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SSAT State-of-the-Art Conference: Current Surgical Management of Gastric Tumors

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Abstract

Introduction—The current era of gastric surgery is marked by low morbidity and mortality rates, innovative strategies to approach resections with a minimally invasive fashion or hyperthermic intraperitoneal chemotherapy, as well as improved understanding of the biology of sporadic and hereditary stromal, neuroendocrine, and epithelial malignancies.

Methods—In 2017, the Society for Surgery of the Alimentary Tract convened a State-of-the-Art Conference on Current Surgical Management of Gastric Tumors with both international experts and emerging leaders in the field of gastric surgery.

Results—Martin D. McCarter, MD of the University of Colorado discussed the current management of gastric gastrointestinal stromal tumors (GIST). Kaitlyn J. Kelly, MD of the University of California, San Diego discussed the management of gastric carcinoid tumors. Jeffrey A. Norton of Stanford University discussed recent advances in the management of gastric adenocarcinoma including a focus on hereditary diffuse gastric cancer (HDGC). Joseph Kim, MD

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of Stony Brook University discussed a systematic approach to minimally invasive gastrectomy for cancer. And, Joyce Wong, MD of Pennsylvania State University discussed the role for cytoreductive surgery (CRS) and Hyperthermic intraperitoneal chemotherapy (HIPEC) for gastric adenocarcinoma.

Conclusion—This review provides gastrointestinal surgeons with a concise update on the current surgical management of gastric tumors.

Update on the Management of Gastric Gastrointestinal Stromal Tumors

Evaluation and Staging of Gastric GIST

Due to the large capacity and relatively mobile nature of the stomach within the abdominal cavity, gastric gastrointestinal stromal tumors (GISTs) frequently present as an asymptomatic incidentally discovered mass or with vague symptoms such as fatigue, anemia, non-specific abdominal pain, fullness, bloating or early satiety. Eventually a diagnostic test such as endoscopy or an imaging study may lead to the diagnosis of GIST that can range in size from a sub-centimeter to over 30 cm in diameter.

Certain imaging features (such as a solid discrete mass with vascular enhancement associated with the gastric wall) or endoscopic features (a firm submucosal mass with or without a central bleeding ulcer) may suggest the diagnosis of GIST, but the definitive diagnosis should be confirmed with a needle biopsy. Endoscopic biopsy is preferred for its relative safety over percutaneous approaches, which may slightly increase the risk of bleeding or rupture. Endoscopic ultrasound (EUS) can be very helpful in defining the size and location of the tumor, as well as aid in directing submucosal biopsies. GISTs are classified as a sarcoma and are believed to originate from the interstitial cells of Cajal (pacemaker cells of the gastrointestinal tract) exhibiting features of mesenchymal tumors with neural and muscle stromal elements.^{1, 2} Histologically, they share many spindle shape cellular phenotypic features with leiomyomas and leiomyosarcomas, yet unlike these entities, they have the distinctive feature of staining immunohistochemically positive for c-KIT (KIT) almost 95% of the time. DOG-1 (Discovered on GIST-1) is a back-up or confirmatory immunohistochemical stain that solidifies the diagnosis when there is doubt.³

Once the diagnosis has been established, staging of GISTs is completed by obtaining a CT abdomen and pelvis. Common sites of metastases of GIST are within the peritoneum via direct shedding of tumor cells, or hematogenously to the liver or less commonly to the lungs.⁴ GISTs rarely spread to local lymph nodes, although this can happen in so called “wild-type” GISTs that lack the usual known mutations in *KIT* and *PDGFRA*, as well as and tend to occur in young adults.⁵

Risk Stratification

Our knowledge and understanding of gastric GISTs natural biologic behavior has benefited from serendipity in that prior to the late 1990s the histologic markers for GIST did not exist and these tumors were classified as leiomyosarcomas. With the discovery of c-KIT as the diagnostic marker for GIST, retrospective studies reclassified the staining of these tumors and were able to detail the expected natural history as there was no prior effective therapy

for leiomyosarcoma or GIST.⁴ From these studies, three key features emerged that help risk stratify gastric GISTs: 1) location (stomach more common than other parts of the gastrointestinal tract except in adolescents and young adults where small bowel is more favorable); 2) size (<5 cm more favorable, >10 cm less favorable); and 3) mitotic rate (<5 mitosis per 50 high power fields more favorable, >5 less favorable).^{6, 7} From these factors, nomograms and risk tables categorize tumors into low-, intermediate- and high-risk for metastases.^{8, 9}

