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The Management of Oesophageal Cancer: The Surgeon's Perspective

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Introduction

Oesophageal cancer ranks seventh in terms of incidence and sixth in mortality overall, being responsible for one in every 18 cancer deaths in 2020 worldwide[1]. There are two main histological types: squamous cell carcinoma and adenocarcinoma. The overall 5-year survival of patients diagnosed with oesophageal cancer is approximately 15%[2]. Apart from some areas in Asia, there is no screening programme worldwide. Hence, patients often present with advanced disease stage and cure is seldom possible. Some 50-60% of patients can be offered treatment with curative intent including surgical and non-surgical modalities[3]. Disease stage, patient's fitness/frailty and expertise of the multidisciplinary team guide decision making.

Anatomy of the oesophagus (figure 1)

The oesophagus is a 25 cm long fibromuscular tube extending from the hypopharynx to the stomach. It lies posterior to the trachea and the heart and passes through the mediastinum and the hiatus in its descent from the chest to the abdomen. It is subdivided into three segments related to anatomical boundaries. Typical endoscopic measurements of each region measured from the incisors depend on body size and height[4,5]:

- Cervical oesophagus: begins at the lower end of pharynx (level of 6th vertebra or lower border of cricoid cartilage) and extends to the thoracic inlet (suprasternal notch); 18-20cm from incisors.
- Thoracic oesophagus: the oesophagus in the thoracic cavity:
    - Upper thoracic: from thoracic inlet to lower border of the azygos vein; from 18-20cm to 23-25cm.
    - Middle thoracic: from lower border of the azygos vein to lower border of the inferior pulmonary vein; from 23-25cm to 30-32cm.
    - Lower thoracic: from lower border of the inferior pulmonary vein to the stomach, including the oesophagogastric junction; from 30-32cm to 40-42cm.
- Abdominal oesophagus: part of lower thoracic oesophagus, it involves the OGJ positioned at the diaphragm/upper abdomen; 40-42cm.

The oesophagogastric junction (OGJ) is the region where the oesophagus joins the stomach. The gastric cardia is the area of mucosa distal to the OGJ and proximal to the oxyntic mucosa of the gastric body, also known as cardiac orifice (the opening of the oesophagus into the stomach). The location of oesophageal cancer is defined by the epicentre of the tumour. According to the Siewert classification,

a cancer of the OGJ is defined as a tumour whose epicentre is located within 5 cm proximal and distal of the OGJ. Siewert type I indicates an epicentre 1-5 cm above the OGJ; type II (cardia cancer) with a centre within 1 cm above and 2 cm below OGJ; type III centre 2-5 cm below the OGJ. Siewert types I and II are staged according to the TNM-system of oesophageal cancers whereas type III, even if the OGJ is involved, are staged according to the principles of gastric cancer.

Diagnostic work-up and staging

Oesophageal cancer is often categorized as early (cT1-T2 N0 M0), locally advanced (cT3-T4 and/or cN1-N3 M0) or metastatic disease (M1) (see Table 1). Clinical staging involves an upper GI endoscopy. The upper and lower border of the tumour (in relation to the incisors), traversibility, and other important landmarks (Z-line, gastric folds, impression of diaphragm) are carefully registered. Multiple biopsies are taken from the tumour for histological assessment. Histological type (adenocarcinoma, squamous cell carcinoma and others) and grade of differentiation are reported by the pathologist. Endoscopic ultrasound (EUS) +/- fine needle aspiration (FNA) of suspicious lymph nodes has the highest accuracy for T- and N-staging. A high resolution CT-chest-abdomen with intravenous contrast is mandatory to assess the relation of the tumour with surrounding anatomical structures and locoregional and distant nodal or organ metastases. A full body PET-CT scan is routinely performed to exclude distant metastases. If the tumour is located at or above the level of the carina, a tracheobronchoscopy should be performed to exclude invasion of the tracheobronchial tree as this influences the plan of treatment. For oesophageal squamous cell carcinoma (SCC), assessment of the patient by an ear, nose and throat (ENT) specialist should be considered to exclude a second primary tumour of the upper aerodigestive tract given common risk factors (tobacco and alcohol).

