

Management of Locally Advanced Gastroesophageal Cancer Still a Multidisciplinary Global Challenge?



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KEYWORDS

• Gastroesophageal cancer • Perioperative • Locally advanced • Chemotherapy

KEY POINTS

- Available data indicate that patients with clinical stage II or III adenocarcinoma of stomach, gastroesophageal junction (GEJ), and esophagus benefit from multimodality treatment approaches.
- Therapy options for western patients include perioperative chemotherapy for both gastric and GEJ cancer, postoperative chemoradiation for gastric cancer, and preoperative chemoradiation for esophageal adenocarcinoma.
- In terms of perioperative chemotherapy protocols, platinum-fluoropyrimidine doublets, such as cisplatin and 5-fluorouracil (5-FU) (CF); triplets, such as epirubicin, cisplatin, and capecitabine (ECX); or docetaxel, 5-FU, leucovorin, oxaliplatin, and docetaxel (FLOT) are appropriate regimens.
- Current studies still do not recommend a preferred chemotherapy regimen but rates of complete pathologic remission differ among the regimens and are approximately at 2% with CF, 7% with ECX, and 16% with FLOT.
- Adding postoperative radiotherapy to established perioperative or adjuvant protocols did not improve survival.
- Future studies will focus on evaluating the role of biologic agents such as trastuzumab and pertuzumab (for HER2-positive disease), or ramucirumab, as well as immunomodulatory antibodies, such as programmed death (PD)-1 or programmed death-ligand (PD-L1) antibodies.

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OVERVIEW AND INTRODUCTION

Although the overall gastric cancer incidence is decreasing, the incidence of adenocarcinoma of the gastroesophageal junction (GEJ) has increased.¹ The global shift of gastric cancer (and esophageal cancer) location toward the GEJ^{2,3} led the International Union Against Cancer (UICC) to adopt the GEJ cancers into its seventh edition of the tumor-node-metastasis (TNM) classification as a new entity.⁴ These tumors were staged as esophageal tumors, triggering a new controversy, because cardia cancer and distal esophageal tumors are treated in a different way in many regions, particularly with regard to the surgical therapy.

The symptoms of gastroesophageal cancer appear relatively late. Therefore, most of affected individuals present with locally advanced disease; that is, with clinical stage of T3 or T4 and/or regional lymph nodes that are affected by disease, or even with distant metastases. As a result, gastric and GEJ carcinomas are commonly fatal diseases with 5-year survival rates of approximately 20% to 30%.^{5,6} Surgery remains the only form of curative treatment but is associated with relatively high rates of regional and distant recurrence. Therefore, it has become a worldwide consensus that surgery alone is no longer the standard of care in the management of these tumors. Numerous multidisciplinary strategies have been evaluated during the last decades to improve the treatment results by adding adjuvant or neoadjuvant systemic therapy, sometimes combined with radiotherapy. These approaches resulted in an absolute improvement in survival of around 10% to 15% over surgery alone but have not been compared head-to-head in appropriately powered clinical trials. Therefore, the optimal therapeutic approach remains controversial and practices vary around the globe. This article summarizes the current evidence of various approaches, highlights some ongoing and planned clinical trials, and suggests options to further improve current treatment strategies and, thereby, prognosis of gastric and GEJ tumors.

DIFFERENCES WITHIN THE CATEGORIES GASTRIC, GASTRIC CARDIA, AND LOWER ESOPHAGEAL ADENOCARCINOMA: DOES LOCATION AND HISTOLOGY MATTER?

Besides the different anatomic regions and lymph node compartments affected by the tumor, substantial differences between gastric noncardia, gastric cardia, and lower esophageal adenocarcinomas exist. Tumors located in the cardia and distal esophagus are predominately intestinally differentiated, compared with the stomach cancers, where diffuse tumors are more commonly located. In terms of epidemiology, stomach cancers are more prevalent in Asian countries, whereas cardia cancer and distal esophageal adenocarcinomas are typically seen in the West (eg, Europe, North America, and South America). The groups are also distinct in terms of the underlying risk factors. Gastroesophageal reflux and consecutive Barrett metaplasia are the major risk factor associated with esophageal adenocarcinoma. This association could not be clearly established for gastric cardia cancer. For more distal stomach cancers, *Helicobacter pylori* infection and nutritional habits are well-recognized risk factors. In the metastatic setting, there is a general consensus that response and survival following chemotherapy is similar among the groups.⁷ However, in curable patients, outcomes after surgical resection and response to perioperative chemotherapy are different.⁸⁻¹²

The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC)¹³ and Fédération Nationale des Centres de Lutte contre le Cancer (FNCLCC)/Fédération Francophone de Cancérologie Digestive (FFCD)¹⁴ studies were the first to show that the benefit from neoadjuvant chemotherapy seemed to be greater in GEJ tumors compared with gastric noncardia or true esophageal

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