Oesophageal Carcinoma: A Review

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4th Year Physiology

INTRODUCTION

Oesophageal cancer is one of the most lethal forms of gastrointestinal (GI) cancer with only a 9% five-year survival rate currently in the United States (US).[1] It is the ninth most common cancer worldwide and has shown an increasing incidence in Western civilisation in recent decades, coinciding with a striking shift in histologic type and primary tumour location.[2] It is curable in its earliest stages, however it usually presents as an advanced disease.[1] In terms of cancer sites characterised by poor survival, it ranks fourth, behind carcinomas of the liver, pancreas and lung.[1] Despite the last two decades of clinical research, the median survival time for the patient with symptoms of a primary oesophageal cancer is less than 18 months.[3]

EPIDEMIOLOGY

Cancer of the oesophagus has the greatest variation in geographic distribution of any malignancy with highest rates being reported in South Africa, China, Brazil and Japan.[4] In the US, it is the fourth leading cause of cancer death among African American males and the seventh among Caucasians, being three times more common in men than in women.[3] In 2003 the American Cancer Society estimated that approximately 13,900 new oesophageal cancer cases would be diagnosed in the US (10,600 men, 3,300 women) and that 13,000 deaths from the disease would occur (9,900 men, 3,100 women).[5]

In Ireland between 1994 and 1996, an average of 445 new cases were diagnosed per year (268 male, 177 female) with an average of 441 deaths per year (266 male, 175 female), with the age standardised incidence and mortality rates for oesophageal cancer being about twice as high in males than in females. Rates of oesophageal cancer in females in Ireland were reported to be almost three times the EU average, and in males were substantially higher than the EU average.[6]

In America, the overall incidence of and mortality from oesophageal cancer has increased by about 15% over the past 3 decades (Figure 1), with the increase mainly being due to adenocarcinomas of the lower oesophagus and gastroesophageal junction.[1,7] Currently, the incidence of oesophageal adenocarcinoma has a rate of increase greater than that of any other cancer in the United States.[3] Although oesophageal squamous cell carcinoma remains the predominant type of oesophageal malignancy in the remainder of the world, adenocarcinoma is now the tumour with the fastest increasing incidence at a rate of 10% per year, the increase being most dramatic among Caucasian males.[8]

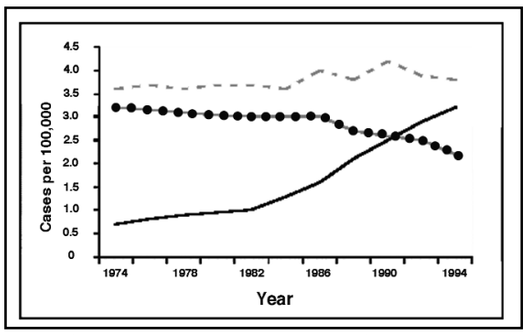

Figure 1. The increase in the incidence of adenocarcinoma in the US over the past several decades.Dashed line: all oesophageal cancers, in all races, men and women; dotted line: squamous cell carcinoma in Caucasian men; solid line: adenocarcinoma in Caucasian men. Data from Spechler[7] and Ries *et al*.[1]

Improvements in diagnostic techniques and changes in cancer classification may explain some of the rise in reported incidence rates, but detection bias and misclassification bias do not appear adequate to explain the increase entirely.

In Asia oesophageal cancers are predominantly of the squamous cell type, and mostly located in the middle third of the oesophagus. In these populations there has been no notable rise in the incidence of adenocarcinoma of the oesophagus and gastric cardia.[9]

PATHOLOGY

More than 90% of oesophageal cancers are either squamous cell carcinomas or adenocarcinomas. On rare occasions other carcinomas, melanomas, leiomyosarcomas and lymphomas may develop as well. Squamous cell (epidermoid) carcinoma arises from the mucosa of the oesophagus. Histologically, it is characterised by invasive sheets of polygonal, oval or spindle shaped cells that run together and are cohesive, with a distinct ragged stromal epithelial surface.