Surgical treatment

Oesophagectomy carries a risk of death within 90-days after surgery in the order of 5%. Postoperative complications are seen in 60% of patients[6]. Indications for surgical resection should be discussed and agreed by a multidisciplinary tumour board (MTB) including an oesophagogastric surgeon, medical oncologist, radiotherapist, radiologist, pathologist and gastroenterologist. When oesophagectomy is considered the best treatment option, the patient's fitness for surgery should be carefully assessed, balancing the risks and benefits of surgery for the individual with the aim to obtain the best outcome in terms of survival and quality of life (QOL).

Tumours located at least 3-5cm from the cricopharyngeus muscle (UES) up to and including the OGJ (Siewert I-II) should be considered for oesophagectomy. Cervical or cervicothoracic oesophageal carcinomas are preferably treated with definitive chemoradiation (dCRT) as laryngo-pharyngo-esophagectomy with a tracheostomy is otherwise needed in these patients, which carries a considerable high risk along with a very significant morbidity over speech and swallowing functions[7].

Early-stage cancer

For early-stage disease (pTis-T1am1/m2N0 squamous cell carcinoma, or superficial pT1a-T1bsm1N0 adenocarcinoma) with histological low risk features (no lymphovascular invasion, well or moderately differentiated carcinoma, diameter ≤2cm, no ulceration) endoscopic resection is often the treatment of first choice given the organ sparing character, lower treatment-related morbidity and better quality of life[8-10].

Locally advanced cancer

Patients with limited locoregional (cT1-T2 cN0 M0) and locally advanced (cT3-T4a or cN1-3 M0) disease are considered candidates for surgery. Tumours with organ metastases and non-regional lymph node involvement, OGJ tumours with supraclavicular lymph node involvement, and T4b tumours with involvement of the heart, great vessels, trachea, vertebrae or adjacent organs including liver, pancreas and spleen are considered unresectable and incurable[8-10].

Primary oesophagectomy has been the standard for many decades. Historically, a fair proportion of patients had tumour-positive resection margins (R1) and overall survival was only 35-40%. Preoperative chemotherapy or chemo-radiotherapy was introduced to minimize the risk of irradical resections and to decrease the development of locoregional and/or distant recurrences. Neoadjuvant chemotherapy or chemoradiotherapy followed by oesophagectomy improve overall survival as compared to surgery alone without a substantial impact on postoperative morbidity and mortality[11,12]. Currently, controversy exist regarding which therapy is superior. Radiotherapy aims to maximize locoregional disease control while chemotherapy has the potential to eliminate micrometastases. However, no robust evidence on the optimal neoadjuvant treatment has been obtained as yet. Large randomized controlled trials like the Neo-AEGIS-II and ESOPEC are now addressing this topic[13].

Non-surgical treatment

Definitive chemo-radiotherapy (dCRT) has been reserved for those patients who are deemed unsuitable for surgery due to poor performance status, comorbidities and/or extent of disease (cT4b), and also for those unwilling to undergo oesophagectomy. It achieves survival rates of 35–40% at 2 years and about 20% at 5 years, although with higher rates of local recurrence and persistent disease compared to multimodal therapy[7,14]. Particularly, SCC histology and stage I disease respond favourable to dCRT (3-year survival rate up to 42%)[14]. It is a good alternative in frail and elderly patients[15], in whom oesophagectomy would lead to unacceptable high morbidity and mortality. As discussed earlier, dCRT is recommended for cervical oesophageal carcinomas. The outcomes of dCRT in cervical oesophageal cancer are comparable to upfront surgery, but with the significant advantage of preservation of laryngeal organ function, such as speech and swallowing. Distant metastasis, rather than local recurrence, is the most common pattern of failure in these patients[7].

Surgical approach

Oesophagectomy for cancer should aim at a radical (margin-negative) resection of the primary tumour and locoregional lymph nodes. It is recommended to resect a minimum number of 15 lymph nodes for adequate nodal staging but this can only be determined once the resection has been done[8]. Oesophageal cancer may advance via submucosal lymphatic channels and this should be carefully assessed at clinical staging and during surgery. This may influence how much oesophagus and/or stomach that needs to be resected in order to achieve a tumour-free margin[16]. For an optimal locoregional lymphadenectomy, a transthoracic approach is recommended as it has demonstrated a higher lymph node yield compared to the transhiatal (abdomen and neck) approach[8,9,17]. It remains unclear if a more extended resection also increases the chance of long term survival. The type of oesophageal resection is dictated by the location of tumour, location and risk of lymph node metastases, as well as the available choices for restoration of continuity. A gastric tube is preferred over the colon or jejunum given the accessibility and better postoperative functional outcomes.

