Oesophageal cancer

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Abstract

There are two main types of Oesophageal Cancer, Squamous Cell Carcinoma (SCC) and Adenocarcinoma (ACA). SCC usually affects the middle third of the oesophagus and is associated with smoking, alcohol and low socio-economic status. ACA affects the lower third of the oesophagus and is associated with gastro-oesophageal reflux disease. The UK has the highest incidence of ACA in the world and it is rising. Treatment may be palliative or curative. Curative treatment for advanced disease consists of Neo-adjuvant chemotherapy or chemoradiotherapy followed by surgery. In the UK the most common operation is a two-phase Ivor-Lewis oesophagectomy. Increasingly surgery is carried out with a minimally invasive approach. Modern management has reduced the morbidity and mortality of the peri-operative period but progress in long-term survival has been slow. Enhanced peri-operative patient pathways and stratified therapies (according to characteristics of the tumour at the molecular level) offer the promise of further improvements. On-going clinical trials are assessing the role of monoclonal antibodies in the treatment of oesophageal cancer.

Keywords Diagnosis; epidemiology; esophageal neoplasms; esophagectomy; pathology; radiotherapy; immunotherapy; enhanced recovery; neoadjuvant:

Epidemiology

There were 456,000 new cases of oesophageal cancer worldwide in 2012. The majority, 398,000, were SCC's with over 315,000 of those cases in Central and South-East Asia and 210,000 cases were in China alone. 52,000 were adenocarcinomas and 6,000 were other cancers (neuroendocrine, lymphoma, choriocarcinoma, etc.). The worldwide incidence of oesophageal SCC is 5.2 per 100,000 but is substantially higher in males (7.7 per 100,000) than in females (2.8 per 100,000). Oesophageal adenocarcinoma (ACA) has a global incidence of 0.7 per 100,000. In many developed countries, however, the incidence of adenocarcinoma exceeds that of SCC. This is especially true of the UK and The Netherlands but is also true in North America, Australasia and Scandinavia. The United Kingdom has the highest incidence of oesophageal adenocarcinoma in the world: 7.2 per 100,000 in men and 2.5 per 100,000 in women(1).

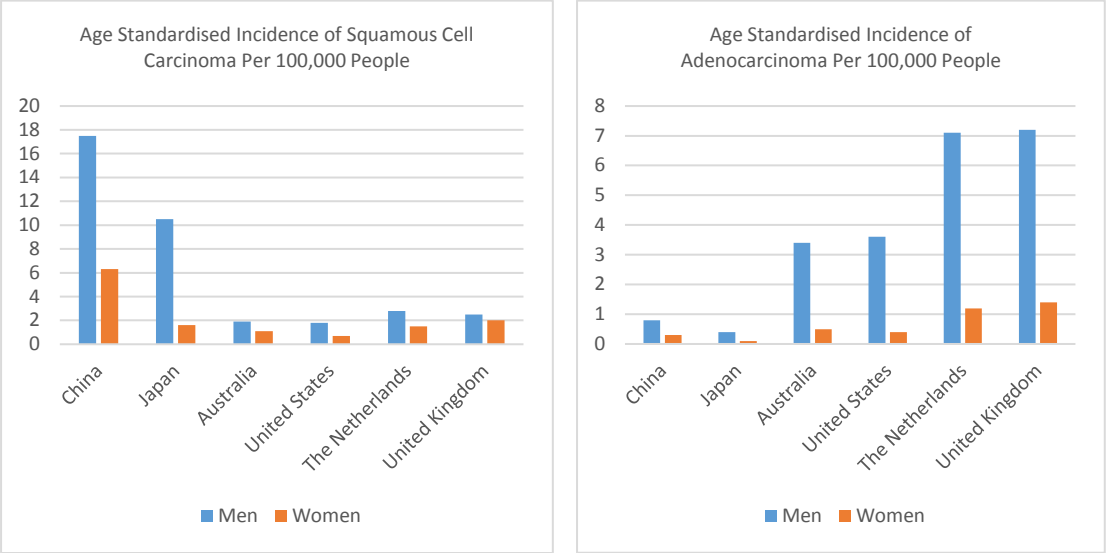

Figure 1: Age standardised incidence of oesophageal cancer by histological subtype. (Adapted from Arnold M et al. 2015)(1)

Outcomes

Cancer of the oesophagus is the 14th most common cancer in the UK but the 6th most common cause of cancer death. Overall survival is poor, in England 1 year survival is 42.3% and at 5 years 14.3%. This is because the majority of patients present with incurable locally advanced or disseminated disease. Less than 40% of patients were suitable for curative treatment in the period 2013-2015. (2)One-year survival for patients treated with curative intent was 73.9% compared to 29.2% for those who underwent palliative treatment.