Adenocarcinoma by definition is a carcinoma derived from glandular tissue or in which the tumour cells form recognizable glandular structures. This gland-like or gland-derived carcinoma arises from three sources: superficial and deep glands of the oesophagus such as mucous glands, embryonic remnants of glandular epithelium and metaplastic glandular epithelium. Approximately 75% of all adenocarcinomas are found in the distal oesophagus whereas squamous cell carcinomas

are more evenly distributed between the middle and lower third.[10]

AETIOLOGY

In general, a high dietary intake of fruits and vegetables have been shown to have a protective effect against oesophageal cancer. High levels of vitamins A and C and riboflavin have been suggested as the responsible protective factors.[11] Certain epidemiological studies have suggested that regular aspirin therapy may also protect against the disease.[12]

A high fat diet along with tobacco smoking and high alcohol intake will increase the risk of disease. Studies have shown the risk of oesophageal cancer correlates directly with the quantity of cigarettes smoked per day and the duration of smoking.[13] A history of mediastinal radiotherapy, such as for the treatment of breast cancer, also predisposes the patient to both histologic types of oesophageal cancer.[14]

Any factor that causes chronic irritation and inflammation of the oesophageal mucosa appears to increase the incidence of squamous cell carcinoma.

Squamous cell carcinoma, but not adenocarcinoma, is clearly linked to low socioeconomic status.[14] Several conditions such as oesophageal diverticula, oesophageal webs and tylosis (a rare autosomal dominant disorder) predispose patients to squamous cell carcinoma. In fact, in affected families tylosis confers up to a 95% risk of squamous cell carcinoma by 70 years of age.[14]

The major risk factor for oesophageal adenocarcinoma is gastroesophageal reflux disease (GORD) and its sequela, Barrett's oesophagus. In Barrett's oesophagus, squamous epithelium damaged by reflux oesophagitis is replaced by a metaplastic epithelium containing several cell types with gastric, small intestinal or colonic features. This metaplastic epithelium can be viewed teleologically as the body's way of protecting tissues from a hostile environment. The problem is that these cells are predisposed to develop DNA alterations that lead to dysplasia and cancer.[15] Barrett's oesophagus occurs in 5%-8% of patients with GORD and for reasons that are not entirely clear, its prevalence has increased from an average of 1 per 1000 upper endoscopies in the early 1980s, to over 55 to 60 per 1000 in the late 1990s. Prospective studies on the incidence of adenocarcinoma in Barrett's oesophagus have provided risk estimates ranging from 0.4% to almost 2% per year.[7]

A recent epidemiological study conducted in Sweden found that patients who experienced heartburn, regurgitation, or both, at least once a week had a risk of developing adenocarcinoma that was increased nearly eight-fold above that of asymptomatic subjects in the general population.[15]

Factors that May Contribute to Barrett's Oesophagus and Adenocarcinomas

The parallel epidemic of obesity, which may increase intraabdominal pressure and thus predispose to GORD, has been implicated. In fact several epidemiologic studies have shown upwards of three-fold excess risk among overweight individuals.[16] The prevalence of *Helicobacter pylori (H. pylori)* infection is steadily decreasing in Europe and the US, and this parallels an increase in GORD and adenocarcinomas of the oesophagus and oesophagogastric junction. It has been postulated that *H. pylori* infection (particularly strains that are positive for the *cagA* protein) may reduce the risk of GORD by reducing gastric acidity.[17]

Supporting this theory, it has been shown that in regions with a higher prevalence of *H. pylori* infection such as in Asia, the percentage of adenocarcinoma is much smaller.[18]

Factors such as hiatial hernia, increased use of lower oesophageal sphincter-relaxing medications and a family history of breast cancer have also been implicated.[14]

MOLECULAR AND CELLULAR CHANGES

During the development of oesophageal cancer there is progression from a premalignant epithelium to a neoplasm that frequently demonstrates a heterogeneous mix of genetic alterations. In the vast majority of oesophageal cancers inactivation of the p53 and p16 genes at an early stage is followed by defects in genes such as retinoblastoma (Rb) and cyclin D1 and E at later stages.

Amplification of the *c-erb* gene is a prognostic factor and predictive of lymph node involvement.[19] Loss of heterogenicity (LOH) of 17p, the p53 locus, has been detected in 52% to 93% of adenocarcinomas in Barrett's oesophagus and in squamous cell carcinomas. P53 alterations have been detected in 55% to 76% of cases.[20] Additionally, several European and North American studies have shown an association between p53 mutations and smoking.

