Featured Article

Overview of esophageal cancer

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Esophageal cancer is a male-dominant aggressive malignancy and a leading cause of cancer-related mortality worldwide. Squamous cell carcinoma and adenocarcinoma are the two predominant histological subtypes with varying geographical and racial distribution. Globally, squamous cell carcinoma remains the most common histological type. In Western countries, however, adenocarcinoma has become the leading histological subtype, corresponding to a rise in the incidence of obesity, gastro-esophageal reflux disease and Barrett's esophagus. The risk of esophageal adenocarcinoma conferred by Barrett's esophagus depends on factors such as genomic instability, race and gender of the patient. Treatment requires a multidisciplinary team approach and optimal therapy is still debated. Endoscopic therapies, including radiofrequency ablation, endoscopic mucosal resection and endoscopic sub mucosal dissection, have become the standard treatment modality for Barrett's esophagus and early carcinoma. Multimodal treatment, which includes chemotherapy, radiation therapy followed by surgical resection or without surgical resection, in varying orders remains the main mode of treatment for most patients. Minimally invasive surgical approaches have become the standard for esophagectomy and the current literature has demonstrated similar oncological outcomes with reduced morbidity. Recently, there has been a modest improvement in the overall survival of patients with esophageal cancer.

Keywords: Esophageal cancer; epidemiology; risk factors; diagnosis; treatment

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Introduction

Esophageal cancer continues to be a largely fatal malignancy, with overall five-year survival ranging from 15% to 20% (1,2). Globally, esophageal squamous cell cancer (ESCC) remains the predominant histological subtype, as 80% of esophageal cancers occur in developing countries where squamous cell cancer is more common. The global incidence of squamous cell cancer has more or less remained stable and it represented 87% of all cases of esophageal cancer in 2012 (3). In contrast, in the Western world, including North America, Western Europe and Australia, esophageal adenocarcinoma (EAC) has become the most common histological subtype of esophageal cancer (4). These areas have seen a decline in the incidence of squamous cell cancer.

Epidemiology and risk factors

Esophageal cancer is the eighth most common cancer worldwide, and the sixth most common cause of cancer related deaths (5). The highest incidence of esophageal cancer is seen along two geographical belts, one from north central China through the central Asian republics to northern Iran, and one from eastern to southern Africa. More than half of all esophageal cancer-related deaths occur in the Republic of China (6).

The epidemiology of esophageal cancer in Western world has significantly changed. Adenocarcinoma of the distal esophagus has become more prevalent than squamous cell cancer of the upper and middle thirds of the esophagus. The incidence of EAC remains low in China, ranging from

1.5%–4.5%. In USA, the incidence of EAC among white men was 0.4 per 100,000 in 1973 to 2.8 per 100,000 in 2012. A similar increase has been noticed in the United Kingdom, Australia, and Northern Europe. In these countries, the ratio of ESCC to EAC amongst white men was 4.7:1 in 1975, reduced to 0.43:1 in 1996–1998 (7,8). During this period, there was an 8–10% annual increase in incidence of EAC, though it has recently declined (9). This significant increase in the incidence of EAC in the Western world and some developing countries coincides with an increase in the prevalence of gastro-esophageal reflux and obesity, known risk factors for EAC (10).

Gender

Esophageal cancer continues to be a male dominant disease. Worldwide, ESCC is two to three times more common in males than females. Generally speaking, this male predominance is even more marked in the EAC histological subtype (6). A global assessment indicated an overall male-to-female ratio of 4.4, which ranged from 1.7 in sub-Saharan Africa to 8.5 in North America. In the United States of America (USA), 76% of cases of adenocarcinoma from 1973 to 2012 have occurred in white males (11). Exceptions to this trend include Iran, where the incidence of EAC is thought to be similar in males and females (12).

Race

The incidence of EAC is four to five times as high among Caucasians as it is amongst African-Americans, Asians/Pacific Islander and Native Americans in the USA (10). From 1992 to 1998, the incidence of esophageal cancer increased only in the Caucasian population. A study investigating the epidemiology of esophageal cancer in Chinese migrants to the United States found 81% of esophageal cancer cases diagnosed in this population were ESCC, while 18% had EAC (13). ESCC was found to be more common in these Chinese migrants compared to Caucasian Americans, while the incidence of EAC in this population is significantly higher than in Chinese living in China, suggesting that lifestyle and dietary factors play a role in the development of EAC.