Aetiology

There are two predominant histological subtypes of oesophageal cancer: squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma (SCC) arises from the normal stratified squamous epithelial lining. Adenocarcinoma arises in fields of metaplastic mucosa that exhibit an eponymous columnar epithelium, a condition known as Barrett's oesophagus.

Squamous Cell Carcinoma

Oesophageal SCC arises through chronic irritation and inflammation of the oesophageal mucosa. Risk factors vary between countries and cultures but in general it is a disease of poor nutrition, poor–oral hygiene and social deprivation. The strongest associations are smoking and alcohol but consumption of hot beverages, high intake of barbecued meat and human papilloma virus infection have all been implicated. Plummer-Vinson syndrome, achalasia and tylosis are all associated with an increased risk of developing oesophageal SCC.

Adenocarcinoma

ACA is rare globally but more common in more affluent, industrialised western nations. It is most common in middle-aged, caucasian, obese males with a history of alcohol consumption and smoking. It is strongly associated with gastro-oesophageal reflux disease (GORD). GORD is a common disease whereas adenocarcinoma of the oesophagus is not, GORD affects 4-9% of adults on a daily basis and up to 20% weekly. Of these 10% will have Barrett's oesophagus, the only known precursor for ACA, and the annual risk of progression to cancer in this population is around 0.12% per year (3) (*see section Pathology and Histology of the Oesophagus and Stomach)*. More frequent, more severe and longer periods of reflux are associated with a higher incidence.

Barrett's may progress through low-grade dysplasia to high-grade dysplasia to carcinoma. Therefore, evidence of high-grade dysplasia or low-grade dysplasia present on two endoscopies 6 months apart is an indication for endoscopic therapy to remove the Barrett's segment and prevent cancer progression.(4) It is important to stress that the majority of patients with Barrett's oesophagus will never develop oesophageal cancer.

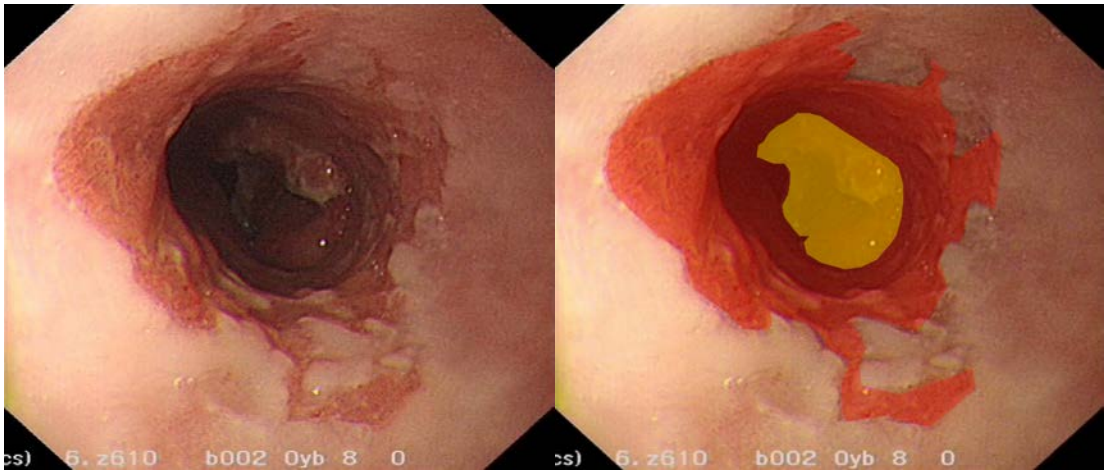

Figure 2: Adenocarcinoma (highlighted yellow) in a field of Barretts oesophagus (highlighted red).

