Changing expectations of surgery for oesophageal cancer

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Oesophageal cancer has traditionally posed a significant challenge for clinicians; however evidence demonstrates that patient outcomes have consistently improved with time. The National Oesophago-Gastric Cancer Audit (NOGCA) was set up in 2006 to improve the quality of care received by this patient population in England and Wales.

The 2014 NOGCA reported on 22,832 patients data collected over a two year-period [1]. This revealed reduced 30 and 90 day mortality for oesophagectomies at 2.4 and 4.4% respectively, compared to 3.8 and 5.7% from the 2010 report. One third of patients undergoing oesophagectomy developed an inpatient postoperative complication – most frequently respiratory – reflecting no significant change from 2010.

In the USA, the Surveillance, Epidemiology and End Results Program (SEER) of the National Cancer Institute has shown a progressive improvement in 5-year relative survival for oesophageal cancer from 12.1% in 1990 to 20.1% in 2011 [2].

There is a multifactorial basis for these advances including: (i) centralisation of oncology and surgical services; (ii) development of novel staging investigations; (iii) precise patient selection and anaesthetic assessment of fitness for surgery; and (iv) incorporation of neoadjuvant chemotherapy/chemoradiotherapy into treatment regimes.

Background

Oesophageal squamous cell carcinoma (SCC) remains the predominant histological subtype of oesophageal cancer worldwide, however in several Western countries including the UK and USA, the incidence of oesophageal adenocarcinoma has rapidly risen to exceed that of SCC. Oesophageal cancer represents the sixth leading cause of cancer-related mortality and is the eighth most common cancer worldwide.

Diagnosis

Early detection of the symptoms and signs of oesophageal cancer is paramount in maximising patient survival, as the best outcomes are achieved for patients with early stage disease.

Tobacco use and excessive alcohol consumption are strongly linked with oesophageal SCC [3]. Barrett's oesophagus, symptomatic gastro-oesophageal reflux disease and obesity [4] represent key risk factors for oesophageal adenocarcinoma. Patients with these risk factors require a lower threshold for further investigation.

Classical symptoms include progressive dysphagia and weight loss. Advanced disease may present with cough, recurrent lower respiratory tract infections or hoarseness as a result of tracheobronchial invasion or recurrent laryngeal nerve palsy.

Oesophagogastroduodenoscopy (OGD) is the initial investigation to establish the diagnosis through biopsy and evaluate the macroscopic extent of proximal and distal tumour invasion.

Staging

Once the diagnosis is confirmed, staging investigations are undertaken to define the small population of patients with operable disease. A CT scan of the chest, abdomen and pelvis is initially performed to provide information regarding local spread, lymph node involvement and the presence of metastases. The introduction over the last decade of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), endoscopic ultrasound (EUS) and diagnostic laparoscopy have enhanced the accuracy of this process.

FDG-PET

The primary role of FDG-PET is to identify occult metastases which therefore preclude curative resection. A prospective multicentre trial demonstrated that FDG-PET identified biopsy-proven distant metastases in at least 4.8% of patients with no evidence of metastatic disease on standard workup [5]. FDG-PET revealed metastases in an additional 3.7% of cases, though these lesions were not pathologically confirmed. This imaging modality may also be useful in assessing the response to induction chemotherapy, thereby highlighting patients who will benefit from completion of neoadjuvant chemotherapy prior to oesophagectomy [6].

EUS

Endoscopic ultrasound allows accurate assessment of the depth of tumour infiltration through the oesophageal wall, as well as providing information on nodal status. EUS delivers greater sensitivity but lower specificity than CT or FDG-PET for the identification of regional lymph node metastases [7]. Its performance is enhanced by the addition of EUS-guided fine needle aspiration for cytological differentiation between reactive and malignant lymph nodes. Furthermore, EUS demonstrates higher sensitivity for the detection of coeliac lymph node metastases than CT [7].

EUS examination is limited by its depth of penetration of approximately 5cm and the potential inability to traverse tight malignant strictures leading to an incomplete examination.

Diagnostic laparoscopy

Laparoscopy (and/or thoracoscopy) provides greater accuracy than FDG-PET for the identification of distant metastases, particularly for lesions less than 1 cm in diameter. It also confirms lymph node metastases with superior sensitivity than CT, EUS or MRI [8]. Simultaneous peritoneal fluid cytology can detect malignant cells, providing evidence of peritoneal dissemination in the absence of macroscopic metastases. However this procedure necessitates general anaesthesia, engenders potential morbidity and is more expensive than noninvasive techniques.

