy or chemoradiotherapy [28]. The main value of CT scan is to detect distant metastatic or T4 disease. The sensitivity of liver metastasis depends on the size of the lesion, 70–80% for lesion larger than 2 cm and <50% for lesion smaller than 1 cm. For T4 disease, obliteration of the fat plane between the oesophagus and the aorta, trachea and bronchi, and pericardium is suggestive of invasion but the paucity of fat in cachectic patients makes this criterion unreliable. When the area of contact between the oesophagus and the aorta extends for more than 90° of the

circumference, an 80% accuracy of infiltration is reported but is inferior to that of EUS. Normal size lymph node may contain metastatic deposits while enlargement of lymph node may be due to inflammatory reactive response, thus the accuracy of CT scan in detecting nodal metastasis is suboptimal. Nowadays, CT scan is complimentary to PET scan when anatomical enlargement of nodes is correlated with metabolic activity.

Therapeutic strategy

Therapeutic options for oesophageal cancer were limited in the past. Both surgical resection and radiotherapy were used for the purpose of cure or palliation. Oesophageal intubation or stenting was used for palliating dysphagia. Treatment strategies are evolving and these include refinement of surgical techniques, more precise radiotherapy delivering approach, combination of radiotherapy and concurrent chemotherapy, and better design of oesophageal stents. The management algorithm for oesophageal cancer at the authors' institution is shown in Fig. 2.

Table 1a Definitions of T, N, M and G of AJCC staging system

Primary tumour (T)	
Tx	Primary tumour cannot be assessed
Tis	Carcinoma in situ / High-grade dysplasia
T1	Lamina propria or submucosa
T1a	Lamina propira or muscularis mucosae
T1b	Submucosa
T2	Muscularis propria
T3	Adventitia
T4	Adjacent structures
T4a	Resectable tumour invading pleura, pericardium, diaphragm, or adjacent peritoneum
T4b	Unresectable tumour invading other adjacent structures, such as aorta, vertebral body, trachea, etc.
Regional Lymph Nodes (N)	
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 seven or more regional lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Histological 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

Summary of changes of the new AJCC staging system:

- 1 Tis is redefined and T4 is subclassified
- 2 Regional lymph nodes are redefined. N is subclassified according to the number of regional lymph nodes containing metastasis
- 3 M is redefined
- 4 Separate stage grouping for squamous cell carcinoma and adenocarcinoma (table 1b & 1c)
- 5 Stage groupings are reassigned using T, N, M, and G classifications
- 6 Tumour location is simplified, and esophagogastric junction and proximal 5cm of stomach are included

Table 1b Stage grouping of the new AJCC staging system for squamous cell carcinoma

Stage grouping: squamous cell carcinoma					
Stage	T	N	M	G	G location
0	Tis/ HGD	0	0	1, X	Any
Ia	1	0	0	1, X	Any
IIB	1	0	0	2–3	Any
	2–3	0	0	1, X	Lower
IIA	2–3	0	0	1, X	Upper, middle
	2–3	0	0	2–3	Lower
IIB	2–3	0	0	2–3	Upper, middle
	1–2	1	0	Any	Any
IIIA	1–2	2	0	Any	Any
	3	1	0	Any	Any
	4a	0	0	Any	Any
IIIB	3	2	0	Any	Any
IIIC	4a	1–2	0	Any	Any
	4b	Any	0	Any	Any
	Any	3	0	Any	Any
IV	Any	Any	1	Any	Any

Location:

Upper or middle - cancers above lower border of inferior pulmonary vein

Lower - below inferior pulmonary vein

Table 1c Stage grouping of the new AJCC staging system for adenocarcinoma

Stage grouping: adenocarcinoma				
Stage	T	N	M	G
0	Tis (HGD)	0	0	1, X
IA	1	0	0	1–2, X
IB	1	0	0	3
	2	0	0	1–2, X
IIA	2	0	0	3
IIB	3	0	0	Any
	1–2	1	0	Any
IIIA	1–2	2	0	Any
	3	1	0	Any
	4a	0	0	Any
IIIB	3	2	0	Any
IIIC	4a	1–2	0	Any
	4b	Any	0	Any
	Any	3	0	Any
IV	Any	Any	1	Any

R0 resection: microscopic and macroscopic clearance of tumour.

Fig. 2 Management algorithm for oesophageal cancer at The University of Hong Kong

Surgery

Surgical resection for oesophageal cancer was once associated with high morbidity and mortality rates. The operative mortality rate reported was 29% in the 1970s and this improved to 13% in the 1980s [29, 30]. Oesophagectomy is a complex procedure and the outcome can be improved when performed in high-volume centre [31, 32]. In high-volume centres, resection mortality rate of 2–3% is achieved in recent years [33–36]. The reasons of improvement can be attributed to advancement of technology in accurate staging, better patient selection for surgical treatment, refinement of surgical technique, better perioperative and intensive care and centralisation in specialised units [37].