Two factors are thought to have contributed to the recent rise in incidence of ACA. The first is the obesity epidemic that has led to a higher incidence of GORD. Male-pattern, intra-abdominal adiposity may be responsible for increased abdominal pressure and therefore reflux, going some way to explain the incident sex difference for cancer. The second is the decreasing incidence of H.Pylori infection that is thought to have a protective effect on the oesophagus perhaps by decreasing the production of gastric acid and by increasing the pH by the production of ammonia from urea.(5)

Molecular Biology of Oesophageal Cancer

The International Cancer Genome Consortium is performing whole genome sequencing of oesophageal adenocarcinomas in the UK. They have demonstrated a highly heterogenous, highly mutated cancer, characterised by chromosomal instability and large structural variations. Several well-known cancer causing genes have been identified. The tumour suppressor gene TP53 ("Guardian of the genome") involved in arresting growth and apoptosis in response to DNA damage is mutated in 81% of adenocarcinomas. ARID1A which regulates transcription is mutated in 17% of patients and SMAD4 a gene involved in regulating transcription downstream of TGF-B signaling was mutated in 16%.(6) Unfortunately the complexity of mutations in oesophageal cancer means that no new single gene target has been identified for novel treatments. However, taking a genome-wide view of oesophageal ACA has identified six patterns of mutation. These "mutational signatures" give clues as to the aetiology of the disease and go some way to explaining the huge variations shown in response to treatment. They also allow a broad molecular classification of ACA with implications for treatment.

Over 50% are mutagenic cancers. These tumours carry the 'typical' mutational signature of oesophageal ACA caused by acid reflux. It is hoped that a corresponding high number of neo-antigens presented at the cancer cell surface will make these tumours amenable to novel immunotherapies. Approximately 20% arise from mutations in DNA damage repair genes (such as BRCA1, BRCA2).

DNA damaging therapies such as radiotherapy are likely to be more effective in this group by exploiting the tumours inability to effectively repair DNA. The final 30% of tumours feature a preponderance of single base-pair mutations. This mutation pattern is more akin to an age related process seen in other cancers. Our understanding of the molecular biology of oesophageal cancer is rapidly progressing and surgeons will need to keep abreast of these developments and the implications that they will have for new and existing treatments.

Diagnosis

The majority of patients are diagnosed with oesophageal cancer following a referral from their general practitioner or another hospital practitioner (84.8%). A very small number (0.6%) are identified from endoscopic Barrett's surveillance programmes. The remainder, 13.7%, present as an emergency. The typical symptoms are of progressive dysphagia, at first to solids and then to liquids. There may be associated weight loss and anaemia. Physical examination is rarely useful except for signs of cachexia and for distant metastatic spread particularly to the supraclavicular lymph nodes and liver.

The initial investigation is upper GI endoscopy with biopsies. Differential diagnoses for dysphagia include obstructions within the lumen, in the wall of the oesophagus, and outside the oesophagus compressing the lumen.

Table 1. Differential Diagnoses for Dysphagia

Within The Lumen	Within The Wall	Outside the Oesophagus
Food Bolus	Peptic/Caustic Stricture	Mediastinal Mass
Foreign Body	Schatzki Ring	Lymphoma
Oesophageal Candidiasis	Pharyngeal Pouch	Thoracic Aortic Aneurysm
	Achalasia/oesophageal dysmotility	Globus Hystericus
	Oesophageal Web	
	Oesophageal Cancer	

Staging

Once a diagnosis of oesophageal cancer has been made the first staging investigation should be a contrast enhanced CT scan of the chest, abdomen and pelvis. The purpose of the CT scan is not only to assess the primary tumour but also to identify gross distant metastatic disease. In those patients where disease is localised on CT and radical treatment is proposed then further imaging in the form of Positron Emission Tomography (PET)-CT and Endoscopic Ultrasound (EUS) with or without fine needle aspiration cytology of any suspicious solid lesions or ascites should be considered (7). Patients whose lesions are staged as T2-T4 on CT rarely benefit from EUS and its routine use may well be restricted to T1 tumours in future.