Mutation Analysis

c-KIT is a tyrosine kinase that signals for cellular growth. In the case of GIST, a mutation in the *c-KIT* (*KIT*) or *PDGFRA* genes results in auto-phosphorylation and unregulated cellular growth. Over time, we have come to understand that specific mutations in the exon coding regions confer different biologic activity and sensitivity to kinase inhibitors. The most common mutation found in gastric GISTs occurs in exon 11 and this also happens to be the most responsive exon mutation to kinase inhibition.^{1, 2, 10, 3} Therefore, in general, gastric GISTs tend to have the most favorable long-term outcome, even in the setting of metastatic disease. Routine mutational analysis is not part of the current risk stratification systems and may not be necessary for most low risk gastric GISTs but it can help direct specific therapy for more advanced GISTs as specific mutations may respond differentially to targeted kinase inhibitors. In addition, we continue to learn more about the biologic significance of other gene mutations or fusions reported in GIST, such as *BRAF*, *KRAS*, *NF1*, *SDH* subunits, *ETV6-NTRK3*, and *FGFR1*.⁵

Surgical Treatment of GIST

The mainstay of treatment for gastric GIST is surgical resection whenever feasible. Significant symptoms such as bleeding or gastric outlet obstruction require more urgent resection. Many gastric GISTs will be cured with resection alone, and in the others, the complete histologic analysis from the whole tumor provides the risk stratification information upon which to make clinical decisions about adjuvant therapy. The goals for surgery are to avoid tumor rupture, obtain a grossly and histologically negative margin, and preserve gastric function. Many smaller (<5 cm) gastric GISTs lend themselves well to a laparoscopic wedge resection provided standard oncologic principals (i.e., avoid tumor rupture, placing the specimen in an endoscopic protective bag, obtain grossly negative margins) are followed.^{1, 2, 4} Larger gastric GISTs that would require a larger incision to extract are better off managed with a standard open operation to ensure proper handling. In some cases with very large gastric GISTs that are abutting and displacing surrounding organs such as the spleen, pancreas, liver or colon, it may be feasible to treat them in a neoadjuvant fashion with a kinase inhibitor (imatinib) with the goal of shrinking the tumor enough to reduce the ultimate magnitude of the operation.¹¹ Unlike gastric adenocarcinomas, GISTs rarely directly invade surrounding structures though the desmoplastic response around a tumor can make it difficult to separate surrounding organs cleanly and therefore require multi-organ resections. Likewise, GISTs rarely spread to lymph nodes and therefore lymphadenectomy is not generally necessary.¹

Medical Treatment of GIST

The successful treatment of a widely metastatic GIST patient (who had failed several lines of conventional systemic chemotherapy) with an oral targeted kinase inhibitor (imatinib) ushered in a new era of treating solid tumors.¹² This single patient proof of principle experiment was quickly recapitulated in larger phase III studies that demonstrated remarkably long survival now measured in years rather than months for patients with metastatic GIST.^{2, 10} Imatinib (the current first-line therapy) is a relatively selective kinase inhibitor that interferes with the phosphate binding site in the mutated c-KIT protein (in addition to the phosphate binding site in BCR-ABL and PDGFRA) and thereby prevents unregulated tumor growth. It is well tolerated by most patients who experience relatively mild side effects while keeping their tumors under control.¹ Several other kinase inhibitors are approved for the treatment of GIST (sunitinib, regorafenib) and still other broad kinase inhibitors (nilotinib, pazopanib) are also reported to be effective in metastatic GIST.² Depending on the specific mutation, most GISTs will respond initially to one form or another of kinase inhibition. Unfortunately, secondary mutations do occur allowing tumors to develop resistance pathways and overcome the effects of kinase inhibition. Much work is ongoing attempting to analyze these resistance pathways and identify better biomarkers of response and/or combination therapies. Another area of active investigation is the question of how long to treat patients with completely resected, high-risk gastric GISTs in the adjuvant setting. The current data supports at least three years of adjuvant therapy though a longer or indefinite duration may ultimately be necessary.^{13, 14}

Summary

The history of the molecular and pathologic characterization GISTs has helped transform the concept of targeted therapy in the treatment of many cancers. Lessons learned, and yet to be discovered, from this disease help inform treatment decisions for gastric GIST and other solid tumors.

