

Limited Gastric Resection

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Although the incidence and death rates of gastric carcinoma have declined since 1930, in 2004 there were still expected to be 22,710 new cases diagnosed and 11,780 deaths from this disease in the United States alone [1]. Furthermore, despite advances in our understanding of the pathogenesis of this tumor, most cases present at a relatively advanced stage. This is reflected by the poor 5-year survival rates from gastric adenocarcinoma, which continue to hover at or below 20% [2]. Thus, there remains considerable controversy regarding the optimal management of these patients, who often have incurable disease. Specifically, debate remains regarding the extent of gastric resection as well as the extent of lymph node dissection. Although Japanese authors continue to promote extended gastric resections with regional nodal dissection, the success of such procedure in a Western population has yet to be validated. This article outlines the argument against extended or total gastrectomy for gastric cancer, and describes the current approach to other less common tumors of the stomach, which may often be treated by nonanatomic or limited gastric resection. The role of surgery in the palliation of patients who have Stage IV disease is outlined, and specific attention is given to gastric lymphoma, gastrointestinal stromal tumors (GIST), and gastric carcinoid tumors.

Extent of resection for gastric ulcer

R0 resection, defined as resection of all gross disease with microscopically negative margins, has been shown to have a clear impact upon overall

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survival after potentially curative surgery [3]. In the German Gastric Cancer Study, a prospective multicenter trial, the calculated 10-year survival rate in the entire population of patients who had gastric cancer was 26.3% versus 36.1% after an R0 resection [3]. Similarly, Hallissey and colleagues [4] found that 19% of patients enrolled in a large, multi-institution adjuvant therapy trial had an R1 resection or resection-line involvement. Only 9% of patients who had Stage I through III disease and a positive margin survived beyond 5 years, as compared with 27% for those undergoing R0 resection. Thus, the goal of any surgery for gastric cancer is the removal of all gross and microscopic disease. Given the propensity for submucosal spread of tumor, proximal margins of 5 to 6 cm, with routine frozen-section analysis, are considered optimal by many authors [5,6].

In an effort to lower the rate of positive margins, total gastrectomy has been proposed as the operation of choice for all operable gastric cancers. This approach was fostered by historical data from single institutions. There have now been at least three trials that have attempted to address this hypothesis [7–9]. Gouzi and coworkers [7] reported results from a prospective multicenter trial of elective total gastrectomy versus subtotal gastrectomy for adenocarcinoma of the antrum operated on with curative intent. Although elective total gastrectomy did not increase mortality in this series of 169 patients, it also did not improve the 5-year survival, which was 48% in both treatment arms. Similarly, Robertson and colleagues [8] randomized 55 patients who had antral cancer to either subtotal gastrectomy or total gastrectomy with an extended lymph node dissection and en-bloc distal pancreatectomy and splenectomy. In their series, total gastrectomy was associated with increased operative time, greater transfusion requirements, and longer hospital stay. Interestingly, median survival was significantly better in the subtotal gastrectomy group (1511 versus 922 days, $P < 0.05$). Finally, Bozzetti and coworkers [9] concluded that subtotal gastrectomy should be the procedure of choice for cancer of the distal half of the stomach, provided that a negative proximal margin can be adequately achieved. This assertion was made based on an equivalent 5-year survival probability for both groups in this study (65.3% for subtotal gastrectomy versus 62.4% for total gastrectomy).

Proximal gastric cancer

Adenocarcinoma of the gastric cardia and gastroesophageal junction (GEJ) appears to be a distinct clinical entity, as compared with distal gastric cancer [10]. Furthermore, with the incidence of proximal gastric cancer escalating across all races and age groups, it is imperative to understand the surgical options for these complex lesions [11]. For tumors originating from the distal esophagus, esophagectomy, either transabdominal with a cervical anastomosis or via the abdomen and right chest (Ivor-Lewis), is clearly the procedure of choice. In an effort to ascertain whether esophagogastrec-