The two main surgical approaches are transhiatal and transthoracic oesophagectomy. In the transhiatal technique, access to the distal thoracic oesophagus (up to the pulmonary veins) is achieved through the abdominal cavity. A cervicotomy is performed to transect the cervical oesophagus. The mid-thoracic oesophagus is bluntly dissected or removed with a vein stripper. Only peri-oesophageal lymph nodes around the distal oesophagus and in the abdomen can be removed whilst subcarinal and paratracheal nodal stations are left in situ. Transthoracic oesophagectomy involves opening of the chest (usually right chest) to dissect the oesophagus under vision and perform a mediastinal nodal dissection. The abdomen is entered for gastrolysis, creation of a gastric tube and nodal dissection. The two most common operations are the Ivor-Lewis technique, in which an intrathoracic oesophagogastric anastomosis is performed, and the McKeown technique, in which the oesophagus is transected via a cervicotomy and the anastomosis is created in the neck. Often the preference of the surgeon determines which technique to use. However, transhiatal oesophagectomy is associated with less pulmonary and cardiac complications and is thus mainly used for frail patients. The Ivor-Lewis

oesophagectomy is associated with less swallowing and speech issues and less problems with gastric conduit emptying and gastroesophageal reflux, as compared to the McKeown technique. Moreover, the anastomotic leak rate is lower for Ivor Lewis (12.3%) compared to McKeown (34.1%), according to a recent randomized clinical trial from the ICAN research group, although in case of a leak, the clinical consequences and management of the leak might be more troublesome with an anastomosis located in the mediastinum[18].
Recommended main surgical options and approaches according to tumour location are summarized in figure 1. Minimally invasive strategies -total laparoscopic and thoracoscopic, robotic assisted or hybrid approaches- may be associated with decreased postoperative mortality, shorter recovery times, and increased long-term survival, in comparison with the open approach[8,19]. Guidelines emphasize that oesophagectomy should always be performed in high-volume centres by experienced surgeons, where better postoperative short and long-term results have been demonstrated[20].

How to select patients for a treatment?
As many patients diagnosed with oesophageal cancer are older than 70 years, patient's fitness should be carefully assessed including any comorbidities, (history of) smoking and alcohol use. Although age and comorbidity are not clearly implemented in current treatment guidelines, they should also be taken into account when balancing risk and benefits before any therapeutic intervention[21]. It is important to judge if surgery is a realistic treatment option and if neoadjuvant chemo(radio)therapy treatment can be applied. For non-curative treatment options, symptoms that can be relieved by palliative interventions should be focused at. Current clinical practice guidelines recommend using the ECOG (Eastern Cooperative Oncology Group) scale and/or the Karfnofsky score (see table 2) in order to measure patient's performance status (PS) and assess the medical fitness for any oncological treatment[8-10]. The discussion of treatment options with the patient should follow a shared decision-making model, where the patient's wishes and preferences for treatment, and the impact of the disease and treatment on quality of life are all taken into consideration.

When the tumour is resectable, and if the patient is considered medically fit for surgery, further evaluations may be needed to assess patient's fitness for surgery. Although there is no consensus, patients aged 75 years or older are generally recognized as elderly[22,23]. There is no absolute contraindication for surgery in elderly patients but clinical trials on which the guidelines are based often exclude elderly[24]. Although some suggest that octogenarians may not benefit from oesophagectomy[22], others state that functional rather than chronological age is more important in decision-making. The consultation of a geriatrician can be very helpful[21,22,24]. Frailty should be routinely assessed in all patients, because a large proportion of older cancer patients are frail or pre-frail[25]. This leads to treatment-associated negative outcomes, including postoperative morbidity and mortality[26]. Assessment of frailty and QOL assessment seem to provide more prognostic information than performance status alone[27,28], but there is still a lack of universally-accepted standard tools for evaluation.
Recently, on the basis of 10 preoperative variables (age, BMI, sex, ECOG performance status, history of myocardial infarction, connective tissue disease, peripheral vascular disease, liver disease, neoadjuvant treatment, and hospital volume), a risk prediction model of 90-day mortality after oesophagectomy for cancer was developed[29]. The model was created and validated based on a retrospective analysis of a total of 8403 patients from 39 institutions in 19 countries, using the International Esodata Study Group (IESG) database, the largest existing prospective, multicentre cohort reporting standardized postoperative outcomes. Although still independent validation of the risk score is needed, the model is easily accessible, provides an adjustment scoring system that permits comparison between practitioners and institutions, and provides an evidence-based schema for allocation of the most appropriate treatment on individual patient, so promisingly it could help in the decision-making process when surgery is being considered. Moreover, the cardiopulmonary fitness of