Obesity

The rapid increase in the incidence of EAC has paralleled the rise of obesity in the western world. A variety of observational studies, systemic reviews and meta-analyses have shown and confirmed association between obesity and EAC. The association between increasing body mass index (BMI) and EAC has been shown to be dose dependent (14). The risk of EAC in patients with a BMI of 30 or more is approximately 16 times greater compared to those with a BMI of 22 or less. Studies have also shown that increasing waist circumference is strongly associated with an increased risk of esophageal adenocarcinoma in a dose dependent manner, independent of BMI (15). This perhaps explains the male dominance of EAC, as abdominal obesity is more common in males. Although the true pathophysiology underlying this association remains unclear, suggested mechanisms include increased intra-abdominal pressure secondary to obesity, facilitating gastroesophageal reflux and esophagitis, which in turn predisposes to Barrett's esophagus (BE). Obesity is also known to have carcinogenic effects via hormonal imbalances.

Helicobacter pylori

Interestingly, *H. pylori* infection is thought to confer a protective effect for esophageal adenocarcinoma. Epidemiological studies have demonstrated a negative association between *H. pylori* infection and esophageal adenocarcinoma (16-18).

There are two potential mechanisms. Firstly, *H. pylori* infection leads to atrophic gastritis and decreased gastric acid production. Secondly, it neutralizes the acid through the production of ammonia. This leads to decreased acid exposure of the distal esophagus, which in turn reduces the chances of esophagitis and EAC (19). The decline in prevalence of *H. pylori* infection in the Western population may play a role in the rising incidence of EAC.

Smoking and alcohol consumption

Smoking is strongly associated with ESCC, and the recent global decrease in smoking may explain the slight decrease in the incidence of ESCC (20). Alcohol consumption has also been associated with the development of ESCC. The association of smoking and alcohol consumption with EAC is less conclusive.

Human papilloma virus (HPV)

The role of HPV infection in the development of esophageal cancer has long been suspected. Although

HPV has been widely studied, the overall rate of HPV infection in ESCC remains controversial, and many studies have attempted to address this question. According to recent meta-analyses and reviews, worldwide HPV-ESCC infection rates range from 11.7% to 38.9% (20)

The well-known association between HPV and oropharyngeal SCC, and the histologic similarities between the squamous epithelium of the oral mucosa and upper esophagus could suggest a similar association. HPV16 and HPV18 are the most frequently detected types in HPV-associated cancers. Studies have shown a significant association between HPV16 and ESCC, but not HPV18 (21). HPV prevalence correlates strongly with high-ESCC-incidence regions, but in Western countries, such as the United States, HPV-ESCC infection rates are low (on the order of 5%–15%) (22). Though the literature supports the association of HPV infection and development of ESCC, there is a lack of robust evidence for a definitive etiological role.

Gastro-esophageal reflux disease (GERD)

GERD is a known risk factor for BE and EAC. A meta-analysis demonstrated that weekly symptoms of GERD increased the odds of developing esophageal adenocarcinoma by five-fold, while daily symptoms increased the risk by seven-fold (23). On the other hand, a Danish study reported only 21% of patients with EAC experiencing reflux symptoms. In the Swedish Inpatient Register, the risk of EAC was increased nine-fold if a patient had endoscopically confirmed esophagitis (24).

Barrett's esophagus (BE)

Patients with BE have been shown to have a 30- to 60-fold increase in the incidence of EAC, although the annual absolute risk of developing EAC is 0.12%, rather than previously expected rates of 0.5% (25). The incidence of BE is two to three times higher in men than women, and male sex is an independent risk factor for malignant transformation. The conservative estimate of the ten-year cumulative risk of EAC is 3–6% in the absence of dysplasia and 7–13% in the presence of low-grade dysplasia (26,27). On the other hand, high-grade dysplasia can be synonymous with microscopic adenocarcinoma in up to 40% of cases, especially if the Barrett's segment is nodular.

The current risk stratification of BE for EAC relies on histological classification and grade of dysplasia. However, histology alone cannot assess the risk of patients with inconsistent or non-dysplastic BE histology. Recently there has been much enthusiasm for using genetic abnormalities to differentiate between patients with dysplastic BE who will progress to EAC, and those who will not. The extent of genomic instability, measured as the mutational load in a biopsy of BE, can predict the risk of progression of BE to EAC in patients who otherwise would have been deemed low risk on the basis of histological findings alone. Mutational load summarizes the presence and clonality of loss of heterozygosity (LOH) mutations and the emergence of new alleles, manifested as microsatellite instability (MSI) mutations, in ten genomic loci around tumor suppressor genes associated with EAC (28,29).

NSAID consumption

Nonsteroidal anti-inflammatory drugs (NSAIDs) can exert antitumor effects through the inhibition of cyclooxygenase 2, as well as actions independent of cyclooxygenase inhibition (30). Several case control and cohort studies show a significantly lower risk of EAC among patients who routinely consume aspirin or NSAID, compared to non-users (31). NSAIDs can have dangerous adverse effects, however, and presently, the use of NSAIDs solely for chemoprevention in BE is discouraged.