tomy would offer a survival advantage over total gastrectomy with an esophagojejunal anastomosis for tumors of the cardia, Rudiger Siewert and coworkers [12] reviewed their experience with 1002 patients who had adenocarcinoma of the esophagogastric junction. After dividing tumors into three types based on location of the tumor, demographic data and long-term survival were analyzed for cancers of the distal esophagus (Type I), cardia (Type II), and the subcardial fundus (Type III). In this study, operative mortality was higher for esophagectomy as compared with extended total gastrectomy. Furthermore, R0 resection and lymph node status were the dominant prognostic factors influencing survival in the study's multivariate analysis. Finally, in Type II lesions, the pattern of lymphatic spread was primarily to paracardial, lesser curvature, and left gastric nodes. These data in toto led the authors to recommend total gastrectomy over esophagectomy if a margin-negative resection can be achieved.

One alternative approach that has been reported for proximal gastric lesions is the proximal subtotal gastrectomy. Although no prospective studies have compared this method to total gastrectomy or transhiatal esophagogastrectomy for GE junction tumors, surgeons from Memorial Sloan Kettering Cancer Center have published their retrospective experience [13]. The study population consisted of 98 patients who underwent either total gastrectomy (TG) or proximal subtotal gastrectomy (PG) for proximal gastric cancer over a 10-year period. There were no differences between the groups in terms of morbidity, mortality, or 5-year survival (43% for PG versus 41% for TG, $P =$ non-significant). It remains to be seen whether such excellent results can be achieved at other centers.

Thus to summarize, there is currently no evidence to support the routine performance of total gastrectomy for lesions of the distal fundus or antrum, so long as histologically negative margins can be achieved without compromising the gastric inlet. Thus, the authors' current practice is to perform a subtotal gastrectomy with Billroth II reconstruction for tumors of the distal stomach. We favor a total gastrectomy with Roux-en-Y esophagojejunostomy for most cancers of the fundus and proximal stomach, particularly if they are clear of the GEJ by 2 to 3 cm, or originate near the GEJ but extend along the lesser curve. For tumors of the cardia, within 1 to 2 cm of the GEJ, we perform either a transthoracic esophagogastrectomy or transhiatal esophagogastrectomy with gastric interposition. This approach is also adopted when there is evidence of significant lymphadenopathy along the distal esophagus on preoperative CT or endoscopic ultrasonography (EUS).

Palliative resection for gastric cancer

In patients found to have Stage IV disease by preoperative staging or at laparoscopy, attempts at radical R0 resection are usually abandoned; however, palliative procedures, either in the form of limited resection or bypass, may be indicated to relieve symptoms, control pain, or improve

quality of life [14]. Traditionally, total gastrectomy was not considered an appropriate palliative procedure, due to the high rates of morbidity and mortality [15]. More recently, with advances in surgical technique, this dictum has been challenged and total gastrectomy has been performed in series of highly selected patients. Monson and coworkers reported a series of 53 patients from the Mayo Clinic who underwent total gastrectomy with palliative intent [16]. The decision to perform a total gastrectomy was based on tumor location in 30% of patients and on extent of disease in 70%. Seventeen percent of patients in this series were diagnosed with linitis plastica. The mortality in this series was a respectable 8%, and median survival was 19 months. A full 24% of these patients survived for 2 years. Perhaps most importantly, quality of life was graded good in 59% of patients and poor in only 13%. Most current series report results that are far less compelling, however. In reporting data from the Dutch Gastric Cancer Trial, Hartgrink and colleagues [17] noted that 285 patients were found to have incurable disease at laparotomy. Although overall survival was greater if a gastric resection was performed (8.1 versus 5.4 months, respectively), morbidity and mortality rates were high (50% and 20%, respectively). Similarly, Miner and coworkers [14] reported the experience of surgeons at the Memorial Sloan Kettering Cancer Center with patients who underwent a noncurative (R1/R2) resection for gastric cancer. Despite the fact that palliative operations less frequently included an esophageal anastomosis, and had less extensive lymphadenectomy, operative morbidity was 54% and mortality was 6%.