the patient is predictive of postoperative major morbidity[30]. Involvement of the anaesthesiologist in patient selection, preoperative and postoperative management has been associated with a lower rate of complications. Therefore, it is strongly recommended to have a specialized anaesthesiologist as part of the MTB[31]. Some tools for the assessment of frailty, performance status and quality of life are shown in table 3. Figure 2 summarizes the evaluation of a patient with oesophageal cancer and the treatments available according to disease stage and patient characteristics.

New developments and future perspectives

New treatments for oesophageal cancer patients are mainly focused on improving life expectancy with better quality of life at lower costs. Immunotherapy aims to increase and restore the immune system's ability to detect and destroy cancer cells by modifying and/or blocking co-stimulatory signals. Phase II and III trials suggest a survival benefit in oesophageal cancer patients treated with immune checkpoint inhibition[32]. Also targeted therapy, i.e., drugs to target specific genes and proteins that are involved in the growth and survival of cancer cells has been introduced. A selection of important drugs used in the treatment of oesophageal cancer are shown in table 4. At present, there are about 40 ongoing trials and 14 recently published trials with preliminary data. In the phase-III CheckMate-577 study, patients after neoadjuvant chemo-radiotherapy followed by oesophagectomy for stage II or III cancer were randomized to adjuvant nivolumab or placebo[33]. Disease-free survival was significantly longer among those who received nivolumab adjuvant therapy than among those who received placebo. Therefore, nivolumab is currently approved by the EMA (European Medicines Agency) and the FDA (Food and Drug Administration, USA) as adjuvant monotherapy for patients with completely resected oesophageal or OGJ cancer with residual pathologic disease who have received neoadjuvant chemo-radiotherapy. In addition, other immunomodulatory approaches such as peptide vaccines and tumour infiltrating lymphocytes (TILs) are currently under development.

Another new direction in the treatment of oesophageal cancer is active surveillance. After neoadjuvant chemo-radiotherapy, roughly half of the patients with squamous cell carcinoma and a quarter of those with adenocarcinoma have a pathological complete response (pCR) of the primary tumour before surgery. Thus, the necessity of standard oesophagectomy after neoadjuvant chemo-radiotherapy is now being called into question. The Surgery-As Needed-for Oesophageal Cancer (SANO) study group is currently evaluating active surveillance as a valid alternative to standard surgery in patients with a complete clinical response after neoadjuvant chemo-radiotherapy[34-36], the first results are expected late 2023.

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Tables and figures

- Table 1. TNM categories and clinical staging of oesophagus and oesophagogastric junction cancer, according to AJCC Cancer Staging Manual, 8th edition [3].
- Table 2. Comparing the ECOG Performance Status and the Karnofsky Performance Status Scales.
- Table 3. Some tools examples for patient's fitness-for-surgery assessment.
- Table 4. Biologic targeted agents and checkpoint inhibitors under assessment for oesophageal cancer.
  HER-2: Human Epidermal Growth Factor Receptor-2; PD-1: programmed cell death receptor 1; PD-L1: programmed cell death ligand 1; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; VEGF: vascular endothelial growth factor; EGFR: epidermal growth factor receptor.
- Figure 1. Recommended oesophageal resections according to the location of the tumour.
  *The preferred surgical treatment for Siewert type I is partial oesophagectomy with transthoracic mediastinal lymph node dissection, but for type II both partial oesophagectomy with mediastinal lymph node dissection or total gastrectomy with extension of the resection to the distal oesophagus may be valid.
  &Cervical or cervicothoracic oesophageal carcinomas less than 3-5cm from the cricopharyngeus should be treated with definitive chemoradiation.
  #A proximal safe resection margin of at least 3.5-5cm must be ensured for a complete resection (R0) and to decrease the risk of local recurrence.
- Figure 2. Simplified decision-making flowchart to be followed by the MTB when an oesophageal cancer is diagnosed.
  ADC: adenocarcinoma; SCC: squamous cell carcinoma; ENT: ear-nose-throat; dCRT: definitive chemoradiation.