Modern Surgical Considerations for Gastric Cancer

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Abstract
Surgical resection remains the mainstay of treatment for localized gastric adenocarcinoma. The type and extent of resection depends on tumor location. Although the incidence of gastric cancer has been declining, a shift has occurred to more tumors involving the proximal compared with the distal stomach. Appropriate treatment depends on a thorough staging process to exclude the presence of distant metastatic disease. Current staging modalities include high-quality CT scan, endoscopic ultrasound, PET, and laparoscopy. The value of peritoneal lavage to detect occult peritoneal disease is under investigation. The principles of surgical resection have always included negative resection margins and adequate lymph node examination. Controversial topics requiring further study include laparoscopic resections and hepatic metastasectomy. This review highlights the salient points of current surgical management of gastric adenocarcinoma. (JNCCN 2008;6:885–894)

Background
Although gastric cancer has been decreasing globally over the past decades, it remains the fourth most common cancer type worldwide. In the United States, it is one of the least common cancer types, accounting for fewer than 2% of all cancers. In 2008, an estimated 21,500 new cases of gastric cancer will be diagnosed and approximately 10,880 deaths will occur.

In addition the proportion of proximal gastric cancers has risen. Based on data collected by the National Cancer Database (NCDB), proximal cancer is more likely to occur in young white men, and distal cancer is more likely to occur in Asians, African Americans, and Hispanics. The study also indicates that tumor location may influence treatment. Although surgical resection remains the primary treatment modality, patients with proximal gastric cancer are more likely to undergo adjuvant therapy, particularly preoperative therapy. This article focuses on surgical options, provides an overview on the diagnostic tests used to assess resectability, describes the principles of surgical resection, and presents controversial topics, such as laparoscopic surgery, peritoneal lavage, and hepatic metastasectomy (Table 1).

Determining Resectability
Once a patient is diagnosed with gastric adenocarcinoma, usually from endoscopic gastric biopsy, further workup is needed to assess medical fitness, staging, and resectability. A thorough history and physical examination are cost-effective tools for evaluating comorbidities and performance status. Chest radiograph and CT scans of the abdomen and pelvis are gold standards for examining possible metastases or regional lymphadenopathy.

Two recent studies reported that the accuracy of endoscopic ultrasound (EUS) ranges from 57% to 83% for staging depth of tumor invasion and 50% to 78% for nodal involvement. Therefore, EUS, with or without fine needle aspiration, can significantly influence treatment selection, particularly if neoadjuvant therapy is considered. However, EUS is not indicated in patients with metastatic disease, and its use should be limited to potentially resectable cancers.
Metabolic imaging with PET using 18F-fluorodeoxyglucose is used in various malignancies, but its role in gastric cancer still must be determined. Although PET is 94% sensitive in detecting gastric cancer,\(^7\) it was found to be less accurate than spiral CT in staging locoregional involvement, but better at diagnosing distant metastases.\(^8-10\) However, PET scan detected 5 of 40 (15%) positive nodes missed by CT.

In a small series of patients (N = 68), PET scan added diagnostic value in 15%, upstaging 6% and downstaging 9%.\(^7\) A meta-analysis comparing PET, ultrasound, CT, and MRI determined that PET scan was the most sensitive imaging modality for detecting hepatic metastases.\(^11\) PET may also be useful in determining therapeutic response to chemotherapy. Ott et al.\(^12\) found that tumors that responded metabolically on PET correlated highly with histopathologic response and better patient survival. Therefore, PET scan should be used in selected cases, such as locally advanced tumors in which the metastatic potential is high or in cases for which neoadjuvant treatment is being considered.