Presentation and diagnosis

Barrett's Esophagus is usually diagnosed on routine endoscopy for GERD or other esophageal or gastric issues. Four-quadrant, 1 cm apart jumbo biopsies are recommended. Endoscopic mucosal resection (EMR) should be performed for nodular BE as a diagnostic and possibly a therapeutic modality for superficial esophageal cancer.

Patients with esophageal cancer usually present with dysphagia, prompting endoscopy and biopsy. Gastric cardia tumors can present with bleeding rather than dysphagia. Once the diagnosis is confirmed, the next step is clinical staging for which computed tomography (CT) and positron-emission tomography (PET) are the two most useful imaging tools. Both modalities complement each other in the clinical staging of esophageal cancer (32,33). The enthusiasm for routine use of endoscopic ultrasound (EUS) for staging is slowly fading away. Multiple studies have shown its low utility in early stage esophageal cancer. Patients who present with dysphagia usually have at least T2 or T3 disease. These patients are recommended to receive neo-adjuvant therapy irrespective of para-esophageal lymph

node involvement, decreasing the importance of EUS (34). The EUS clearly is more sensitive to evaluate local invasion into peri-esophageal soft tissue. MRI is rarely indicated to evaluate liver, spine and other lesions.

Treatment

The past decade has seen significant advances in the treatment of BE. Radiofrequency ablation (RFA) has emerged as the leading ablative therapy modality for BE with excellent results (35). Patients with nodular BE are initially treated with EMR as a diagnostic and therapeutic strategy. If the margins are negative without deeper invasion, then the remaining BE is treated with RFA (36,37). Endoscopic submucosal dissection (ESD) is another excellent diagnostic and therapeutic approach for BE and mucosal carcinoma patients.

Patients with superficial esophageal cancer who are not candidates for endoscopic treatment are best served with esophageal resection. Minimally invasive esophagectomy (MIE) is becoming the standard of care, and one of the largest series from University of Pittsburgh has demonstrated a mortality rate of 1.4% with excellent outcomes (38). This modality is oncologically comparable to traditional open approaches with much less morbidity and mortality. Robotic-assisted minimally invasive esophagectomy (RAMIE) is competing with MIE to become the standard of care. RAMIE has the advantage of improved lymph node dissection and a better platform for training.

Multimodal treatment remains the mainstay of treatment of locally advanced esophageal cancer. Management depends on the location and histological type. Cervical esophageal squamous cell cancers are usually treated with definitive chemotherapy and radiation therapy. Locally advanced tumors of the mid and lower esophagus and gastric cardia are treated with induction therapy followed by esophageal resection. The optimal induction therapy for esophageal cancer remains controversial. Use of perioperative chemotherapy alone followed by esophagectomy is best shown beneficial in the MRC MAGIC (Medical Research Council Gastric Infusional Chemotherapy) trial (39). This trial showed two and five-year survival rates of 50% and 36% respectively. Although only 25% of patients had esophageal and esophagogastric carcinomas, multivariate analysis demonstrated that the benefits are valid irrespective of the site of the tumor. Recently, the CROSS trial from Netherlands showed much better outcomes when chemotherapy and radiation therapy were used in combination for induction therapy (40). In this randomized control trial, 368 patients with resectable esophageal cancer were included. The majority had adenocarcinoma, while 25% had squamous cell cancer. Patients in the induction treatment arm were treated with five weeks of Carboplatin and Taxol with concurrent 41.4 Gy of Radiation. Overall, 29% of patients had a complete response (pCR 49% for SCC and 23% for adenocarcinoma).

In a follow-up of surviving patients, the median overall survival was 48.6 months in the neo-adjuvant chemo-radiotherapy plus surgery group and 24 months in the surgery alone group. Median overall survival for patients with squamous cell carcinomas was 81.6 months in the neo-adjuvant chemo-radiotherapy plus surgery group and 21.1 months in the surgery alone group. For patients with adenocarcinomas, it was 43.2 months in the neo-adjuvant chemo-radiotherapy plus surgery group and 27.1 months in the surgery alone group.

It showed significant benefit for SCC and marginal benefit for adenocarcinoma. Recent trends favor the use of chemotherapy and radiation therapy in combination as adjuvant treatment rather than chemotherapy alone.

Conclusions

Esophageal cancer continues to be a predominantly fatal disease with only modest improvements in survival over the last three decades. Squamous cell cancer continues to be the most common histological subtype globally and accounts for most deaths from esophageal cancer. In the Western world, the incidence of esophageal adenocarcinoma has superseded that of esophageal squamous cell carcinoma, with most cases occurring in Caucasian males. Advances in the understanding of the role of genomic instability in Barrett's esophagus will facilitate identifying patients at risk for malignant transformation who would benefit from early intervention. Multimodal treatment using a combination of chemotherapy and radiation as induction therapy has emerged as the preferred induction therapy approach. Similarly, MIE and RAMIE are becoming the standard of care for esophageal resection.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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