Patient selection

Surgery is justified only when low morbidity and mortality rates can be achieved, and when a reasonable prognosis is expected. A curative (R0) resection with clear resection margin has been persistently shown to be one of the most important prognostic factors in oesophageal cancer treatment. With the availability of other palliative modalities, oesophagectomy with a clear palliative intent

is infrequently performed. Careful pretreatment evaluation of the tumour stage can thus avoid unnecessary palliative resection.

Another factor to consider in selecting patients for this complex surgery is the patient's physiological reserve and ability to withstand the procedure. This assessment is generally based on surgeons' experience and intuition, rather than an exact science, although studies have shown that objective scores can help assess operative risk and patient selection [38, 39]. Cardiopulmonary function, liver and renal function should be stringently evaluated before subjecting the patient for this major surgery. Many factors have been reported to be associated with increased morbidity and mortality rate after oesophagectomy, such as advanced age, poor performance status, nutritional depletion, more proximally located tumour, poor pulmonary function, liver cirrhosis and abnormal cardiac function [39–41].

Operative approach

There are many aspects to consider on deciding the operative approach, which mainly involves consideration on whether a thoracotomy is desirable and the intended extent of lymph node dissection. Surgical expertise, experience and

preference are also important factors. All these will affect the overall outcome.

Transthoracic or transhiatal approach

The controversy on the superiority of transthoracic (TTE) or transhiatal (THE) approach in oesophagectomy remains unresolved over last few decades. The latter method involves a blunt mobilisation of the thoracic oesophagus from the abdomen without a thoracotomy; oesophageal dissection is mostly a peri-oesophageal one with limited lymphadenectomy. Proponents of THE argue that the pulmonary complication rate can be reduced by avoiding a thoracotomy [42], and the benefit of extended lymphadenectomy is unproved. Advocates of TTE claim that the procedure allows more thorough mediastinal lymph node dissection, thus improving the staging accuracy and overall prognosis [43], low complication and mortality rates can also be achieved. When the different tumour types between the East and West are considered (lower oesophageal adenocarcinoma in the West and more proximally located squamous cell cancer in the East), the transthoracic access is more appropriate and safer in the East. The common practice of more extended mediastinal nodal dissection in the East also makes TTE the preferred method. In Western countries, both TTE and THE have their advocates. However even in the Netherlands, a recently published randomised control trial comparing TTE and THE for patients with adenocarcinoma of the lower oesophagus and cardia showed that there was a survival advantage for TTE in those with limited nodal disease (1–8 positive nodes), though a slightly higher postoperative pulmonary complication rate was found [44]. With either approach, the surgical procedure should be performed properly and preferably in specialised centres, a clear resection at proximal, distal and axial margins can provide maximum survival benefit to the patients.

Regardless of whether a transthoracic approach is used, the propensity of submucosal spread demands a sufficiently long proximal resection margin; thus for patients with upper third tumours, a cervical anastomosis is indicated; in patients with middle or lower third tumours, a choice exists for an intrathoracic or cervical anastomosis. At the authors' institution, current preference is for tumours at any level to have a cervical anastomosis. This maximises the proximal resection margin, and also allows the most thorough mediastinal lymphadenectomy. In addition, most resections are performed using a minimally invasive approach, and an intrathoracic anastomosis is technically more demanding compared to a simple hand-sewn anastomosis in the neck.

Minimally invasive surgery

Minimally invasive surgery (MIS) has dramatically altered

surgical practice. Application of MIS in oesophagectomy was first introduced by Cuscheri in early 1990s [45]. A variety of MIS techniques have evolved but a single best method has not been accepted [46]. These include different combinations of thoracoscopy, laparoscopy, thoracoscopic-assistance (with mini-thoracotomy) and laparoscopic-assistance (with mini-laparotomy). The most popular approach is perhaps thoracoscopic oesophageal mobilisation with laparotomy [47–50]. The reported advantages of MIS include better cosmetic outcome, less blood loss, analgesic requirement, pulmonary complication rates, recurrent laryngeal nerve injury, shortened intensive care or hospital-stay. There have been few studies that directly compare the open procedure to minimally invasive oesophagectomy; conclusive result of which approach is superior is lacking. A learning curve does exist for this complicated procedure [51].

Lymph node dissection/extent of dissection

Related to the THE versus TTE debate detailed above, is the controversy related to the extent of lymph node dissection. Proponents of extensive lymphadenectomy believe that more accurate pathological staging can be achieved, local control of the disease is better and long-term survival is improved. On the contrary, others claim that extensive nodal dissection only leads to stage migration without improving the overall prognosis, and should complications occur, postoperative recovery and long-term quality-of-life are adversely affected.