The *Erb* family of receptor tyrosine kinases and their growth factor ligands, epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-α), have also been implicated with increased expression of TGF-α and the EGF receptor being detected in Barrett's metaplasia.[21] This is seen in both oesophageal adenocarcinoma and squamous cell carcinomas.[21]

The overexpression of cycloxygenase (COX) enzyme has also been shown to contribute to the process of apoptotic resistance of oesophageal cancer cells. Overexpression of COX-2 has been detected in oesophageal carcinomas and recent studies have shown that selective COX-2 inhibitors significantly decrease proliferation and increase apoptosis *in vitro* in oesophageal squamous and adenocarcinoma cell lines.[20]

CLINICAL FEATURES

Like other cancers of the GI system, oesophageal cancers are rarely found early when they are small and more easily treated. More frequently, the patient presents late because the distensible oesophagus compensates readily for partial obstruction of the lumen by a tumour. The tumours are characterised by extensive local growth, lymph node metastasis and invasion of adjacent structures before wider dissemination. The poor prognosis of oesophageal cancer patients is influenced by the proximity of the aorta and trachea and the absence of a serosal covering.

The typical presenting patient is a male between 55-65 years old with a long-standing history of cigarette abuse and heavy alcohol intake. Dysphagia and weight loss are the initial symptoms in 75% of cases.[10]

Most patients complain of food sticking at a point in their throat at the level of the sternal notch. Odynophagia is seen in about 25% of the patients with tumours.[10] Regurgitation of undigested food, retrosternal or epigastric pain or aspiration pneumonia may be present. Advanced lesions may present with haematemesis, melaena, cough from a tracheoesophageal fistula, haemoptysis or problems related to nerve involvement. Tumours of the oesophagus may present with superior vena cava syndrome but this is rare in the absence of dysphagia.

DIAGNOSIS

Endoscopy is usually the first diagnostic test in people with suspected oesophageal cancer. Early cancers can be detected this way but are usually incidental findings. Following this, a computed tomographic (CT) scan of the chest, abdomen and pelvis with intravenous contrast medium is preformed to detect metastasic disease.[14]

More recent advances in diagnosis include endoscopic ultrasonography (EUS) and positron emission tomography (PET). EUS is a procedure that, according to recent studies, might be even more accurate than CT scans and endoscopy in determining the size of an oesophageal cancer and the degree of invasion.[22]

Positron emission tomography (PET) is being described as the most promising non-invasive procedure for the evaluation and management of patients with oesophageal neoplasms and is beginning to replace invasive thoracoscopic and laparoscopic staging in many institutions. PET has been shown to be accurate in the identification of primary oesophageal neoplasms of either histologic type, to be more accurate than CT in preoperative evaluation for the identification of distant metastatic disease and also to be more accurate as a restaging procedure for the detection of regional and distant site recurrance.[23,24]

Fusion of CT or magnetic resonance images (MRI) with PET images also shows great promise as a valuable tool in helping to deliver more accurate staging and yield better sparing of normal tissue.

SCREENING AND SURVEILLANCE

The poor prognosis and lethal nature of oesophageal cancer along with the lack of efficacy of chemotherapy and radiation therapy provides the rationale for promoting surveillance endoscopy in patients with chronic GORD symptoms, particularly those with Barrett's oesophagus. It is known that progression from metaplasia to invasive cancer occurs in a stepwise process,[25] so it is reasonable to assume that effective surveillance programs such as that outlined in figure 2 can be developed for patients known to have Barrett's oesophagus.

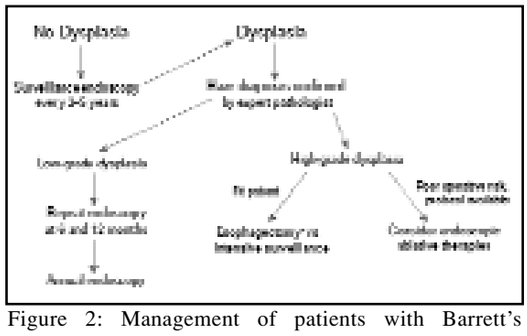

Figure 2: Management of patients with Barrett's oesophagus. Adapted from Spechler[7]

Indirect evidence suggests that surveillance for Barrett's oesophagus may be beneficial. Several studies have shown that patients whose oesophageal carcinomas are discovered during surveillance for Barrett's oesophagus have tumours in earlier stages and have better survival rates than patients whose cancers are discovered because they have symptoms such as dysphagia and weight loss.[7]

All opposing argument is that the relatively low incidence, absence of early symptoms and the

rarity of a hereditary form of the disease make population based screening untenable except in certain high-risk areas of the world.