Although once only amenable only to open gastrojejunostomy, distal obstructions may now be alleviated by the endoscopic placement of self-expanding endoluminal stents [18]. Such stents have been effective in up to 85% of cases, with an average uninterrupted duration of function of 5 to 6 months. In one recent series [19], stent placement was successful in 100% of patients, with 97% of patients able to tolerate some form of oral intake. Perhaps more importantly, nonoperative approaches to gastric outlet obstruction allow patients who have Stage IV disease to proceed to palliative chemotherapy without delay. Because randomized clinical trials have suggested a benefit for chemotherapy versus best supportive care in patients who have Stage IV gastric cancer, this advantage is clinically meaningful [20]. Thus, whenever possible, patients who have M1 disease should be approached by nonoperative means. Gastric resection or bypass may have a role in an occasional highly-selected patient; however, the high rates of morbidity and mortality, even in experienced hands, rarely justify a total or even distal gastrectomy.

Gastric lymphoma

Lymphomas of the stomach are the second most common gastric malignancy. Lymphomas of the stomach are of the non-Hodgkin's type, and in the United States compose 2% to 9% of malignancies of the stomach. The

stomach is the most common site of extranodal non-Hodgkin's lymphoma (NHL), and accounts for nearly 50% of all such cases [21]. Presenting symptoms, like those of gastric adenocarcinoma, are nonspecific, and include loss of appetite, weight loss, vomiting, and bleeding. B symptoms (fever, night sweats) are relatively rare, and occurred in fewer than 12% of patients enrolled in a recent multicenter trial [22]. Risk factors for gastric lymphoma include *Helicobacter pylori* infection, immunosuppression after solid organ transplantation, celiac disease, inflammatory bowel disease, and HIV infection [23]. Diagnosis is most frequently made by endoscopy with biopsy. Staging studies include a complete blood count; lactate dehydrogenase and comprehensive chemistry panel; CT scans of the chest, abdomen and pelvis; and often a bone marrow biopsy. All pathology slides should be reviewed by an experienced hematopathologist [24].

Numerous staging systems have been used to stage gastrointestinal NHL, with the most commonly applied system being a modification of the Ann Arbor staging system for lymphoma [23]. For the surgeon, the most important determination is whether the NHL is confined to the stomach and perigastric nodes (Stages I and II), involves other intra-abdominal nodes and organs (Stage III), or exists beyond the abdomen (Stage IV) [25].

Over the past decade, the management of patients who have gastric lymphoma has undergone significant changes, with a shift away from surgical management, even in relatively localized (Stage I and II) cases [26]. Such changes have come about not only from the historic success of chemotherapy alone for more advanced (Stage III and IV) cases, but also from a better understanding of the etiology of gastric lymphoma [27]. Approximately 45% of all gastric lymphomas are low grade mucosa associated lymphoid tissue (MALT) lymphomas [22]. The gastric mucosa is normally devoid of lymphoid tissue. Thus, it is hypothesized that MALT develops in the stomach in response to chronic *H pylori* infection [28].

Patients who have low-grade MALT lymphomas usually present with Stage I or II disease and have an indolent course. Since the first report of regression of low-grade MALT lymphoma following eradication of *H pylori* in 1993, numerous trials [29] have documented the efficacy of such therapy, with complete remission rates between 50% and 100% [26]. In the German MALT Lymphoma Study [29], the complete remission rate was 81%; 9% of patients had only partial responses and 10% were nonresponders. More advanced low-grade lymphomas or those that do not regress with antibiotic therapy can be treated with combinations of *H pylori* eradication, radiation, or combination chemotherapy [30]. For localized persistent disease, modest doses of radiation, on the order of 30 Gy, may be used. When chemotherapy is required, multiagent regimens such as cyclophosphamide, vincristine, prednisolone (COP) are often used.

Conversely, approximately 55% of gastric lymphomas are high-grade lesions, which can occur with or without a low-grade MALT component [22]. These lymphomas are treated with chemotherapy and radiation

therapy according to the extent of disease. In these aggressive lesions the cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) regimen has been the treatment most frequently employed. More recently rituximab, an anti-CD20 monoclonal antibody, has been either added to standard therapy or used alone, with encouraging results [31].