Update on Gastric Neuroendocrine Tumors

Gastric neuroendocrine tumors (NETs), or carcinoids, are a clinically diverse group of tumor types that arise from enterochromaffin-like (ECL) cells in the oxyntic gastric mucosa, most often in the body of the stomach. Gastrin acts on ECL cells to stimulate histamine release, which in turn stimulates parietal cells to secrete hydrochloric acid. Gastrin also has a trophic effect on ECL cells and is known to cause ECL hypertrophy and hyperplasia. It is thought that gastric NETs account for approximately 8% of all NETs, but the true incidence is likely unknown because the inclusion of these tumors in cancer registries is variable. Recent evidence suggests that the incidence is increasing.^{15, 16}

In the 1990s, gastric NETs were classified into three distinct subtypes based on clinicopathologic factors. More recently, a fourth type, neuroendocrine carcinoma, has been recognized.^{17, 18} Table 1 summarizes the features of the different clinicopathologic subtypes. Gastric NETs are also classified by TNM staging by the National Comprehensive Cancer Network (NCCN) and by histopathologic grade according to the World Health Organization (WHO).

Type I Gastric NETs

Type I gastric NETs arise in the setting of pernicious anemia, or autoimmune atrophic gastritis. They are the most common of the subtypes, constituting 70 to 80% of gastric NETs.¹⁹ Hypergastrinemia results from chronic achlorhydria, and the chronic high gastrin levels cause ELC hypertrophy. A hyperplasia to dysplasia to neoplasia pathway ensues and gastric NETs develop. The diagnosis is supported by the clinical picture, the presence of hypergastrinemia, elevated gastric pH, vitamin B12 deficiency, and the presence of anti-intrinsic factor antibodies. Type I gastric NETs tend to be small, superficial (involving only mucosa or submucosa), and multiple. Histopathologically, they are usually grade I (<2 mitoses per 10 high-power fields and a Ki-67 index less than 3%).

Endoscopic resection and surveillance is usually appropriate for these tumors as the rate of locoregional metastasis is <5%. The NCCN guidelines recommend cross-sectional imaging be performed when lesions are >2 cm. Antrectomy can be considered for patients with type I gastric NETs with multiple lesions (6 or more has been suggested as a cut-off) or in whom frequent endoscopic re-resection is required. Jenny and colleagues reported a series of 52 patients with type I gastric NET treated with endoscopic polypectomy versus laparoscopic antrectomy. The average number of EGDs needed per year of follow-up was significantly lower in the antrectomy group as was the risk of recurrent gastric NET (11% vs 44%) with a median follow up of approximately 5 years.²⁰ Regardless of the treatment modality, the prognosis for type I gastric NETs is excellent. In a recent study with 15-year follow-up, the 3-year recurrence free survival for type I gastric NET was 33% and disease-specific survival was 100%.²¹ Patients with type I gastric NET have a normal life expectancy.

Type II Gastric NETs

Type II gastric NETs are rare, accounting for only 5 to 10% of all gastric NETs. Hypergastrinemia is again the inciting factor, but the etiology is MEN-1 related gastrinoma (Zollinger-Ellison Syndrome, ZES) rather than autoimmune atrophic gastritis. Interestingly, patients with sporadic gastrinoma only rarely develop type II gastric NETs.²² Patients typically present with signs and symptoms more related to the gastrinoma than to the gastric NET. Type II lesions, while also indolent, have more malignant potential than type I. Lymph node metastasis is present in 5 to 35% of cases.²³ Histopathologically, they are usually WHO grade 1 or 2.

Treatment of type II gastric NET ideally includes resection of the primary gastrinoma and removal of hypergastrinemia if possible. If not, somatostatin analogues should be used to suppress gastrin levels. Endoscopic resection and surveillance of type II gastric NETs is appropriate if they are not invasive beyond the submucosa, but formal gastrectomy is recommended if they are. Therefore, endoscopic ultrasound (EUS) should be performed. Long-term outcome for type II gastric NET is dictated the primary gastrinoma.^{24, 25} Mortality associated with type II gastric NETs themselves is less than 10%.¹⁹

Type III Gastric NETs

They account for 10 to 15% of all gastric NETs. Type III gastric NETs are sporadic tumors not associated with hypergastrinemia or other clinical syndromes. Patients therefore present

with symptoms related to NET, such as early satiety, vomiting, upper GI bleeding, anemia, or weight loss. These tumors are usually solitary, > 2 cm in size, and the surrounding gastric mucosa is normal. Histopathologically, they are usually WHO grade 3.²⁶ Type III tumors have a high propensity for invasion and metastasis, with over 50% of patients having distant metastatic disease at presentation. The most common site of metastasis is the liver. EUS and staging evaluation with cross-sectional imaging are therefore recommended.