Management

Mucosal tumours

Endoscopic mucosal resection and/or ablation are increasingly employed for the treatment of Barrett's oesophagus with high-grade dysplasia and squamous cell carcinoma or adenocarcinoma limited to the mucosa (T1a). Observational studies have shown that with adjustment for patient and tumour factors, those who received endoscopic treatment had similar overall survival-times when compared to patients treated with surgical resection [9]. However a recent systematic review regarding endoscopic and surgical management of mucosal and submucosal disease revealed positive resection margins in 33% and local recurrence in up to 17% of patients treated endoscopically [10]. Although mucosal tumours are considered low risk for lymph node involvement, surgical resection specimens of mucosal tumours revealed multifocal neoplasia, lymphovascular invasion or nodal metastases in a third of patients prompting some to suggest that endoscopic therapy should be reserved for patients at high surgical risk [11]. However, in experienced hands this remains a very effective treatment for early disease.

Locally advanced disease

Tumours that have invaded through the muscle layer (>T2) with lymph node involvement are defined as locally advanced. Current optimal management consists of neoadjuvant chemotherapy or chemoradiotherapy combined with oesophagectomy. The introduction of neoadjuvant therapy has improved the outcomes for this stage of disease. Meta-analysis of ten randomised controlled trials (RCT) comparing preoperative chemotherapy versus surgery alone for resectable thoracic oesophageal cancer, revealed a survival advantage and significantly higher rate of complete (R0) resection with chemotherapy [12]. A further meta-analysis demonstrated that perioperative chemotherapy for adenocarcinoma of the lower oesophagus, gastro-oesophageal junction and stomach conferred a 9% absolute improvement in survival at five years: from 23% for patients treated with surgery alone to 32% for those who received perioperative chemotherapy [13].

Advanced and recurrent disease

Patients with metastatic or disseminated oesophageal cancer are considered to have advanced disease. Symptomatic relief from obstructive symptoms can be achieved with endoscopic stenting or intraluminal brachytherapy. Palliative chemotherapy agents are selected based on predicted response, performance status and toxicity profile. Two small RCTs have compared chemotherapy with best supportive care for metastatic disease and did not demonstrate any survival benefit [14].

Recent interest has focused on the human epidermal growth factor receptor 2 (HER2) oncogene as a potential target. The prevalence of HER2 positive disease in patients with oesophageal cancer is 26%, with a significantly higher rate within the squamous cell carcinoma population [15]. A recent meta-analysis of patients with oesophageal cancer demonstrated a decreased average survival rate of 7 months for cases with HER2 positive disease [15]. The randomised controlled Phase III ToGA trial [16] comparing the monoclonal antibody trastuzumab and chemotherapy versus chemotherapy alone for advanced or metastatic gastric and gastro-oesophageal cancer, revealed a 2.7 month improvement in median overall survival for patients treated with trastuzumab. It is hoped that similar results will be observed within the oesophageal cancer population.

Surgical Management

Centralisation of the treatment of patients with oesophageal cancer is thought to improve outcomes. A meta-analysis assessing the relationship between surgeon or hospital volume and outcomes following oesophagectomy identified a significant pooled estimate effect size in favour of high volume settings for both postoperative mortality and survival [17]. Similar results were seen for high volume surgeons though these did not reach statistical significance.

The precise surgical approach is determined by the location of the tumour. These include the two-stage Ivor Lewis oesophagectomy with combined abdominal and right transthoracic access, as well as the thoracoabdominal approach and the three-stage McKeown oesophagectomy involving a laparotomy, thoracotomy and cervical anastomosis. Transhiatal oesophagectomy can also be performed for distal tumours.

Minimally invasive surgical techniques are being increasingly employed in an attempt to mitigate the otherwise significant potential morbidity incurred with open oesophagectomy. Single-lung ventilation in the lateral decubitus position together with a painful thoracotomy wound are thought to contribute to atelectasis and subsequent pulmonary complications [18]. In contrast, the thoracoscopic stage of the minimally invasive oesophagectomy is typically performed in the prone position with only partial right lung collapse. There is currently little evidence of significant differences in outcomes compared to open surgery.

Enhanced recovery after surgery (ERAS) pathways streamline care in the postoperative period. In the context of oesophagectomy these have been shown to reduce length of stay with associated cost savings [19]. A recent systematic review and pooled analysis of studies comparing outcomes between conventional postoperative care and ERAS suggested reduced incidence of anastomotic leak and pulmonary complications with no significant change in postoperative mortality or rate of readmission [20]. Enteral feeding is initiated at an early stage as part of ERAS to meet patients' nutritional requirements, although controversy persists regarding the optimal postoperative point at which it should be initiated.

Conclusion

Oesophageal cancer poses a significant challenge even when treatment is initiated at an early stage. Advances in staging techniques allow more accurate

classification of patients to better inform treatment choices. Anaesthetic assessment of fitness for surgery precisely selects patients capable of withstanding an oesophagectomy. This targeted patient selection inherent to current practice forms a key part of raising the expectations of oesophageal surgery. It is only offered to patients who will both benefit from the intervention and who can be expected to make a good postoperative recovery.

Parameters of effective surgical treatment are improving as evidenced by the 2014 NOGCA data, and the application of minimally invasive surgical techniques is expected to enhance the postoperative recovery phase. The integration of oncological and surgical advances is hoped to contribute to the continued progress in the management of this complex disease.

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