Surgical resection, once thought to be paramount in the diagnosis, staging, and treatment of early stage disease, is now used only in patients who develop complications of bleeding or perforation. In the German Multicenter Study group trial [22], 185 patients who had Stage I or II gastric lymphoma were enrolled, and treated with either gastrectomy followed by radiation, or chemotherapy plus radiation in the cases of high-grade lesions; versus chemotherapy and radiotherapy alone. In this nonrandomized trial, there was no significant difference in survival between the 79 patients receiving surgery and the 106 patients receiving nonoperative therapy, with overall 5-year survival rates of 82% and 84%, respectively. In this study, no patient experienced perforation, and there was only one case of hemorrhage in a patient treated with chemotherapy alone. Similarly, in a single-institution, prospective, randomized trial of chemotherapy versus chemotherapy plus surgery for Stage I and II lymphoma [26], Aviles and coworkers [32] noted no instances of perforation and only three instances of gastrointestinal bleeding in the chemotherapy group, versus two bleeding episodes in the surgery plus chemotherapy group. Thus, the authors conclude that patients who have early-stage, high-grade gastric lymphomas are best treated with chemotherapy or radiation therapy. Only rarely will these patients require surgical intervention for complications encountered during therapy. Patients who have locally advanced (Stage III) or disseminated gastric lymphoma (Stage IV) are universally treated with chemotherapy, with or without radiation. Surgery is occasionally indicated in such patients for residual disease confined to the stomach, or to palliate bleeding or obstruction that fails to resolve with nonoperative therapy. Primary surgical therapy is to be avoided in such cases because of the significant risk of complications and the delay in initiating systemic therapy.

Gastrointestinal stromal tumor

Although a relatively rare tumor, GIST is the most common sarcoma of the gastrointestinal tract [33]. The annual incidence is approximately 6000 cases in the United States alone, and the stomach is the most common site of involvement (60%–70%) [34]. The remainder occur in the small intestine (25%), rectum (5%), esophagus (2%), and a variety of other locations. Due to their appearance by light microscopy, GISTs were previously thought to be of smooth muscle origin, and the majority were classified as leiomyosarcomas [35]. Thus, extended gastric resection, often including contiguous organs, was advised. Recurrence after R0 resection occurred in approximately 50% of cases [36]. With the advent of immunohistochemistry

and electron microscopy, it has become clear that these cells have both smooth muscle and neural elements, and the cell of origin is felt to be the interstitial cell of Cajal, an intestinal pacemaker cell [37]. In fact, the diagnosis of GIST is now secured by immunohistochemical staining for the tyrosine kinase receptor KIT (CD 117), which highlights the presence of interstitial cells of Cajal. Over 95% of GISTs exhibit unequivocal staining for KIT [34]. Approximately two thirds of GISTs will also express CD34. Histologically, these tumors exhibit a spindle-cell pattern, an epithelioid pattern or a mixed subtype.

The median age of incidence is 63 years, and tumors range between 0.5 and 44 cm at the time of diagnosis, with a median diameter of 6 cm [34]. Thus, these tumors may present with mass-related symptoms, such as abdominal pain, bloating, or early satiety. Another common presentation is melena or anemia due to overlying mucosal ulceration. A small subset of patients present with peritonitis caused by tumor rupture, with subsequent hemorrhage. Finally, many of these tumors are discovered incidentally during surgery, abdominal imaging, or endoscopy.

Although the majority of gastric GISTs will exhibit a benign course, there is a wide spectrum of biologic behavior. Among the prognostic factors examined, tumor size and mitotic rate appear to be the most valuable. Tumors less than 2 cm in size, with a mitotic count of less than five per high powered field (HPF) are considered to have a very low risk for an aggressive disease course. Conversely, tumors greater than 10 cm in size, or with greater than 10 mitoses per HPF, or greater than 5 cm with more than five mitoses per HPF are considered to be at high risk for aggressive clinical behavior. All others are considered to be of intermediate risk [34].

