

Current Progress in the Adjuvant Treatment of Gastric Cancer

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KEYWORDS

- Gastric cancer • D2 resection • Adjuvant chemotherapy • S-1 • Capecitabine
- Cisplatin • Oxaliplatin • Infusional 5-FU

KEY POINTS

- Staging of gastric cancer should include laparoscopy.
- Perioperative chemotherapy improves survival in addition to surgery.
- Postoperative chemotherapy after D2 resection improves survival after surgery.
- After less than a D1 resection adjuvant chemotherapy and radiation therapy improve survival.
- For gastroesophageal junction cancers, combined chemotherapy and radiation therapy may be needed to improve R0 resection rates.

Gastric cancer is a leading global health problem and accounts for the third most common cause of cancer-related death.¹ In the United States in 2016 there will be an estimated 26,370 new cases and 10,730 deaths, accounting for 1.6% of new cancer diagnoses.² The disease is most common in East Asia, and China accounts for more than half the of world's gastric cancer burden. *Helicobacter pylori* infection, which is the cause of a substantial portion of gastric cancer globally, is declining in incidence and may account in large part for the steep reduction in cases of gastric cancer in the West over the past century.³ Progress has been made in the surgical management of locally advanced disease, and trials have established a clear role for combining systemic chemotherapy in the adjuvant or neoadjuvant setting with surgery. The application of adjuvant radiotherapy is shifting in utilization with the increasing use of preoperative and postoperative chemotherapy, and its relative benefit may be a function of the adequacy of surgical management performed.

The author has nothing to disclose.

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Surg Oncol Clin N Am ■ (2016) ■-■

<http://dx.doi.org/10.1016/j.soc.2016.10.008>

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STAGING AND SURGICAL MANAGEMENT OF GASTRIC CANCER

In the West, there is no effective screening for gastric cancer, given the relative rarity of the disease compared with diseases like breast and colorectal cancer, which have active screening programs. As a consequence, most patients diagnosed with gastric cancer present with locally advanced and often symptomatic disease, and up to 40% of patients present with overt metastatic disease. In high-incidence countries, such as Korea and Japan, there are population-wide screening programs leading to earlier stage at diagnosis. Stage for stage, survival outcomes appear superior in Japan and Korea, which may reflect inherent biologic differences in gastric cancer in the East and West.⁴ Recent genomic profiling studies indicate similar molecular subtypes of gastric cancers between Eastern and Western patients with gastric cancer, but immune signatures may differ.⁵⁻⁷

The standards for surgical staging and management of gastric cancer have been developed largely in Asia. The American Joint Committee on Cancer has recently updated the staging of gastric cancer, using nodal count to reflect N substage and in an attempt to harmonize with Eastern staging systems.⁸ After diagnosis with upper endoscopic assessment and biopsy confirmation, gastric cancer staging includes imaging with a computed tomography (CT) scan of the chest, abdomen, and pelvis. If metastatic disease is revealed on imaging, biopsy confirmation of metastatic disease may be required, as clinically indicated, before consideration for primary treatment with palliative chemotherapy. PET with fludeoxyglucose (FDG-PET) imaging is not yet routinely accepted as part of staging, but recent studies suggest that up to 15% of patients may have occult metastatic disease identified on FDG-PET scan that is not seen on CT imaging,⁹ indicating an ability independently to upstage patients to metastatic disease. Diffuse gastric cancers, however, appear to have a high proportion of FDG-PET scan nonavidity. If no metastatic disease is seen on CT scan imaging, endoscopic ultrasound is performed to assess T and N stage. For early T1N0 tumors, endoscopic mucosal resection and endoscopic mucosal dissection have emerged as preferred therapy options for superficial T1A mucosal lesions.¹⁰ For more deeply penetrating T1b lesions, limited gastrectomy and assessment of sentinel lymph node involvement is also an emerging surgical strategy.¹¹

Unfortunately, in the West most patients have more extensive T3 or T4a and node-positive disease. If endoscopic ultrasound identifies T2 or greater T stage or node-positive disease, staging laparoscopy is performed to assess for peritoneal disease, often poorly imaged or missed altogether on routine CT or PET scan imaging. In the absence of visible peritoneal disease, the finding of a positive cytology on peritoneal washings is also now classified as stage IV disease and should direct patients away from surgery and toward chemotherapy-based management of metastatic disease.⁸

Surgery remains the mainstay of curative treatment. There is an emerging consensus about the appropriate surgical management of locally advanced gastric cancer. In Asia, the surgical standard of care combines a subtotal or total gastrectomy with D2 lymph node resection, which encompasses greater and lesser curvature nodes taken in a D1 resection, and also includes gastrohepatic, celiac, and splenic nodes. Extending surgery to include more extensive nodal resection, including retroperitoneal nodes in a D3 resection, has not been shown to improve outcome in a randomized trial conducted in Japan comparing D2 and D3 resections.¹² Although earlier small, comparative trials of D2 versus lesser resections in the West failed to indicate a survival advantage for a D2 resection and suggested greater operative morbidity and the potential need for splenic and pancreatic resection,¹³⁻¹⁵ more contemporary series and updates of earlier series indicate superior survival for a D2 resection.^{16,17}

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