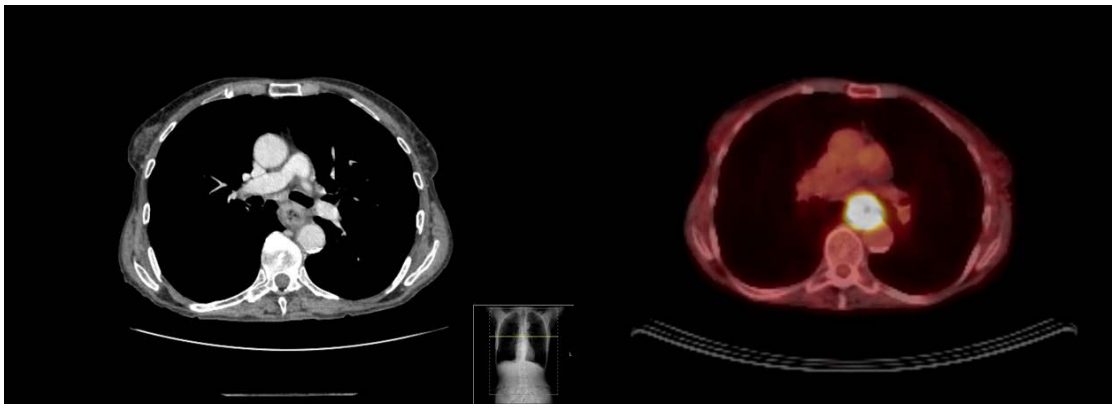

Figure 3 High Resolution Contrast Enhanced CT scan (Left) and FDG PET CT showing a thick walled oesophagus and corresponding high metabolic activity in a patient with ACA.

In patients with tumours of the lower oesophagus or gastro-oesophageal junction staging laparoscopy should be considered in order to identify early peritoneal and hepatic metastases. In very early cancers these imaging techniques are unhelpful and staging should be performed on pathological specimens after endoscopic mucosal resection.

Once imaging and histopathological assessment is complete, tumours are staged according to the UICC/AJCC TNM classification of malignant tumours, now in its 8th edition(8).

Table 2. Tumour Node Metastasis Classification of Oesophageal Tumours

T (Tumour)		N (Lymph Nodes)		M (Metastases)	
Tis	High Grade Dysplasia	**N0**	No regional lymph node metastases	**M0**	No distant metastases
T1	Tumour invades lamina propria or submucosa	**N1**	1 or 2 regional lymph nodes involved	**M1**	Distant metastases
T1a	Tumour invades lamina propria or muscularis mucosae	**N2**	3 to 6 regional lymph nodes involved		
T1b	Tumour invades submucosa	**N3**	>6 regional lymph nodes		
T2	Tumour invades muscularis propria				
T3	Tumour invades adventitia				
T4	Tumour Invades adjacent structures				
T4a	Tumour invades pleura, pericardium, diaphragm or adjacent peritoneum				
T4b	Tumour invades other adjacent structures, such as aorta, trachea, vertebral body				

Historically for prognostic purposes the staging of a tumour has been based on the pathologic findings after surgical resection or if no resection has been performed on the available imaging and histology. TNM 8 separates these distinct snapshots in time into three: cTNM, pTNM, and ypTNM are used to describe the clinical (c) and pathological (p) staging. The prefix yp- is used for pathological staging when neoadjuvant therapy has been used.