Patients are deemed resectable if they are medically fit, have limited involvement of contiguous structures, and have no evidence of distant metastases. With locally advanced tumors, the tail of the

### Table 1 Salient Points

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| Diagnostic studies      | • History and physical examination  
                          • Endoscopy and biopsy  
                          • CT scan of the abdomen  
                          • Endoscopic ultrasound for potentially resectable disease  
                          • PET scan helpful in advanced disease with high risk for metastasis and for patients being evaluated for chemotherapeutic response  
                          • Diagnostic/staging laparoscopy for patients undergoing neoadjuvant therapy                                                                 |
| Surgical resection      | • Main principle of surgical oncology is microscopically negative margins  
                          • Adequate nodal samplings                                                                                                                                 |
| Lymphadenectomy         | • Japanese institutions are performing a D2 for early gastric cancer and a D3/4 (para-aortic lymph node dissection) for advanced, but resectable disease\(^6\)  
                          • Western societies (Dutch trial\(^32\)) found a D1+ is adequate; D2 or above has higher morbidity but no significant benefit  
                          • NCCN guidelines\(^91\) recommended at least 15 nodes be examined                                                                                                                                 |
| J-pouch reconstruction  | • Decrease intestinal transit time  
                          • Better quality of life assessments in postoperative months 30-60, with no significance < 30 months or > 60 months                                                                 |
| Laparoscopic surgery    | • Less invasive  
                          • Risks for port site recurrence and vascular injury  
                          • Feasible for early gastric cancers                                                                                                                                 |
| Peritoneal lavage       | • Additional prognostic information  
                          • Low yield  
                          • Further clinical studies needed                                                                                                                                 |
| Recurrent disease/palliative gastrectomy | • Patient is medically fit  
                          • Usual indication: obstruction or excessive bleeding                                                                                                                                 |
| Hepatic metastasectomy  | • Improved survival if an R0 was achieved  
                          • Limited hepatic involvement, adequate functional residual liver volume, and no extrahepatic disease                                                                 |
| Adjuvant therapy        | • MacDonald trial\(^87\) (SWOG-9008, INT-0116, RTOG-9018, NCCTG-90-41-51, ECOG-6290, CALGB 9195) showed survival benefit with adjuvant chemoradiation  
                          • Cunningham et al.\(^89\) (MAGIC trial) showed survival benefit with perioperative chemotherapy  
                          • Multidisciplinary management is recommended                                                                                                                                 |
pancreas, hilum of the spleen, head of the pancreas, and lateral segment of the liver may be involved through direct extension, but these patients are still deemed resectable. However, postoperative morbidity increases as more organs are resected to achieve negative surgical margins.

Some experts have found staging laparoscopy for advanced gastric cancer to have significant impact on decision-making, especially in patients for whom aggressive surgical treatments are planned. Blackshaw et al. reported unexpected metastases found during staging laparoscopy in 21 of 258 patients (8%) with potentially resectable gastric adenocarcinoma, whereas Sarela et al. reported a much higher rate of occult metastases found on laparoscopy: 85 of 718 (25.8%) patients with gastric cancer who were previous deemed stage M0 based on CT scan.

**Gastric Resection**

The type and extent of surgical resection depends on tumor location. For a tumor involving the antrum or prepyloric area, a distal or subtotal gastrectomy is performed with approximately 4- to 5-cm grossly negative margins and reconstructed with a gastrojejunostomy. A prospective randomized trial comparing subtotal with total gastrectomy for tumors in the distal half of the stomach found similar oncologic outcomes. The 5-year survival for the subtotal group was 65% compared with 63% for the total group. Given the technical challenges of total gastrectomy, higher splenectomy rate, and decreased quality of life, a subtotal gastrectomy is acceptable for distal cancers if adequate negative margins are obtained.

For tumors involving the proximal stomach, significant controversy exists regarding the optimal surgical treatment. For tumors involving the cardia without gastroesophageal junction involvement, either a proximal or total gastrectomy is an option. In a non-randomized study comparing them, Harrison et al. report equivalent mortality and survival. Despite the equivalent oncologic outcome, multiple studies have shown a significantly higher rate of anastomotic strictures and reflux esophagitis with proximal gastrectomy. Because of the reflux that develops after proximal gastrectomy, the authors prefer to perform a total gastrectomy for tumors in this location.