Patients who are suspected of having a GIST should undergo chest, abdominal, and pelvic imaging by either CT or MRI. Endoscopy with or without EUS may occasionally help with surgical planning, but rarely provides a tissue diagnosis because of infrequent mucosal involvement [38]. Surgical consultation should be obtained to determine whether the tumor is resectable. Biopsy is to be avoided in patients who have resectable tumors, because of the theoretical risk of tumor rupture with intra-abdominal dissemination. Biopsy may be required if the patient has widespread disease, or if entry on to a neoadjuvant trial is being entertained. In these cases, biopsy may be obtained percutaneously, or at the time of EUS.

As opposed to gastric adenocarcinoma, the role of surgery in GIST is to resect the tumor with grossly negative margins, and an intact pseudocapsule. Because lymph node involvement is rare in GIST, no effort is made to perform an extended lymph node dissection. The tumor should be handled with care to avoid intra-abdominal rupture. Formal gastric resection is rarely required, and usually only indicated for lesions in close proximity to the pylorus or gastroesophageal junction (Fig. 1).

If the tumor is determined to be metastatic, or so locally advanced as to render surgical therapy excessively morbid, then patients are treated with

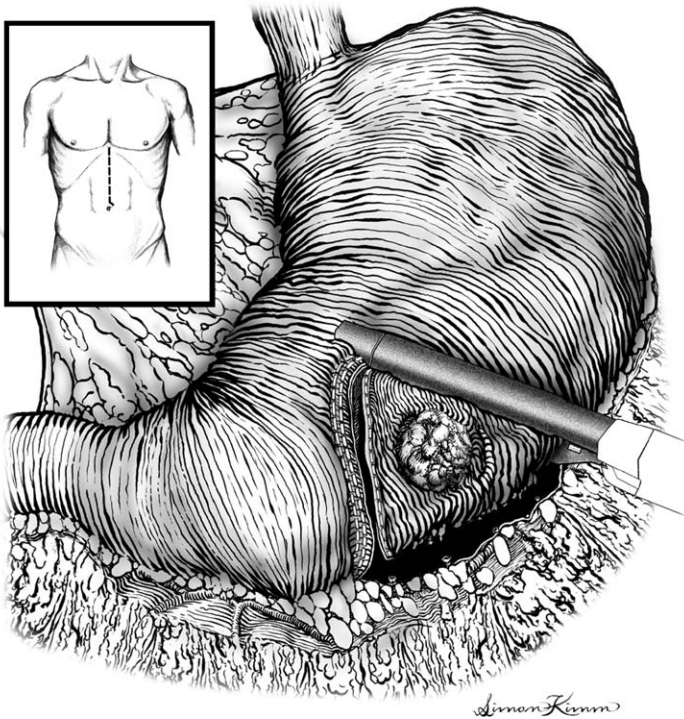


Fig. 1. Wedge resection of a gastrointestinal stromal tumor emanating from the lesser curve of the stomach.

the tyrosine kinase inhibitor imatinib mesylate. Imatinib is a selective inhibitor of a family of protein kinases, including the KIT-receptor tyrosine kinase (CD117), which is expressed in the majority of GISTs. Originally indicated for the treatment of chronic myelogenous leukemia, imatinib was approved for the treatment of KIT-positive GIST in 2002. Phase II clinical trials demonstrate a sustained objective response in a majority of patients who have advanced unresectable or metastatic GIST [39]. Patients who have borderline lesions should be treated until maximal response by CT and positron emission tomography (PET), and then surgery may be undertaken to resect and residual foci of disease. Similarly, although patients who have metastatic disease are unlikely to achieve a complete response to imatinib therapy, they should be periodically re-evaluated and considered for resection should this become technically feasible [38].