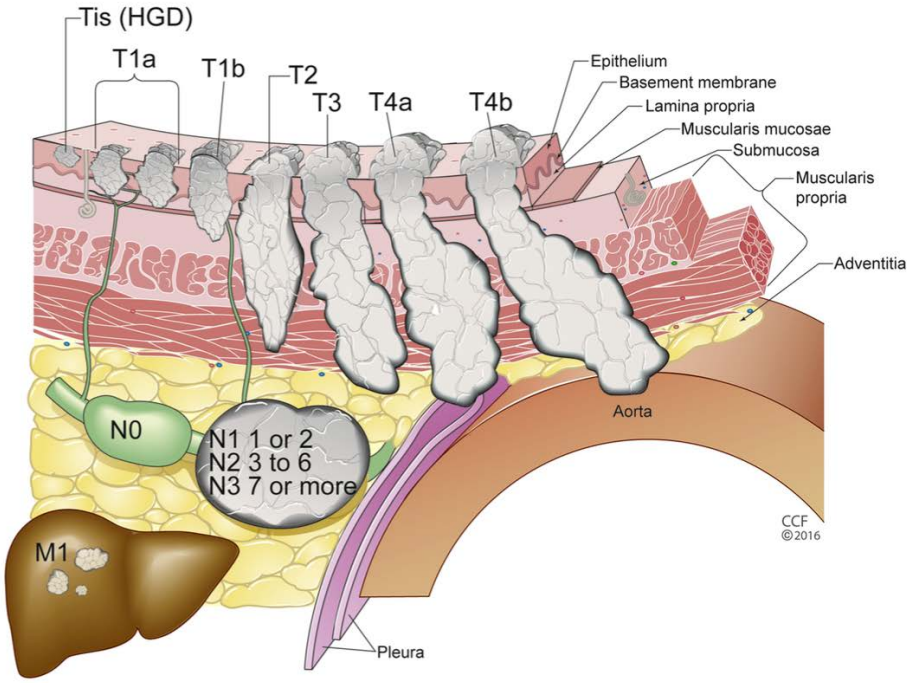

Figure 4 Pictorial representation of the TNM8 classification

Tumours within five centimetres of the gastro-oesophageal junction (GOJ) may be gastric or oesophageal in origin and are therefore classified according to the Siewert classification. Type I have their epicentre 1 to 5cm above the GOJ and are usually true oesophageal ACA. Type II are located 1cm above to 2cm below the GOJ. Type III tumours arise 2 to 5cm below the GOJ and are likely to be gastric in origin. Siewert type III tumours should be treated as gastric cancers and staged accordingly. Anatomical classifications such as this are becoming less useful as the availability of next-generation sequencing technologies delivers more

informative biological classifications and sub-groups that are pertinent to personalised treatments.

Treatment

Once staging has been completed a management plan will be developed and tailored to individual patients. Factors considered will include stage of disease, co-morbidities and WHO performance status, along with the wishes of the patient and their family. Currently only 37.6% of patients are suitable for treatment with curative intent, meaning that the majority (62.4%) are treated palliatively.(2)

Treatment with curative intent

Definitive Endoscopic Therapy

Carcinoma confined to the mucosa should be resected endoscopically. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are potentially curative procedures that provide a specimen for histological assessment and accurate staging. While they represent a far less invasive procedure than oesophagectomy complications can be severe and R1 (microscopic disease at the resection margin) resections are relatively common. Regardless of the technique used and histopathological result on-going endoscopic surveillance is necessary. Circumferential lesions are susceptible to stricture formation. Ablative techniques such as radio frequency ablation (RFA) can be used but they have the disadvantage of not providing a specimen for assessment and their use should be restricted to the treatment of Barrett's oesophagus with dysplasia or after EMR to eradicate residual Barrett's.

Localised squamous cell carcinoma of the oesophagus is increasingly treated with definitive chemoradiation. Residual disease can be treated with surgical resection but although local control is improved there is no overall survival benefit from the addition of surgery to definitive chemoradiotherapy. Current (2011) British Society of Gastroenterology guidelines advocate definitive chemoradiation in preference to surgery for tumours of the upper third and chemoradiation with or without surgery for tumours of the lower third(7). The latest national audit demonstrated that 52% of SCC treated with curative intent receive chemoradiotherapy as definitive treatment.

Peri-Operative Chemotherapy and Radiotherapy

Patients whose tumours have advanced beyond the mucosa and/or have lymph node metastasis, and are fit for radical treatment are considered for neo-adjuvant therapy. A number of clinical trials have been completed that show the benefits of neoadjuvant therapy in overall survival from oesophageal cancer.

The UK's OEO2 trial showed that surgery alone provided a 17.1% 5 year survival rate which could be improved by 6% to 23% by the addition of Cisplatin and 5-Fluorouracil (CF) in 2 pre-operative cycles(9). This result was not repeated in

the US where the Intergroup 113 study compared 3 cycles of CF pre-operatively with surgery alone. In the US trial there was no significant survival benefit between the two groups overall but there was a subgroup of patients who demonstrated a pathological response to chemotherapy in their resected specimens in whom a significant survival advantage was demonstrated.

The MAGIC trial compared 3 pre-operative cycles of Epirubicin, Cisplatin and 5-Fluorouracil (ECF) followed by surgery and then a further 3 cycles of ECF in the post operative period. Five-year survival rates were 36.3% among patients in the perioperative-chemotherapy group and 23.0% among those in the surgery group, but only 41.6% of patients completed all six cycles of chemotherapy(10).

