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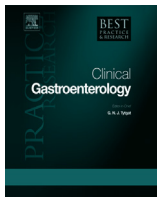

15

Chemoradiation in oesophageal cancer

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A B S T R A C T

Oesophageal cancer is the 8th most common cancer worldwide, and has significant mortality and morbidity rates. The two most common histological types, squamous cell carcinoma and adenocarcinoma, have different localizations, distinctive risk factors, and molecular mechanisms. Survival for patients with locoregional oesophageal cancer is poor when treated with surgery only, with 5-year survival less than 10–15%. Radiation therapy has limited efficacy when given alone. Concurrent chemoradiation improves local-regional control and facilitates margin-free resection when delivered preoperatively. Chemoradiation prolongs survival when given as definitive treatment or combined with surgery. Neoadjuvant chemoradiation also reduces risk of distant recurrence. To date, there is no data supporting the addition of targeted therapy to concurrent chemoradiation. Understanding molecular pathways regulating both radiosensitivity and tumorigenesis/invasion may lead to the discovery of new targeted agents, improving outcome of chemoradiation in terms of both locoregional and systemic control, ultimately resulting in prolonged survival.

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Introduction

Oesophageal cancer is the eightth most common cancer in the world [1], and the fifthth most common gastrointestinal cancer in the U.S., with an estimated 18,170 new cases and 15,450 deaths in 2013 [2]. Oesophageal cancer histology varies by location, with squamous cell carcinoma (SCC) more prevalent in the upper and middle thirds of the oesophagus and adenocarcinoma (ADC) more prevalent in the lower third of the oesophagus and at the gastro-oesophageal junction (GOJ). Worldwide, SCC represents the majority of oesophageal cancer cases and is predominant in the highest risk geographic area referred to as the 'oesophageal cancer belt' which stretches from the Middle East to central and eastern Asia. In Western countries, there is an increasing incidence of lower oesophageal adenocarcinoma accompanied by a decline in SCC, which is attributed to changes in lifestyle, including increasing obesity and the associated gastro-oesophageal reflux disease.

Oesophageal cancer patients frequently present with dysphagia, weight loss, and/or bleeding. Barium oesophagography can be an initial evaluation, but tissue biopsy is often obtained during oesophagogastroduodenoscopy (OGD) to confirm diagnosis. Endoscopic ultrasound (EUS) allows accurate assessment of invasion depth, and biopsy of regional lymph nodes. EUS-guided fine needle aspiration to diagnose N stage has a sensitivity of 84.7%–96.7% [3]. Computed tomography (CT) should be performed to assess for possible metastatic disease, including hepatic metastasis and distant lymphadenopathy (such as celiac, retroperitoneal, or supraclavicular). ^{18}F-fluorodeoxyglucose PET (FDG-PET) is increasingly being used to detect distant metastasis [4], and is now a standard staging modality [5].

For patients with localized disease, the goal of surgery is to remove the tumour with curative intent, while relieving local symptoms. However, the long-term outcome of surgery alone has been disappointing, with 5-year survival of only approximately 15–20% [6]. Although transthoracic resections had significantly higher early morbidity (pulmonary) and mortality rates, 5-year survival was similar between transthoracic and trans-hiatal resections [7]. The early RTOG 85-01 trial demonstrated chemoradiation with cisplatin and fluorouracil achieved a median survival of 14.1 months and 5-year survival rate of 27% in localized oesophageal cancer [8], and opened a new chapter of treatment of this disease. Understanding the pathogenesis, genetics, and mechanisms of radiosensitivity will further improve outcome of chemoradiation. Although Barrett's oesophagus is only associated with adenocarcinoma of oesophagus, most trials in oesophageal cancer included patients with squamous or adenocarcinoma of the oesophagus. As the risk factors, genetics, epidemiology, and treatment are different between these two different cancer types, it is essential to review squamous oesophageal cancer as well.

Risk factors and genetics

Frequent genetic alterations in SCC of the oesophagus include somatic copy number variations (SCNV) involving 3q26, 9p21, 11q13.3 and 8q24.3, as well as somatic mutations in *PIK3CA* [9], *TP53* and *NOTCH1* [10]. A recently reported whole-exome/targeted deep sequencing of 139 paired SCC cases, and analysis of somatic copy number variations (SCNV) of over 180 oesophageal SCCs identified additional mutated genes including *FAT1*, *FAT2*, *ZNF750* and *KMT2D* [11]. Dysregulation of the receptor tyrosine kinase (RTK)-MAPK-PI3K pathway, cell cycle progression, and epigenetic regulation of gene expression appear to be the most common molecular alterations identified in oesophageal SCC. Similarly, a Chinese study with 158 SCC cases, as part of the International Cancer Genome Consortium research project, using whole-genome sequencing and array comparative genomic hybridization analysis, identified 6 well known tumour-associated genes (*TP53*, *RB1*, *CDKN2A*, *PIK3CA*, *NOTCH1*, *NFE2L2*), and two additional significantly mutated genes (*ADAM29* and *FAM135B*) [12]. The study also identified microRNA *MIR548K* as a novel oncogene which enhances malignant phenotypes of SCC cells. In addition, several important histone regulator genes (*MLL2*|*KMT2D*, *ASH1L*, *MLL3*|*KMT2C*, *SETD1B*, *CREBBP* and *EP300*) involved in the Wnt, cell cycle, and Notch pathways are also frequently altered in ESCC. These pathways play important role in tumorigenesis, epithelial-to-mesechymal transition (EMT), invasion, and maintaining cancer stem cell survival [13].Thus, targeting these genes or other components of these pathways may be an effective strategy in treating SCC, particularly by eliminating

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