TREATMENTS

Early Forms of the Disease: Barrett's Oesophagus and High-Grade Dysplasia

The management of patients with Barrett's oesophagus with high-grade dysplasia is controversial. Those who are good operative candidates have traditionally been offered surgical resection because of the high risk of adenocarcinoma. However, surgery is associated with significant mortality.[14]

An alternative method is based upon the observation that the destruction of intestinal metaplasia using a variety of thermal and chemical methods may be accompanied by regrowth of normal appearing squamous epithelium, particularly if the patients are treated with proton pump inhibitors.

Endoscopic mucosal ablative therapies would seem to be ideally suited for the ablation of dysplastic Barrett's epithelium and early oesophageal cancer because these diseases are localised to the oesophageal mucosa. Therapies that have been specifically used for Barrett's with high grade dysplasia include: photodynamic therapy (PDT), laser ablation (Nd:YAG), cryotherapy and endoscopic mucosal resection (EMS). The combination of EMS and PDT has been shown to be an effective and safe therapy and appears to be the most promising approach, but the long-term effects of ablative therapy are not known and continued surveillance is still advised.[26] Data on the use of PDT for Barrett's oesophagus seems to be slightly more favourable than those for thermoablation.[27]

Localised Cancer

Survival figures for surgery have improved in recent decades due to earlier diagnosis, more accurate staging, prudent patient selection and altered surgical techniques. A recent multi-institutional randomised trial reported that patients undergoing surgery as the sole treatment had median survival rates ranging from 13 to19 months, 2 year survival rates ranging from 35% to 42%, and 5 year survival rates from 15% to 24%.[14]

To improve outcomes clinical trials have assessed the role of other modalities of treatment in conjunction with surgery. The combination of cisplatin and 5-flurouracil (5-FU) are considered the optimal chemotherapy agents, but results of trials are conflicting as to the benefit of preoperative therapy. Radiation therapy alone either pre- or postoperatively has also failed to improve survival indices. Postoperative radiotherapy has even been shown to have a detrimental effect on survival.[28]

At least eight randomised trials have been conducted to address the potential benefit of preoperative chemotherapy with radiotherapy. Only two studies enrolled sufficient numbers of patients to provide statistically meaningful results and neither reported an advantage of neoadjuvant combined modality therapy.[14] The one positive trial by a group from St James's Hospital and Trinity College in 1996 showed a benefit of combined therapy.[29] This trial came under criticism for small numbers and poor surgical outcome but appears to have influenced thoracic surgeons and oncologists substantially.

Postoperative combined treatment is frequently offered to patients whose tumour cells extend to the surgical margin but there is no documented evidence that postoperative chemotherapy or radiotherapy is beneficial in the absence of residual disease.[14]

Chemotherapy and radiotherapy have been shown to lead to long-term survival in 25% of patients, an outcome similar to that associated with surgery alone or surgery after preoperative therapy.[29]

Advanced Metastatic Disease

In patients with distant metastases a more palliative approach should be considered. Local symptoms such as relief from dysphagia may be controlled with oesophageal stents, external beam radiotherapy, brachytherapy or mucosal ablative therapies. The results of small randomised trials comparing stenting, laser ablation and PDT suggest that stenting offers a similar degree of relief from dysphagia and at a lower cost but may cause severe acid reflux and tumour ingrowth.[30]

Although chemotherapy can palliate symptoms in many patients, the response to it typically lasts no longer than a few months and survival is short, rarely exceeding one year. Combination chemotherapy is likely to improve response rates over single agent therapy but this may not translate into a significant survival benefit.[31]

FUTURE OUTLOOK

As the epidemiology of oesophageal cancer evolves, current practice must change accordingly to keep pace with evidence based data so as to treat patients with the best option available. Progress with newer chemotherapeutic agents, optimal radiotherapy prescriptions and/or innovations and alternative forms of systemic treatment merit further investigation. The elucidation of the basic mechanisms of oesophageal carcinogenesis brings with it the

promise of developing treatment and preventive strategies that are based on the molecular biology of these tumours, such as antagonists of the EGF receptor or COX-2-inhibitors.

In Ireland, further investigation is needed into the possible factors accounting for the disproportionately high rates of oesophageal cancer among women. Screening initiatives for high-risk groups should also be considered.

The population should be encouraged to stop smoking, eat a diet with a high level of fresh fruit and vegetables and moderate alcohol consumption.

One of the major issues surrounding the disease is that patients often do not understand the potential significance of their symptoms and present quite late, often too late. It is the job of health care professionals and the government to educate and inform people more about the disease so as to increase awareness of the primary symptoms such as dysphagia and weight loss and reduce the incidence of this deadly disease.

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