Proximal gastric cancers with involvement or near involvement of the gastroesophageal junction can be treated with either gastrectomy or esophagogastrectomy (Ivor-Lewis or transhiatal). In a retrospective review comparing options, Ito et al. reported no difference in mortality rate, but a higher morbidity rate with esophageal resection. However, gastrectomy was associated with microscopically positive margins in 38% of the patients as opposed to 7% for esophagogastrectomy. Clearly, no single surgery type is best for tumors in this area; resection type should be based on ability to achieve negative margins with acceptable morbidity.

Although no randomized prospective trials have assessed optimal surgical margins, Bozzetti et al. noted that surgical resections of 6 cm or greater proximally and 3 to 5.9 cm distally are associated with 100% negative margins. A few recent studies have shown worse survivals for patients with positive margins and negative nodes. For patients with positive nodes, especially those with 5 or more, margin positivity confers no significant survival difference. Today, most surgeons routinely request intraoperative frozen section examination of the margins before reconstruction. Regardless of type of resection and length of margins, the main principles of surgery are microscopically negative margins (R0 resection) and clearance of regional lymph nodes in patients with no distant metastases.

**Lymphadenectomy**

Although uniform consensus is that nodal sampling is necessary, dichotomy exists between Eastern and Western practices. In 1981, the Japanese Research Society for Gastric Cancer published general rules for studying gastric cancer and its pathology through defining lymph node stations. Since then, numerous studies have examined the clinical relevance of the extent of nodal dissection in gastric cancer resection. Despite the difference in practice, the authors have accepted the following definitions: D0 dissection means gastrectomy with any lymph node removal that is less than a D1; D1 dissection entails gastrectomy and resection of the greater and lesser omenta (which would include the lymph node of station 1–6, right and left cardiac, along lesser and greater curvature, suprapyloric along the right gastric artery, and infrapyloric, respectively); D2 dissection is a D1 plus the anterior leaf of the transverse mesocolon and all the nodes along the left gastric...
artery, common hepatic artery, celiac artery, splenic hilum, and splenic artery (station 7–11, respectively); and D3 dissection is more extensive than D2 because it includes the para-aortic lymph nodes (station 16; Figure 1).31 The extent of lymphadenectomy has been among the most controversial issues in gastric cancer surgery. Multiple retrospective reports have found an improved survival in patients undergoing D1 lymphadenectomy compared those undergoing D2, and consequently several prospective randomized trials have been performed. The largest of these was conducted by the Dutch Gastric Cancer Group.32 After 11 years of follow-up the authors reported a 30% survival rate for D1 resections, which was similar to 35% for D2 (P = .53). Any potential survival benefit of D2 was offset by an increase in perioperative mortality: 10% versus 4% (P = .004). When hospital deaths were excluded, survival rates improved to 32% for D1 and 39% for D2 (P = .10), with a statistically significant decrease in relapse risk favoring D2. In addition to D2, age older than 70 years, splenectomy, and pancreatectomy were factors associated with increased morbidity and mortality. The authors concluded that extended lymph node dissection could be beneficial if perioperative morbidity and mortality could be reduced. Similar findings were reported from a prospective randomized trial conducted by the British Medical Research Council.33 Splenectomy and distal pancreatectomy were part of the Japanese D2 dissection to better evaluate lymph node stations 10 and 11. However, the Dutch trial found that splenectomy is associated with greater postoperative morbidity.32 Similarly, multiple studies from around the world showed that curative gastrectomy with concurrent splenectomy or pancreateciosplenectomy provided no statistically significant survival benefit for patients with gastric cancer, and that it is associated with increased pancreatic and infectious complications.34–41 Splenectomy or pancreaticosplenectomy is only beneficial when there is direct extension of the tumor or very bulky lymph node disease is present at the splenic hilum.41 A recent nonrandomized phase II trial of pancreas preserving D2 resections reported a mortality rate of 3.1% and a 5-year survival of 55%.42 In the United States, greater emphasis has been placed on number of nodes removed and examined than on location. In a retrospective review of more