The OEO5 trial compared the OEO2 CF protocol with a modified MAGIC protocol of 4 cycles pre-operatively to determine if more chemotherapy improved outcomes. The trial has yet to publish its results in full but similar 3-year survival rates 39% vs. 42% despite better progression free and disease free survival suggest that more chemotherapy is not necessarily better. (11)

The Dutch CROSS trial compared neoadjuvant chemotherapy (intravenous carboplatin and paclitaxel) and concurrent radiotherapy (41·4 Gy,) with surgery alone and demonstrated a survival benefit from neoadjuvant therapy. The respective overall survival rates at 5 years were 47% in the chemoradiotherapy–surgery group, compared with 34% in the surgery only group(12). There is no current consensus on whether a CROSS or MAGIC protocol should be used for oesophageal cancer and the NEO-AEGIS trial is currently recruiting to address this question

The survival benefit of neoadjuvant therapy in oesophageal cancer is limited to a sub-population <20% who demonstrate a pathological response to therapy, according to the Mandard tumour regression grade (TRG), at the expense of the many who derive no benefit at all, and who may be harmed by over-treatment. Current researchers are striving to predict who these patients will be before and during therapy in order to spare patients unnecessary treatments.

Surgery

Surgery remains the mainstay of curative treatment. The aim of surgery is to remove the tumour, the oesophagus, the lymphatic drainage and the surrounding tissue en bloc and to restore continuity of the alimentary tract. By far the most commonly performed operation is a two-stage Ivor-Lewis oesophagectomy.

In this procedure the stomach is mobilised within the abdomen. The left gastric artery and the short gastrics are divided while taking care to preserve the right gastro-epiploic artery. The duodenum is mobilised so as to allow the pylorus to reach the oesophageal hiatus with ease. The lymph nodes of the coeliac axis, common hepatic and splenic arteries are taken with the specimen. The greater curve of the stomach is fashioned into a tubular neo-oesophagus with a linear stapler taking a line of division from the lesser curve to the highest point of the

gastric fundus. The oesophago-phrenic ligament is taken and a cuff of diaphragm resected en bloc with the specimen. The thoracic oesophagus is initially mobilised with surrounding tissue by dissecting transhiatally via the abdominal approach. The abdomen is closed and the thoracic stage of the operation is begun.

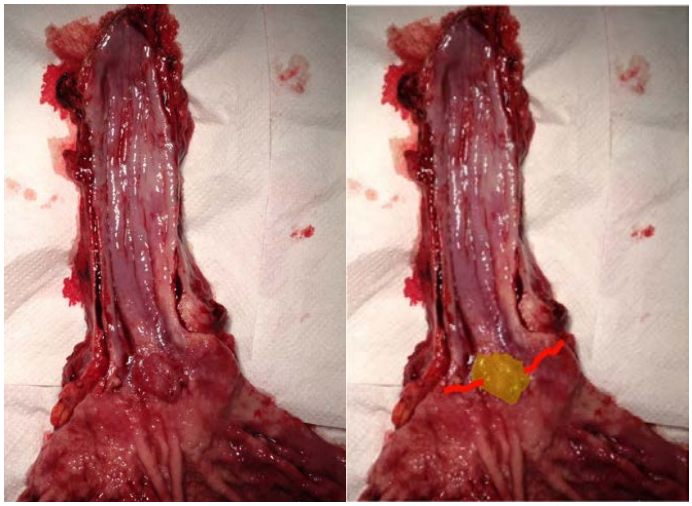

Figure 5: Resected oesophagus from an Ivor-Lewis Oesophagectomy showing the tumour (yellow) and the gastro-oesophageal junction (red line)