Three-field lymph node dissection (3-FL) was pioneered in Japan that entails lymph node dissection of the upper abdomen, mediastinum and both sides of the neck [52]. Although it could be demonstrated a significant proportion of patients will have preoperatively unsuspected cervical nodes after 3-FL, whether its routine application would lead to better prognosis remains controversial. Such high-risk surgery should only performed in specialised centre. Current staging system defines regional nodes as extending from the neck through the mediastinum to the celiac axis. However, most would recommend a two-field lymphadenectomy for lower and middle third tumours, while additional cervical lymphadenectomy should be performed for upper third tumours. There is increasing evidence to show that extended lymphadenectomy is related to survival. One international multicentre study showed that the number of lymph nodes resected was an independent prognostic factor in addition to age, gender, cell type, presence of nodal metastases, number of nodes involved, and depth of tumour invasion [53]. A recent international multicentre study shows that in order to maximise survival, the optimal number of lymph node that should be dissected is related to the T stage: 10 nodes should be resected for T1 lesions, 20 for T2, and 30 or more for T3/T4 disease [54]. Of course, in practice it is impossible to count the

number of nodes removed at the time of surgery, this is merely used in retrospect to assess the quality and adequacy of lymphadenectomy. One should aim at resecting as many regional nodes as possible to provide therapeutic benefit in terms of locoregional disease control and long-term survival, balancing the extent of lymphadenectomy with morbidity.

Combined multimodality treatment

In multimodality treatment, surgery, chemotherapy and radiotherapy are combined. Owing to the geographic difference in epidemiology and results of locally conducted clinical trials, the use of multimodality treatment varies among different countries. In the United Kingdom, preoperative chemotherapy followed by surgical resection is a well accepted treatment whereas in United States, chemoradiation is more widely practiced. In Asia, surgical resection remains the main treatment strategy in resectable cancer although increasingly multimodality treatment is being explored.

In the United Kingdom, the MRC trial (OE02) randomised 802 patients to a surgery alone or a preoperative chemotherapy (two courses of cisplatin and 5-fluorouracil [5-FU]) followed by surgery group [55]. It demonstrated a superior survival in the preoperative chemotherapy plus surgery group. This trial has changed practice in the United Kingdom, making neoadjuvant chemotherapy a standard-of-care. Although cisplatin combined with 5-FU is the most commonly used regimen, other chemotherapeutic agents have been studied. Combination of paclitaxel and platinum compounds is given frequently and response rates ranging from 40% to 52%, higher than that of cisplatin - 5-FU, have been reported. Pathological complete response rate of around 15% is obtained, whereas generally a <10% complete response rate is seen with cisplatin - 5-FU combinations [56, 57].

In the United States, chemoradiation has gained popularity since the publication of the landmark study Radiation Therapy Oncology Group (RTOG 85-01) trial of chemoradiation versus radiotherapy in the early 1990s. This study demonstrated superiority in local and distant control as well as overall survival in patients who received chemoradiation than those treated with radiotherapy alone [58, 59]. The 5-year survival rate reported in RTOG 85-01 was 26% for chemoradiation compared with 0% for radiation alone. This survival rate was claimed to be comparable to surgery alone. Chemoradiation has been recommended as an alternative treatment option for surgery particular in those with poor surgical risk. Direct comparison with surgical resection is lacking; the role of chemoradiation as neoadjuvant therapy has been widely investigated both for squamous cell carcinoma and adenocarcinoma, respectively, the results have been conflicting [60]. It seems

that for early cancers where a R0 resection can be carried out with confidence, surgical resection alone can be performed. In patients with more advanced cancers, neoadjuvant therapy is a clear option. In summary, multimodality therapy is gaining popularity. How to select the most appropriate combination of treatment for individual patient remains a challenge. Close collaboration between different specialties or regular meetings involving multidisciplinary experts probably can help in the therapeutic strategy formulation process.

Palliation

The most common symptom that requires palliation in advanced staged oesophageal cancer is dysphagia. Other symptoms that require palliation include cancer pain, odynophagia, malnutrition, or aspiration related to presence of tracheoesophageal fistula. For palliation of dysphagia, various endoscopic methods are available including placement of an oesophageal prosthesis, laser therapy, electrocoagulation, intralesional injection of various substances, and photodynamic therapy. The most popular is perhaps insertion of self-expanding metallic stents (SEMS) [61]. A major advantage of SEMS is that it can quickly relieve dysphagia safely. Potential complications associated with SEMS are stent migration, tumour ingrowth, acid reflux (if stent is placed across the gastrooesophageal junction). Foreign body sensation, pain, odynophagia and airway compression are the main potential problems if the stenting zone is close to the cricopharyngeus.

Summary

Improvements have been made in the management of oesophageal cancer. Therapeutic options are evolving. Surgeons play a vital role in the management of this disease. How to best integrate surgical resection with other non-operative programmes remains a challenge. Screening in high incidence area is an approach to achieve diagnosis at an early stage that can improve the prognosis of this deadly disease. Advancement of technology allows more accurate staging and provides guidance on patient selection for different therapeutic options. The procedure of surgical resection is complicated and centralisation in specialised units may reduce the morbidity and mortality rates. Extent of surgical resection should be balanced between the risk and benefit. Chemoradiation and other non-operative treatment programmes are gaining popularity but they are not without risks. Treatment of patient should be individualised and close collaboration among multidisciplinary specialists in formulating therapeutic strategy is the key to achieve success.

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