Figure 1A and B Lymph node stations according to the Japanese Research Society for Gastric Cancer.31,32
Key: 1, right cardiac; 2, left cardiac; 3, lesser curvature; 4, greater curvature (4S, superior greater curvature; 4D, distal greater curvature); 5, suprapyloric; 6, infrapyloric; 7, left gastric artery; 8, common hepatic artery; 9, celiac axis nodes; 10, splenic hilum; 11, splenic artery; 12, portal hepatis; 13, posterior pancreatic head; 14, root of the mesentery; 15, transverse mesocolon; and 16, para-aortic.
than 1000 patients, Karpeh et al.\textsuperscript{43} noted that number of nodes involved has greater prognostic significance than location. Furthermore, significance was greatest when at least 15 lymph nodes were examined; thus, the current American Joint Committee on Cancer (AJCC) staging for gastric cancer recommends examining at least 15 nodes for accurate staging.\textsuperscript{44} Although this recommendation is not driven by prospective randomized trials (level 1 data), it is supported by large retrospective studies.\textsuperscript{45–47}

More recently, the ratio of positive nodes to nodes examined was found to have greater prognostic significance than absolute number of positive lymph nodes.\textsuperscript{48,49} The AJCC stratifies positive lymph nodes as N1 (1–6), N2 (7–15), or N3 (> 15). However, lymph node ratio identifies subsets of patients with different survival rates within groups.\textsuperscript{49} Lymph node ratio may have a different prognostic value because it accounts for patients with fewer lymph nodes and the absolute number of nodal positivity.

**Reconstruction**

Although most surgeons agree on extent of surgical resections for a specific gastric cancer, many options are available for restoring intestinal continuity. Some studies report that a J-pouch reconstruction is more physiologic and allows for slower food transition time, and thus less dumping and better nutrient absorption.\textsuperscript{50} McAleese et al.\textsuperscript{51} found that patients with J-pouch reconstruction had less postprandial pain, better nutrition, and fewer dietary restrictions than those who underwent standard esophagojejunostomy reconstruction. Recently, a prospective randomized study comparing esophagojejunostomy with pouch reconstruction after total gastrectomy reported improved long-term quality of life in patients who had pouch reconstruction, but only after 30 months, and it lasted for approximately 2 years.\textsuperscript{52} At 78 months postgastrectomy, the authors saw no significant difference in any quality of life assessments between the groups. In addition, although the authors noted this improvement in assessments, they did not find any difference in postoperative weight, number of meals per day, or quantity of food consumed. Despite other small studies reporting similar benefits of pouch reconstruction,\textsuperscript{53–55} no consensus exists as to the optimal method of reconstruction.

**Laparoscopic Surgery**

In the past 2 decades, laparoscopic surgery has gained popularity because it offers less pain, shorter hospital stay, and quicker recovery. Laparoscopic-assisted Billroth I gastrectomy was introduced 1994 by Kitano et al.,\textsuperscript{56} and surgeons from Japan,\textsuperscript{57} Korea,\textsuperscript{58} and Italy\textsuperscript{59} have reported outcomes after laparoscopic gastrectomy. Although they have shown that laparoscopy-assisted distal, subtotal, and total gastrectomies with lymph node dissection are feasible with acceptable morbidities and mortalities, most of these patients had early gastric cancers. In a multicenter study on the long-term oncologic outcome of laparoscopic gastrectomy for early cancers in Japan, Kitano et al.\textsuperscript{57} found that 5-year disease-free survival was 99% for stage I and 86% for stage II disease.\textsuperscript{59} The most serious complication for this procedure is vascular injury during lymph node dissection, especially when the surgeon is inexperienced.\textsuperscript{60} Although Kitano et al.\textsuperscript{57} did not find any in their study, published case reports describe port site recurrence after laparoscopic gastrectomy, especially in advanced disease.\textsuperscript{61} Despite numerous studies showing the safety and feasibility of laparoscopy, no randomized prospective trial has shown the long-term outcome for this procedure; therefore, its role for potentially curable patients still must be determined.