The right lung is collapsed and a thoracotomy performed. The thoracic oesophagus is mobilised with its surrounding adipose tissue and para-oesophageal lymph nodes, denuding the surface of the aorta and pericardium and carefully dissecting the sub-carinal lymph nodes. The thoracic duct is ligated and divided in the lower thorax. The azygous vein is ligated and divided taking care to preserve the right bronchial artery. The oesophagus is divided high in the chest to ensure a long proximal resection margin and in some cases (usually squamous cell cancers) the anastomosis may need to be in the cervical oesophagus in which case a three stage (McKeown) operation is needed with a third incision in the left neck. There is some debate as to whether the dissection should include the lymph nodes of the cervical region in the specimen (a three field dissection), in Japan it is standard practice but in the UK most surgeons make an individual patient assessment.
The neo-oesophagus is pulled up into the chest and after resecting the specimen, an anastomosis is fashioned between the proximal oesophagus and the gastric neo-oesophagus. The right lung is re-inflated under direct vision. Chest drains are placed and the wounds closed. In the UK 96% of oesophagectomies are performed in this way. The remaining 4% are performed with a transhiatal approach with no thoracotomy and the anastomosis performed in the neck.(2)

Minimally Invasive and Robotic Oesophagectomy

The role of minimally invasive and robotic surgery is expanding in oesophageal cancer. The perceived advantages are shorter recovery times, a reduction in pulmonary complications and less post-operative pain. The UK's ROMIO trial (Randomised controlled trial of minimally invasive or open oesophagectomy) coupled with similar trials in France (MIRO) and Holland (TIME), is designed to

compare the clinical and cost-effectiveness of minimally invasive and open surgical procedures in terms of recovery, health related quality of life, cost and survival.
There is no current high quality evidence to support the use of robotic surgery for oesophageal cancer, but a number of groups are beginning to develop case series showing potential for this approach, particularly for the thoracic phase of surgery.

Perioperative Patient Pathway

In recent years there has been a significant improvement in mortality associated with oesophagectomy. In hospital mortality has fallen from 4.5% in 2007-09 to 1.9% in 2013-2015 with similar improvements in 30 day (3.8% vs. 1.6%) and 90 day (5.7% vs. 3.2%) mortality. This probably represents an aggregation of marginal gains rather than any single great leap forward. Enhanced recovery after surgery (ERAS) aims to harness those marginal gains into a patient pathway. ERAS has been shown to reduce length of stay and morbidity in colorectal surgery but studies in upper gastro-intestinal surgery are limited.

In a single-centre series (106 Upper GI resections, 81 oesophagectomies) a reduction in length of stay, respiratory morbidity and overall major morbidity were reported (18% pre-ERAS to 10% post ERAS)(13). A systematic review of enhanced recovery in oesophageal cancer published in 2014 demonstrated a reduction in the incidence of anastomotic leak, respiratory complications and length of stay. There was no significant change in post-operative mortality or readmission rate.

The fundamental components of ERAS can be separated into pre-, peri- and postoperative phases. ERAS requires the input of the key stakeholders in the multi-disciplinary team including the patients themselves. Pathways should be bespoke to individual units but within a recognised framework of best practice. Pre-operatively patients are assessed and risk stratification is completed which may involve cardiopulmonary exercise testing (CPET). Patients and their families and carers are given extensive education on the role of the ERAS pathway and what to expect. Thorough nutritional assessment is required to evaluate levels of malnutrition, which are corrected by appropriate nutritional support. Physical activity levels have been shown to affect both in hospital morbidity and long-term disease recurrence and progression in cancer patients. It is hoped that further work will demonstrate an effect on survival and work continues in this field.

During surgery anaesthesia is optimised with goal directed fluid therapy and maintenance of normothermia. Regional anaesthesia in the form of epidural catheters or pleural catheters inserted under general anaesthetic reduce the post-operative pain, improve respiratory function and reduce reliance on opiate pain relief.

In the post-operative period drains and catheters including naso-gastric tubes are removed early. Early and consistent mobilisation accompanied by aggressive

goal setting is achievable with adequate pain control. Oral intake can be started early without the need for routine fluoroscopic contrast studies. In some centres this is supplemented by enteric tube feeding (jejunostomy) or parenteral nutrition.

Regardless of the surgical approach (open, laparoscopic or robotic) it is clear that optimisation of the treatment pathway should be considered a priority as it delivers clear patient benefit.

Oesophagectomy is a major procedure and sequelae may continue to affect the lives of our patients long after they have left the hospital. Patients must re-learn how to take meals in order to avoid problems such as mal-nutrition and the dumping syndrome. A comprehensive guide to managing the GI consequences of chemotherapy, radiotherapy and surgery in upper GI cancer patients has been published and is accompanied by algorithms to inform investigation and management of these patients.(14)

Treatment with palliative intent

Chemotherapy

Palliative chemotherapy is directed at slowing the progression of disease and prolonging survival while maintaining quality of life.

