Gastro-Oesophageal Cancer

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Introduction

Gastro-oesophageal cancer remains a devastating diagnosis for the patient and a challenge for the clinician. Although rare, they cause disproportionate mortality in comparison to more commonly encountered malignancies. Survival figures remain relatively poor, partially due to the fact that significant proportion of patients present with advanced disease. The incidence of gastro-oesophageal cancer has striking geographical variation as does the gold standard treatment. Here we explore the epidemiology, aetiology and clinical aspects of this group of cancers. Further, we explore the treatment practices in different parts of the world and assess their impact on survival.

Oesophageal Cancer

Cancer of the oesophagus is the eight commonest worldwide, affecting more than 450 000 people. While incidence is increasing overall 5-year survival remains poor making this relatively rare cancer the 6th leading cause of cancer related death world-wide [1-3]. Incidence is highest in the Far East, and in China it is as high as 100 cases per 100 000 of the population [4,5]. In comparison, incidence is far less in the Western world, with 16 470 cases being diagnosed in the USA in 2009 and 14 530 mortalities in the same year [3]. Oesophageal cancer is group comprising several histological types, chiefly squamous cell (SCC), adenocarcinoma, leiomyosarcoma and other rarer types. SCC remains the commonest type worldwide, although adenocarcinoma is commoner in Western countries [6].

SCC is strongly associated with tobacco use and alcohol consumption. Other predisposing factors include a history of achalasia, caustic substance ingestion, radiation exposure and poor nutrition [7,8]. Additionally, recent studies have shown an association between oesophageal SCC and mutations in genes governing enzymes related to aldehyde metabolism [9]. In contrast to adenocarcinoma, SCC appears to be commoner in lower socioeconomic groups [10]. Oesophageal adenocarcinoma is also associated with tobacco use, with a higher incidence in men [7]. Interestingly, and perhaps accounting for its geographical distribution, it is associated with obesity, Barrett’s oesophagus, and chronic gastro-oesophageal reflux disease, largely diseases of the West [11,12]. The latter is a very strong risk factor, and likely related to the increasing prevalence of obesity. Barrett’s oesophagus has a prevalence of up to 6% in the general population. The protective changes in the lower oesophagus brought about by persistent acid exposure can result in dysplasia, with a 0.5% risk of development of adenocarcinoma per year [13]. Obesity, reflux and genetic abnormalities all themselves are risk factors for developing Barrett’s oesophagus [12].

Although symptoms are variable, most patients present with dysphagia. In the case of adenocarcinoma, this may be accompanied by symptoms relating to reflux disease. For SCC, weight loss is the most commonly associated symptoms. Initial assessment by upper gastrointestinal endoscopy enables precise localization of the tumor and histopathological diagnosis by analysis of tissue samples. Adenocarcinomas have a predilection for the area from the distal third of the oesophagus to the gastro-oesophageal junction. SCCs are located more proximally. As part of pre-operative planning, the stomach is also assessed to ensure that a ‘neo-oesophagus’ can be fashioned from the stomach. Endoscopic ultrasonography is now routinely part of the staging protocol in most large centers. It allows a more detailed assessment of the dimensions of the tumor, and can assess for the presence of local pathological nodes. Using this technique, infiltration of the tumor into the wall of the oesophagus can be ascertained with an accuracy of up to 89% and nodal status up to 84% [14]. Computerised Tomography (CT) and Positron Emission Tomography (PET) is used to assess for metastatic disease. Staging laparoscopy can be performed pre-operatively enabling assessment for resectability, nodal status and possible intra-abdominal metastases in locally advanced disease particularly if lesions are under 1cm on scanning [15]. Staging laparoscopy is always performed if the tumor invades the stomach; in cases of tumor limited to the oesophagus, it is the surgeon’s choice whether or not to perform a laparoscopy. Staging facilitates a multidisciplinary decision about the best course of treatment. The TNM classification system is most widely used based on the consensus formulated by the American Joint Cancer Committee [16].

Treatment is multifaceted. For tumors staged up to T3 with or without nodal disease treatment intent is curative [17]. This invariably involves surgery. An open approach with an oesophagectomy with primary anastomosis can be performed by several techniques: thoracoabdominal approach, Ivor-Lewis (laparotomy or laparoscopy with right thoracotomy), the McKeown approach (laparotomy, right thoracotomy and neck dissection), or a transhiatal approach (laparotomy and neck anastomosis). Minimally invasive surgery is gaining favor in most units now with all or parts of the procedure performed laparoscopically [18]. The type of surgery performed will depend on the surgeon’s preference and the location of the tumor. There is no convincing evidence to favour one surgical technique above the others in terms of overall survival [19,20].

Minimally invasive surgery has been shown to reduce post-operative morbidity and time of hospital stay. Although debated, some studies have suggested reduced 30-day mortality and improved survival with laparoscopic techniques [18]. Further, laparoscopic surgery offers far less long-term morbidity when compared with laparotomy with a decreased incidence of incisional hernia and adhesions and so can therefore be argued to contribute towards improved quality of life long-term [21]. The extent of lymph node dissection also remains controversial. In the Far East, particularly in Japan, three-field dissection is performed (abdomen, chest and neck). In Western countries however only abdominal and chest nodes (two-field dissection) are cleared routinely. There is some debate as to additional complications associated with more extensive node dissection especially as there is no apparent survival advantage and no convincing evidence that three-field dissection provides more accurate sampling and therefore staging [22]. Oesophagectomy remains a difficult operation carrying significant morbidity and mortality, estimated to be between 1-23% [23].

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By far most common subtype is adenocarcinoma; other subtypes maximum of 25% [1].

