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Invited Review

Esophageal cancer: The latest on chemoprevention and state of the art therapies

Gregoire F. Le Bras[a], Muhammad H. Farooq[a], Gary W. Falk[b], Claudia D. Andl (Ph.D.,) (Associate Professor)[a,*]

[a] Burnett School of Biomedical Sciences, College of Medicine, University of Central Florida, Orlando, FL, United States
[b] Division of Gastroenterology, Department of Internal Medicine, University of Pennsylvania, Philadelphia, PA, United States

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ABSTRACT

Esophageal cancer is currently the 8th most common cancer worldwide and the 6th leading cause of cancer-related mortality. Despite remarkable advances, the mortality for those suffering from esophageal cancer remains high, with 5-year survival rates of less than 20%. In part, because most patients present with late-stage disease, long-term survival even after resection and therapy is disappointingly low. As we will discuss in this review, multiple characteristics specific to the disease stage and patient must be considered when choosing a treatment plan. This article will summarize current standard therapies, potential application of chemoprevention drugs and the promise and partial failure of personalized medicine, as well as novel treatments addressing this disease.

Contents

* Corresponding author at: University of Central Florida, Burnett School of Biomedical Sciences, College of Medicine, 4110 Libra Drive, Building 20, BMS 223, Orlando, FL 32816, United States.
E-mail address: Claudia.andl@ucf.edu (C.D. Andl).

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1. Introduction

Esophageal cancer is currently the 8th most common cancer worldwide and the 6th leading cause of cancer-related mortality [1–3]. This year, an estimated 17,000 adults (13,500 men and 3500 women) in the United States will be diagnosed with esophageal cancer. It is expected that almost 16,000 deaths from this disease will occur this year. In the period from 2005 to 2011 the 5-years survival was 17.9% according to the SEER Cancer Statistics review.

As we will discuss in this review, multiple characteristics specific to the disease stage and patient are considered when choosing a treatment plan. With incidence rates rising and the 5-year survival being stagnant at below 20%, we must develop better diagnostics and therapies. In part, because most patients present with late-stage disease, long-term survival even after resection and therapy is disappointingly low. For advanced cancer, multimodal therapy such as chemoradiation or combination chemotherapy are the current standards. Yet, targeted therapies, e.g. against the programmed cell death protein 1 signaling pathway (PD1-PDL1), a so-called immune checkpoint, show promise.

Upon review of clinical presentation and diagnosis, we will focus on standard therapies and the promise of personalized medicine and novel treatments addressing this devastating disease.

2. Epidemiology

Two major histological subtypes arise: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Overall, esophageal cancer incidence is three times higher in men than women and varies geographically by subtype [3].

2.1. ESCC

ESCC prevalence is highest in East Asia, Eastern and Southern Africa and some parts of Europe [4]. ESCC incidence has decreased over the past three decades in developed countries, where annual incidence rates are generally less than 10 per 100,000 per year [5], on the other hand, ESCC incidence has remained high in less-developed countries with incidence rates exceeding 100 per 100,000 per year, particularly in high-risk areas of China [6], Iran [7,8] and South Africa [9]. The use of tobacco products, including cigarettes, cigars, pipes, and chewing tobacco, is a major risk factor together with alcohol consumption for developing esophageal cancer [10,11]. ESCC is also a disease with health disparities affecting more black males in Western countries and the United States, especially in the context of high risk behavior [12].

2.2. EAC

With ESCC rates declining, EAC now constitutes half of the esophageal cancer cases in Western countries [13]. The increased incidence rates are a reflection of life-style changes leading to high rates of obesity and acid reflux, major factors contributing to Barrett's esophagus, a premalignant lesion, which predisposes the patients for a higher risk of developing EAC [14]. Overall, incidence rates rise steadily with advancing age [15]. A meta-analysis of population-based studies showed a 5-fold increased risk for EAC for weekly acid reflux symptoms [16]. Obesity, in particular a body mass index of >30 is associated with an approximate 2-fold increased risk for EAC [17]. Strong epidemiologic risk factors include aging, male gender, obesity and smoking [18]. The regional differences observed in the incidence of EAC indicate that race is a strong risk factor for EAC. In the United Kingdom, the incidence of EAC is much lower among people of Asian and African descent compared with Caucasians [19]. In the United States, Asian and African Americans have a greatly decreased risk of EAC compared with non-Hispanic white people, with white Hispanics having an intermediate risk [20].

3. Clinical diagnosis and presentation

The clinical presentation of patients with esophageal cancer can be attributed to the direct effects of tumor growth on local and regional structures. Both, ESCC and EAC show similar manifestations, such as difficulties swallowing (dysphagia) being the most common symptom. Dysphagia initially occurs upon ingestion of dense solid food, and progresses gradually to interference with the consumption of soft foods and ultimately even liquids. Pain is a common symptom even in the absence of dysphagia, so is weight loss, which correlates with the occurrence of tumor-related anorexia [21].

Imaging modalities such as endoscopy, endoscopic ultrasonography, narrow band imaging or computed tomography and others are used in the diagnosis and staging of ESCC. Endoscopic screening as well as brush cytologic testing has been performed in China for patients with mild, moderate and severe dysplasia who have in increased risk of developing squamous cell carcinoma [22]. Screenings can prevent progression to more aggressive tumor growth and thereby aid the reduction of mortality [23].

As Barrett's esophagus is considered a risk factor for esophageal adenocarcinoma, patients with gastroesophageal reflux diseases (GERD), who are at risk for high grade dysplasia ot Barrett's esophagus, undergo endoscopy for screening [24]. Barrett's esophagus patients undergo surveillance endoscopy yet less than 15% of EAC are detected and most Barrett's patients will never progress to develop esophageal adenocarcinoma [25]. Subjecting biopsy material to next-generation sequencing has been shown to identify patients with Barrett's esophagus who might have an increased risk for EAC, based on common mutations for example in tumor suppressors such as TP53, as well as APC and CDKN2A [26]. So far, screening, counseling on lifestyle changes and preventative treatments are recommended [27,28].

4. Prevention

Acid reflux is a risk factor for Barrett's esophagus and for the progression to esophageal cancer. Therefore, the use of proton pump inhibitors is recommendedfor the reduction of gastric acid production. Yet, recent studies also found a reduction in cancer risk in people with Barrett's esophagus who take aspirin or similar. Some studies identified statins, which are commonly used to treat high cholesterol, to be effective in lowering cancer risk but are not prescribed as a preventative as they have serious side effects.

4.1. Proton pump inhibitors (PPI)

Proton pump inhibitors reduce stomach acid secretion through inhibition of the H+/K+-ATPase in the stomach. This treatment targets patients with GERD as a risk factor for Barrett's esophagus and esophageal adenocarcinoma. A significant association of PPI treatment with a decreased risk of high-grade dysplasia and adenocarcinoma has been shown in clinic-based cohort studies for patients with Barrett's esophagus [29–31]. The indirect evidence supporting PPIs as a cancer-preventative promises a cost-effective treatment for all patients with Barrett's esophagus after they have been informed of the potential risks of long-term PPI therapy [32]. There is some controversy as prolonged PPI use possibly promotes progression to EAC through increased gastric pH associated with bile salt toxicity [33].