**Peritoneal Lavage**

Despite adequate surgical treatment, a common site of recurrence is peritoneal carcinomatosis.\textsuperscript{62} In 1978, Nakajima et al.\textsuperscript{63} found that peritoneal cytology was a good prognostic indicator of peritoneal recurrence. However, in a study of advanced gastric cancer without metastatic disease, Abe et al.\textsuperscript{64} found no correlation between peritoneal recurrence and positive peritoneal cytology. The development of peritoneal disease occurred in 22% of patients with negative cytology and in 18% with positive. The incidence of positive peritoneal cytology absent visible peritoneal disease is low (6%–15%).\textsuperscript{65,66} Several studies have reported decreased survival in patients with positive peritoneal cytology.\textsuperscript{57,67} These studies report a correlation between serosal involvement and lymph node positivity with positive peritoneal lavage.

Despite the prognostic significance of positive peritoneal cytology, a recent report from M. D. Anderson suggests that resection after neoadjuvant
therapy may improve survival in some patients.\textsuperscript{66}\)

Unfortunately, the data on peritoneal cytology are from retrospective studies performed at single institutions, which often include patients with macroscopically positive disease.

To increase the sensitivity of peritoneal lavage, great interest has been shown in evaluating the fluid with biologic markers. Asao et al.\textsuperscript{49} showed that carcinoembryonic antigen (CEA) levels in peritoneal washings negatively correlated with survival, and the study in 155 gastric cancer patients by Nishiyama et al.\textsuperscript{50} supported the finding that elevated CEA level in peritoneal washings predicts a shorter interval to peritoneal recurrence.

Real-time reverse transcriptase–polymerase chain reaction (RT-PCR) was developed to analyze peritoneal lavages. Although CEA enzyme-linked immunosorbent assay can detect 100 ng/g of protein, RT-PCR could reliably detect mRNA copies of CEA in the presence of as little as 100 cells.\textsuperscript{71} The technique is sound, but the detection system is still not perfect because a molecule specific to all cancer cells has not yet been identified. CEA is a good test; its disadvantages are that not all gastric cancer cells express CEA and some circulating peripheral blood leukocytes of healthy people express low levels.\textsuperscript{71}

Katsuragi et al.\textsuperscript{27} proposed to measure the mRNA levels of CEA and cytokeratin-20 (CK20), a protein specific for cells of gastrointestinal origin. Separately, CEA and CK20 RT-PCR have a sensitivity of 65% and 51% and a specificity of 82% and 81%, respectively. Used together, the sensitivity of either gene positivity increased to 81%, but specificity decreased to 80%.\textsuperscript{72} Routine peritoneal lavage has not been uniformly adopted as a staging modality in gastric cancer; the authors believe additional clinical studies are required for widespread acceptance.

### Recurrent Disease

Recurrence after curative resection is common, especially in advanced cases. Surgical intervention in recurrence is usually for palliative reasons and is infrequently curative in patients with limited disease. The most common palliative surgical interventions are for patients with intestinal obstruction or excessive bleeding. In a retrospective review, Song et al.\textsuperscript{62} examined the role of surgery in the treatment of recurrent gastric cancer and found that only approximately 25% of patients evaluated underwent complete resection of the recurrent disease. These patients had gastric remnant recurrence or hepatic or ovarian metastases. Compared with patients who underwent exploration with palliative or no other intervention, those who underwent complete resection had a much better mean survival duration of 52 versus 13 (palliative) and 8.7 months (laparotomy alone).\textsuperscript{62}