After a R0 resection of a GIST, no adjuvant therapy is indicated outside of a clinical trial. The American College of Surgeons Oncology Group (ACoSOG) is currently conducting two trials of imatinib in the postoperative setting. A Phase II trial (Z9000) of imatinib 400 mg/day for patients who have high-risk GIST, has reached accrual, and a Phase III trial

randomizing patients who have intermediate risk GIST to 1 year of 400 mg/day of imatinib versus placebo (Z9001) is under way.

Gastric carcinoid

Gastric carcinoid tumors are rare, accounting for between 11% and 30% of all gastrointestinal neuroendocrine tumors, and fewer than 1% of all gastric tumors [40]. The median age at diagnosis is 62, and tumors are equally distributed among men and women. These lesions are often discovered during endoscopic evaluation for chronic abdominal pain. Other presenting symptoms include vomiting and diarrhea. These tumors rarely present with symptoms of the carcinoid syndrome. Diagnosis is usually confirmed by endoscopic biopsy, and EUS is helpful in determining the extent of gastric wall penetration and regional lymph node involvement.

Based primarily on their association with hypergastrinemia, gastric carcinoid tumors have been divided into three types. Type I tumors are associated with chronic atrophic gastritis, are generally small (<1 cm), and are often multiple and polypoid. Biologically, these lesions exhibit slow growth and only rarely metastasize to regional nodal basis or distant sites. Type II gastric carcinoid tumors are associated with the Zollinger-Ellison syndrome and multiple endocrine neoplasia (MEN)-Type I. These lesions are also usually small and multiple. Although they also grow at a slow rate, they may metastasize more frequently than Type I gastric carcinoids. The most biologically aggressive tumors are the Type III or sporadic gastric carcinoid tumors. These lesions are often large (>1 cm) at the time of diagnosis, and are not associated with hypergastrinemia. Type III lesions often exhibit metastasis to regional nodes (54%) and to the liver (24%) [40].

Endoscopic polypectomy or open resection via gastrotomy (local excision) is recommended in patients who have small, solitary Type I tumors. In the cases of multiple tumors or tumor recurrence, antrectomy is indicated to remove the source of hypergastrinemia. Patients who have Zollinger-Ellison or MEN-1 syndrome may be treated in a similar fashion to patients who have Type I lesions, with the extent of gastric resection being determined by the size and number of lesions. In contradistinction, patients who have Type III (sporadic) lesions require either distal or total gastrectomy with extended lymph node dissection [41]. All patients undergoing less than total gastrectomy should be followed by serial endoscopy at regular intervals [42].

Summary

Until recently, adjuvant therapy for gastric cancer was of little proven benefit. Thus, surgery was considered the sole mode of treatment for

curative intent. This led many authors, especially in Asia, to propose radical, multivisceral resection with regional nodal dissection as a method for improving the dismal survival rates seen for patients who have adenocarcinoma of the stomach. Unfortunately, the benefit of extended gastric resection, either by total gastrectomy or with an extended D2 lymph node dissection, has never proven to be of benefit in terms of overall survival in a prospective, randomized trial from a Western center. Thus, it is the authors' current practice to perform a subtotal gastrectomy for antral lesions when a proximal margin of 5 to 6 cm can be obtained, and to perform dissection of all perigastric lymph nodes along the branches of the celiac axis. This will usually provide for the requisite 15 lymph nodes to be sampled for accurate staging, according to the 6th edition of the American Joint Committee on Cancer (AJCC) staging system.

General surgeons, gastrointestinal surgeons, and surgical oncologists alike will encounter less common gastric tumors such as gastric lymphoma, gastrointestinal stromal tumors, and gastric carcinoid tumors. Such tumors are often amenable to local resection, either by laparoscopic or open means, or may be treated by nonoperative means. Thus, techniques for limited gastric resection should be in the armamentarium of all such surgeons.

Finally, when faced with an unresectable tumor, it is now clear that operative intervention should be avoided to allow for early intervention with palliative or even potentially curative systemic therapy. This is true of GISTs, Stage IV adenocarcinoma, and Stage II and IV gastric lymphoma. Although palliative gastrectomy may be performed for intractable bleeding or perforation, it is almost always at the cost of a high rate of morbidity and postoperative mortality.

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