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 perioperative period but progress in long-term survival has been slow. Enhanced perioperative 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; enhanced recovery; epidemiology; immunotherapy; neoadjuvant; oesophageal neoplasms; oesophagectomy; pathology; radiotherapy

Epidemiology

There were 456,000 new cases of oesophageal cancer worldwide in 2012. The majority, 398,000, were squamous cell carcinomas (SCCs), 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 (ACAs) and 6000 were other cancers (e.g. neuroendocrine, lymphoma, choriocarcinoma). 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 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).

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Outcomes

Cancer of the oesophagus is the fourteenth most common cancer in the UK but the sixth 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 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, industrialized 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 Pathology and Histology of the Oesophagus and Stomach on pages 00–00 of this issue). More frequent, more severe and longer periods of reflux are associated with a higher incidence (Figure 2).

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.

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 *Helicobacter pylori* infection that is thought to have a protective

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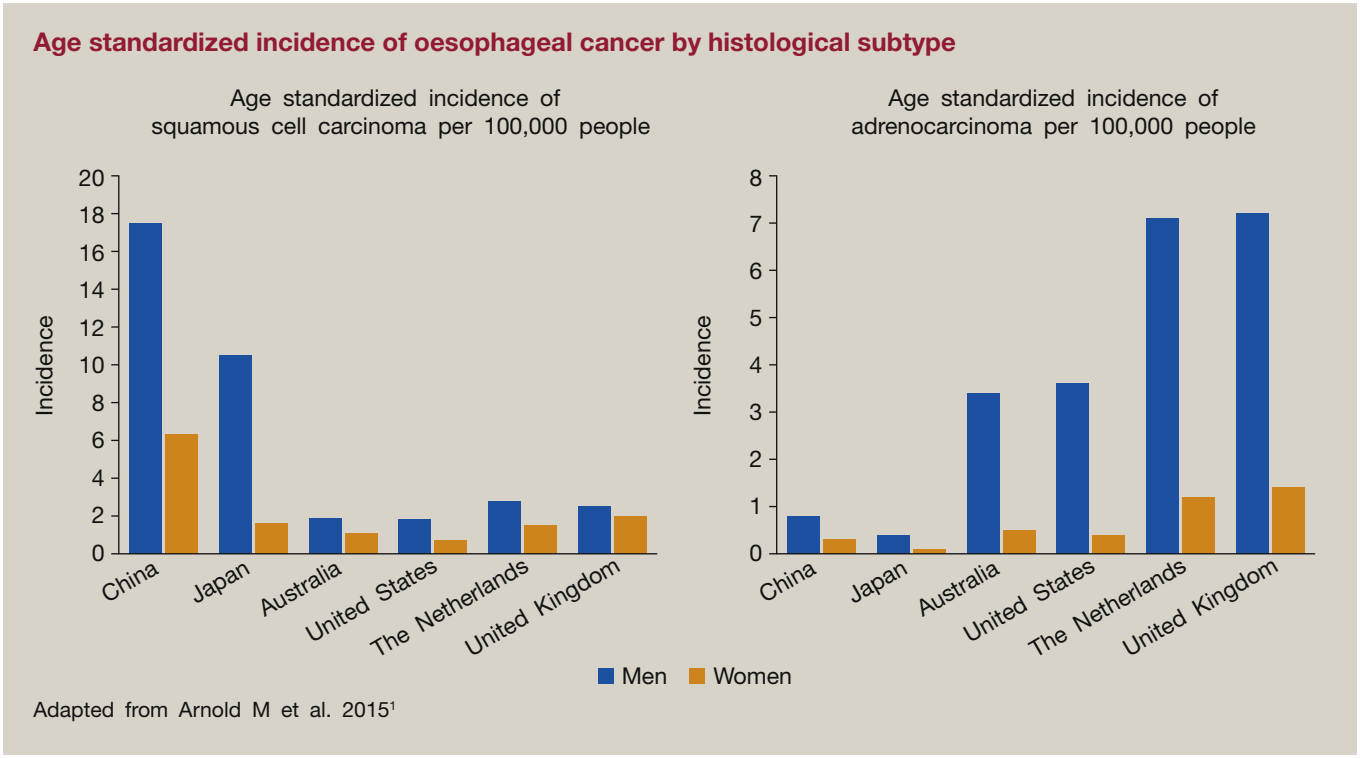

Figure 1

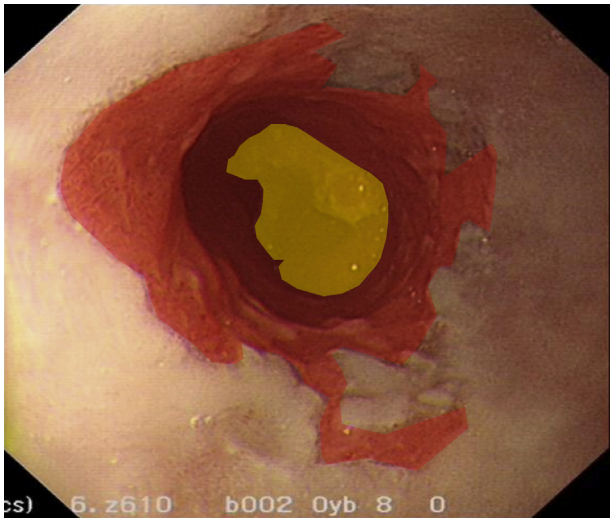

Figure 2 Adenocarcinoma (highlighted yellow) in a field of Barrett's oesophagus (highlighted red).

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 heterogeneous, highly mutated cancer, characterized 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 signalling, 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.

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