As figure 1 demonstrates, the 5-year survival remains poor despite optimal treatment in specialist centres. The studies in figure 1 demonstrate survival in patients undergoing curative treatment of resectable disease, but overall survival across all stages is estimated at a maximum of 25% [1].

Gastric Cancer

Gastric cancer has a worldwide incidence of 1 000 000 cases per year, and is the second leading cause of cancer related mortality [5,34]. It is most prevalent in the Far East, where the incidence is in the region of 70 cases per 100 000.36 It affects men twice as commonly as women [35]. By far most common subtype is adenocarcinoma; other subtypes include lymphoma and stromal tumors. In high incidence countries, screening programmes are well established. This has perhaps, in part, contributed to the variation in 5-year survival figures ranging from 52% in Japan to 25% in Europe and USA [36].

*Helicobacter pylori* are a gram-negative microaerophilic bacterium whose colonisation of the stomach may have devastating consequences. By varying mechanisms, *H pylori* stimulates gastrin related acid production, and when this becomes overwhelming, chronic inflammation ensues. Such changes may cause dysplasia and adenocarcinoma formation [37]. Studies have suggested a very strong link between *H pylori* and the development of gastric cancer: up to a 6 fold increase in risk in patients who are colonized with gastric *H pylori* [38]. Hereditary gastric cancer accounts for up to 3% of cases and is thought to relate to a mutation in the CDH1 gene, which regulates the activation of adhesion molecules [39]. The lifetime risk for carriers of this mutation for developing gastric cancer is 83% for women and 67% for men [34,40]. Other genetic conditions such as Lynch syndrome and Peutz-Jeghers disease may also infer an increased risk of developing cancer. Smoking, high salt intake, pernicious anaemia and chronic inflammation are all associated risk factors. It is interesting to note that although the incidence of distal gastric cancer has reduced, the incidence of proximal cancers has risen, and this may be associated with obesity [35].

There are no typical symptoms which will confer a diagnosis of gastric cancer, but patients may present with epigastric pain, weight loss, symptoms suggestive of anaemia, or with symptoms of advanced disease. Rarely, patients may present with significant complications, including perforation, obstruction or bleeding. Diagnosis is again confirmed by upper gastrointestinal endoscopy with tissue samples taken for histological diagnosis. Staging investigations are identical to those for oesophageal cancer. Again, laparoscopic staging with or without peritoneal fluid sampling is a useful adjunct and forms part of the staging protocol in most units. In Gastric cancer, PET is not routinely used as a staging investigation.

Surgery involves a total gastrectomy for resectable disease, or for distal cancers a subtotal gastrectomy is sufficient as long as clear margins are achieved. Randomized control trials have confirmed that there is no difference in survival in total or distal gastrectomies for distal cancers [41,42]. The extent of lymph node dissection remains both variable and debatable. Indeed, there are 16 lymph node compartments in close proximity to the stomach which may be resected [43]. Two general types are used practically: D1 resection, where the N1 group of nodes and the omentum are resected; and D2, where additionally, the N2 groups of nodes are dissected. Various trials and studies have been performed to ascertain whether there is any advantage with D2 resection, which may be associated with increased morbidity. As yet, there is no clear trial that has shown improved survival with D2 resection without increased mortality and morbidity [44-47]. Whereas in the USA and many European countries a resection and D1/D2node dissection is preferred, in Japan and the Far East, a D2 or even D3 (N3 group of nodes along the splenic artery, hepatoduodenal ligament and mesenteric root) resection is mostly performed [45,46]. Further, a locally advanced tumor may infiltrate into the spleen, colon or pancreas, and these organs often need to resected too, resulting in increased morbidity [48].

The MAGIC trial in the UK showed an overall survival advantage in administering pre- and post-operative chemotherapy for resectable disease of 13%.26Similarly, a French trial detected similar findings [49]. Trials assessing the use of chemoradiotherapy in the pre-operative setting have been promising, but this has not yet translated...
into clinical practice. Trials have assessed the use of a short course of pre-operative radiotherapy, and these have had favorable results [50]. However, given that surgery alone has a prime outcome, the use of pre-operative treatment is still being determined and debated. The role of adjuvant treatment is better established. Radiotherapy has been used, with some studies showing better loco regional outcomes [51,52]. This is an especially effective modality where positive margins are found. For unresectable disease, palliative radiotherapy can provide good symptom relief, and it can also be used to treat bleeding from the tumor. Chemotherapy in the palliative setting also has been shown to improve symptoms, but survival is generally unaffected. Stents or palliative bypasses can be utilized in gastric outlet obstruction [53,54].

Long term survival is certainly improving for gastric cancer, but still remains worrying. Figure 2 shows the 5-year survival values for resectable disease with optimal treatment. Whereas these results are relatively good, overall survival across all stages remains worrying at between 25-52% [36]. It is this variability which needs to be addressed, as there is still no uniform strategy on the extent of surgery or on the administration of neo-adjuvant or adjuvant treatment.

Conclusions

It is imperative, bearing in mind that incidence is increasing, that we maintain research into both the mechanisms of gastro-oesophageal oncogenesis and optimizing the best standard of treatment. A number of trials are in progress either refining current standards or assessing new techniques, but these must be translated into clinical practice. Survival for this group of cancers remains poor, and we must redress this urgently. Newer studies assessing biological therapies, screening programmes or cancer prevention strategies must be supported, and we must learn from our past experiences. There is a geographical variation in both incidence and survival, and these patterns need to be studied further to elucidate the causes, with optimal treatment strategies being adopted. It is clear that, as ever, there is scope for improvement, and this must be enacted and focused, so that raw data can be transformed into good clinical practice with improved outcomes for patients.

References


Figure 2: 5-year survival for gastric cancer for resectable disease [29,30,54-55].


