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ScienceDirect

Chronic Diseases and Translational Medicine xx (2018) 1−10

www.keaipublishing.com/en/journals/cdtm/

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Perspective

Customization of therapy for gastroesophageal adenocarcinoma patients

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Received 12 December 2017

Abstract

Gastroesophageal adenocarcinomas (GEACs) remain a global health problem. These are most often diagnosed at advanced stage and the estimated 5-year relative survival rate is about 5%. Although cure is not possible for patients with advanced GEAC, systemic therapy (chemotherapy or biochemotherapy) can palliate symptoms, improve survival and provide a better quality of life. One of the most promising options for some patients with advanced stage GEAC is immunotherapy, which can result in durable responses. Numerous phase III trials evaluating targeted therapies in different lines are ongoing and it is hoped that better biomarkers will emerge to identify patients who can benefit from targeted agents and immunotherapy in the future. Surgery remains as the corner stone for localized GEAC and adjunctive therapies can increase the survival rates by about 10%. The high toxicity and low completion rates of adjuvant therapy led to the strategies of preoperative treatment. With the results of ongoing pre-operative therapy trials we will be able to determine the optimal adjunctive approach for resectable GEAC.

Keywords: Therapy; Gastroesophageal adenocarcinoma; Esophageal adenocarcinoma; Gastric adenocarcinoma

Introduction

Gastroesophageal adenocarcinomas (GEACs), originating from esophagus, esophagogastric junction (EGJ) and stomach, remain as a worldwide health problem with an estimated 1,407,400 new cases and 1,123,300 deaths in 2012, globally.[1] These are highly lethal cancer types and constitute about 15% of all cancer related deaths.[1] In recent decades, location of esophageal carcinoma has shifted from proximal to distal location and gastric cancer has migrated from distal location to proximal one in West.[2] This trend is also found in Asia and South America. Changes in the

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Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.cdtm.2018.02.003

locations are mostly related to increased incidence of obesity, gastroesophageal reflux disease (GERD), Barrett's esophagus and decreased incidence of *H. Pylori* infection (Fig. 1).[3–6] This trend is occurring in other regions as well and EGJ adenocarcinoma (adenocarcinomas that have their epicenter in the 10-cm segment encompassing the 5 cm above and 5 cm below EGJ) constitutes the major burden of GEACs. Selecting appropriate therapy for GEAC may be possible after accurate stage is determined and patients discuss with a multidisciplinary team consisting of medical oncologists, surgeons, radiation oncologists, radiologists, pathologists and supportive care specialists. With the American Joint Committee on Cancer (AJCC) 8th edition, staging and definition of esophageal, EGJ and gastric cancers are more clear.[7] According to the AJCC 8th edition, a tumor involving the EGJ with its epicenter $\leq$ 2 cm below EGJ, should be classified as esophageal cancer, all others below EGJ should be classified as gastric cancer. This classification is important to deciding on the right surgical approach. Surgery is the most important component of treatment for localized GEACs but unfortunately most of the patients are diagnosed with an advanced stage.[3,4] For intramucosal GEACs, minimally invasive approaches like endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) can be alternatives to surgery in experienced centers.[8,9]

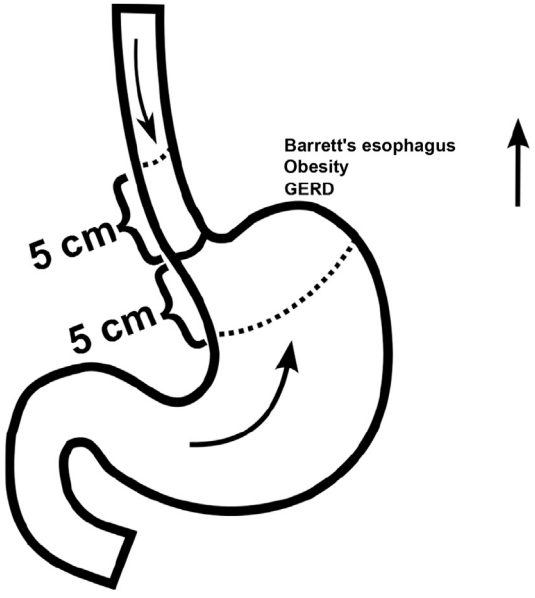

Fig. 1. The location changing trend of gastroesophageal adenocarcinomas. GERD: gastroesophageal reflux disease.

Therapy for localized esophageal adenocarcinoma

Surgery remains as the corner stone treatment for operable esophageal adenocarcinoma (EAC). However, the reported median overall survival (OS) durations for patients treated only with surgery were less than 18 months in different trials.[10,11] Therefore, preoperative strategies have become popular. It was shown that post-treatment pathologic stage is the best prognosticator of survival for EAC and the OS was significantly better for patients with no residual carcinoma.[12]

Radiation Therapy Oncology Group trial 8911 (RTOG 8911) compared surgery alone with preoperative cisplatin plus fluorouracil (CF) in localized esophageal and EGJ tumors mostly composed of adenocarcinoma.[10,13] In this trial, adding CF to surgery did not prolong the survival [16.1 months for surgery-only group and 14.9 months for pre-operative CF group; hazard ratio (*HR*), 1.07; 95% *CI*: 0.87–1.32; $P = 0.53$] and margin negative (R0) resection rates were similar for both groups (59% for surgery-only group and 62% for pre-operative CF group). However, a similar trial conducted by the United Kingdom Medical Research Council (OE02)[11,14] demonstrated longer OS for pre-operative CF patient group (13.3 months for surgery-only group and 16.8 months for pre-operative CF group; *HR*, 0.79; 95% *CI*: 0.67–0.93; $P = 0.004$) and R0 resection rates were parallel (53% for surgery-only group and 60% for pre-operative CF group) with the rates reported by RTOG8911. The long-term follow-up of both of these studies showed that performing an R0 resection is the most important factor related with longer OS.[13,14] A recent study, OE05, compared two cycles of pre-operative CF with four cycles of pre-operative epirubicin, cisplatin, and capecitabine (ECX).[15] There was no survival benefit with intensified therapy (median OS; 23.4 months in the CF group and 26.1 months in the ECX group; *HR*, 0.90; 95% *CI*: 0.77–1.05, $P = 0.19$). Moreover, the number of patients that could complete the pre-operative therapy was significantly higher in CF than ECX group (96% of CF group *vs.* 81% of ECX group; $P < 0.0001$) and more patients discontinued the therapy due to toxicities in ECX group (10% *vs.* 2%).

In a study from France, peri-operative CF was compared with surgery alone in a patient group mostly consisting of patients with esophageal and EGJ adenocarcinoma.[16] It resulted in a longer OS benefit in favor of the peri-operative treatment group (*HR*, 0.69; 95% *CI*: 0.50–0.95; $P = 0.02$). However, only 50% of the peri-operative treatment group could receive the planned post-operative treatment. This trial was

Please cite this article in press as: Kaya DM et al., Customization of therapy for gastroesophageal adenocarcinoma patients, Chronic Diseases and Translational Medicine (2018), https://doi.org/10.1016/j.cdtm.2018.02.003