### Palliative Gastrectomy

Patients with stage IV gastric cancer are typically not treated with surgical therapy but offered systemic treatment. Management of symptoms caused by primary tumor growth can be managed with various modalities, including radiation therapy, endoscopic interventions, or even surgical procedures (e.g., bypass). The role of gastrectomy in these patients tends to be limited, because higher morbidity and mortality are associated with incurable malignancy. Several small studies have suggested gastrectomy has a survival benefit in patients with metastatic gastric cancer.\textsuperscript{73–77} The benefit is typically reserved for young patients (< 70 years) with limited metastatic tumor burden, good performance status, and resectable tumors. Because of the apparent selection bias inherent in these studies, it is difficult to draw any meaningful conclusions. However, with appropriate patient selection and multidisciplinary discussion, a minority of patients with metastatic disease may benefit from gastrectomy. A multicenter, prospective, randomized trial comparing gastrectomy with chemotherapy and chemotherapy alone in patients with stage IV cancer is being conducted in Japan and Korea.\textsuperscript{78}

### Hepatic Metastasectomy

As a result of improvements in liver surgery, hepatic metastasectomy has been performed for gastric cancer. However, determining its benefits is difficult because solitary liver metastases are rare. Linhares et al.\textsuperscript{79} reviewed his institution’s record and found that isolated liver metastases occurred in fewer than 0.5% of cases over 5 years. Even in the East, the rate of isolated liver metastases from gastric cancer is only 0.53%.\textsuperscript{80}

Although rare, long-term survivors have been reported. Koga et al.\textsuperscript{81} reported a median survival of 34 months in a series of 42 patients with hepatic metastases, with 8 patients surviving more than 5
years. Okano et al. suggested that synchronous or metachronous liver lesions without peritoneal or other distant metastases should be evaluated. Patients with synchronous liver resection have lower in-hospital mortality and better 5-year survival than those with synchronous metastasectomy. Ambiru et al. recommended attempting complete resection of hepatic metastases only when residual liver function is adequate. Similar to the colorectal experience, hepatic metastasectomy for solitary lesions has better outcome than for multiple nodules, but multiple nodules within 1 lobe should still be considered. A negative surgical margin of at least 1 cm is preferable. Hepatic metastasectomy for gastric adenocarcinoma is controversial and still requires further investigation.

Adjuvant Treatment

Despite potentially curative resection, most patients with gastric adenocarcinoma will experience relapse and die of the disease. Past trials using adjuvant therapy failed to show a survival advantage compared with surgery alone. Furthermore, 2 meta-analyses showed small (if any) benefit. Therefore surgery alone remained standard treatment. In 2001, Macdonald et al. reported the outcome of a Southwest Oncology Group/Intergroup 0116 study that randomized patients with completely resected (R0) stage IB to IV M0 gastric cancer to chemotherapy (5-fluorouracil) followed by concurrent chemoradiation or observation. Median survival for patients undergoing chemoradiation was 35 months compared with 26 in the surgery-only group (P = .006). Similarly, 3-year survival favored the treatment arm (50% vs. 41%; P < .001).

After their success with perioperative chemotherapy for esophageal cancer, the Medical Research Council conducted a randomized trial of perioperative chemotherapy with observation. Patients with potentially resectable stage II to IV M0 gastric, esophageal, and lower third esophageal adenocarcinoma were eligible. Treatment consisted of 3 cycles of epirubicin, cisplatin, and fluorouracil preoperatively and postoperatively. Use of perioperative chemotherapy improved 5-year survival from 23% (surgery-only) to 36% (treatment arm; P = .009). These studies represent pivotal changes in the treatment of gastric cancer and emphasize the importance of multidisciplinary management. Both postoperative chemotherapy with concomitant chemoradiotherapy and perioperative chemotherapy improved survival in patients with resectable gastric cancer; they represent 2 acceptable treatment options.

Conclusions

Although this article did not discuss other modalities of therapy for gastric cancer in detail, it recommends that patients be managed by a multidisciplinary team. Surgical resection remains an integral part of treatment; however, several recent studies have shown the value of adjuvant and neoadjuvant treatment. Ongoing areas of investigation include improved staging (peritoneal cytology and PET scans) and resection techniques (laparoscopy and endoscopic mucosal resection), and expanded limits of potentially curative resection (hepatic metastectomy).

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