Historically, chemotherapy regimes have consisted of platinum based compounds (Cisplatin, Oxaliplatin) and 5-Fluorouracil or Capecitabine (an oral pro-drug which is metabolised to 5-FU). Triple therapy, with the addition of Epirubicin to Cisplatin and 5-FU (ECF) has been shown to be superior to Cisplatin and 5-Fluorouracil (CF) alone. Systemic chemotherapy with Epirubicin, Oxaliplatin and Capecitabine (EOX) is the current standard for palliative treatment of oesophagogastric and gastric cancers in the UK.(15)

Immunotherapy in the Palliative setting

Trastuzumab (Herceptin), a monoclonal antibody against human epidermal growth factor receptor 2 (HER2) was shown to be beneficial in the palliative treatment of HER2 positive locally advanced or metastatic gastric or junctional cancers in terms of progression free and overall survival (median OS 13.8 months vs 11.1) in the TOGA trial(16). More recently Nivolumab (Opdivo) a human monoclonal IgG4 antibody which blocks the human programmed cell death-1 (PD-1) receptor has also been shown to prolong progression free and overall survival.

Palliative Endoscopic Therapy

Endoscopic treatment is directed at controlling dysphagia and odynophagia. Oesophageal covered stents maintain luminal patency and further stents can be placed to deal with local progression. Ablation with laser argon plasma

coagulation can be used to de-bulk the tumour. Enteral nutrition can be maintained by passing naso-enteric feeding tubes.

Best Supportive Care

When further therapeutic intervention is unnecessary or futile the aim of further management may be shifted to minimising suffering and controlling symptoms. This may involve withholding life prolonging therapies in favour of quality of life.

Future Developments

Despite improvements oesophageal cancer still carries a dismal prognosis. Cancer Research UK has identified oesophageal cancer as a cancer of unmet need and a research priority. Building on earlier trials of neo-adjuvant therapy the NEO-AEGIS trial is now recruiting and is randomising patients suitable for radical multi-modal therapy to either the CROSS trial protocol of chemoradiotherapy or a modified MAGIC protocol of pre-and post-operative triple chemotherapy. A similar Australasian trial (TOPGEAR) is recruiting currently.

Monoclonal antibodies such as Herceptin have been shown to be beneficial in the treatment of breast and gastric cancer. Monoclonal antibodies of interest in oesophageal cancer include Trastuzumab, Nivolumab (PD-1) and Lapatinib (HER-2). As our understanding of the immunology of cancer and the interactions between the cancer cells and the tumour microenvironment grows, more and more potential targets for therapy are being identified.

Not all promising developments have been successful. Bevacizumab (Avastin) is a monoclonal antibody to vascular endothelial growth factor (VEGF) and was added to the MAGIC protocol in the UK's ST03 trial. It was hoped that it would confer a survival advantage having shown that it improved pathological response to chemotherapy in advanced gastric cancer. Unfortunately no survival advantage was apparent and patients in the Avastin arm had a higher incidence of anastomotic leak after oesophago-gastrectomy and wound healing complications.(17)

In the past, studies in oesophageal cancer have combined histological and molecular subtypes and treated all oesophageal cancer as though it is one disease. It is, however, becoming increasingly clear that oesophageal cancer is far more complex. Sub-group analyses have shown that patients who demonstrate a pathological response to neoadjuvant treatment have a far better prognosis than headline results suggest. The question for researchers is how do we identify who will benefit from which treatments and can we convert non-reponders into responders.

The next generation of clinical trials will involve stratification of patients according to the expression profile of their tumour and their predicted response

to therapy. The treatment regimes of future sufferers will be bespoke to the characteristics of an individual's disease and the mutation profile of the tumour.

Immunotherapy is likely to transform the way we think about oesophageal cancer and may well blur the lines between palliative and curative treatment intent. Oesophageal cancer may become a chronic disease that sufferers live with over many years. The increase in survival rates and reduction in morbidity makes it a very exciting time to be involved in treating oesophageal cancer. The blunt, one-size-fits-all approach will make way for a new wave of intelligent, precision-guided treatments in the fight against oesophageal cancer.

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