For localized disease, oncologic gastrectomy with lymphadenectomy is the treatment of choice. In the setting of metastatic disease, gastrectomy or gastric wedge resection may still be considered for palliation of symptoms. Metastasectomy is appropriate in some cases and long-term survival / cure has been reported.²⁷ For patients with unresectable or recurrent metastatic disease, treatment options include local ablative therapies or systemic treatment with somatostatin analogues or cytotoxic chemotherapy. In the aforementioned single institution series with 15-year follow up, the 3-year recurrence free survival (RFS) and disease specific survival (DFS) rates after curative intent resection of localized type III gastric NET were 85% and 75%; respectively.²¹

Type IV Gastric NETs

The more recently recognized fourth subtype of gastric NET is the most aggressive type. Like type III, these tumors are considered sporadic, but associated atrophic gastritis can be found in up to half of patients.¹⁷ These tumors tend to be solitary and large, with a median size of about 5 cm. Patients may present with symptoms related to the primary tumor as in type III, or to disseminated, distant metastases. Histopathologically, type IV tumors are composed of poorly-differentiated small cells and are described by the WHO classification as being histologically identical to small cell carcinoma of the lung. Most patients have widely metastatic disease at presentation, so systemic cytotoxic chemotherapy is the mainstay of treatment. The median survival is on the order of 8 months.²⁸

Summary

While gastric NETs share a common cellular origin, they are a clinically and histologically diverse group of tumors. Knowledge and familiarity with the different clinicopathologic types is critical for appropriate work up, treatment, and surveillance. Endoscopic surveillance every 6 months to 1 year is appropriate following treatment of all subtypes. For patients with type III tumors, surveillance with cross-sectional imaging is indicated. The ability to summarize most of what is known about gastric NETs in a few short pages highlights the fact that current understanding of these tumors is poor. In the current era of cancer genotyping and personalized therapy, there is a great deal of room for improvement in the understanding and treatment of gastric NETs.

Gastric Adenocarcinoma-focus on recent advances and hereditary diffuse gastric cancer (HDGC)

Gastric cancer is the third most common cause of cancer-related deaths globally.²⁹ There are approximately 26,000 new cases each year in the United States with approximately 11,000 deaths.³⁰ This cancer is most common in east Asia and China, which accounts for half of the

gastric cancers in the world. *Helicobacter pylori* infection, as a cause of gastric cancer, is declining in incidence and may be an explanation for the recent decline in gastric cancer in western countries. Much progress has been made in the treatment of gastric cancer, especially in the use of chemotherapy as either an adjuvant or neoadjuvant regimen with surgery. The use of adjuvant radiation therapy is decreasing, as the efficacy of chemotherapy is improving.³¹

Staging and Surgery for Gastric Cancer

Because screening for gastric cancer in western countries is not routinely performed, most patients present with advanced disease and 40% have distant metastases. On the other hand, in eastern countries, where screening is done, earlier stage disease is more frequently identified. Obviously early stage tumors are associated with improved outcomes. Recent genomic profile studies of gastric cancer indicate that tumors are the same in eastern and western countries; however, immune signatures appear to be different.³²

Gastric cancer is generally diagnosed by upper endoscopy with biopsy. Assessment includes endoscopic ultrasound, computed tomography (CT) of the chest, abdomen and pelvis, and positron emission tomography (PET) scan to exclude distant metastases. If these studies identify T2 or T3 primary disease and/or lymph node metastases, staging laparoscopy should be performed with peritoneal washing to exclude peritoneal micro-metastases.

Surgery remains the only potentially curative treatment and adequacy of surgical resection clearly influences outcomes and may enhance the relative contribution of adjuvant chemotherapy. Standard of care requires a D2 lymph node dissection that meticulously excises gastrohepatic, celiac and splenic nodes. Recent long-term follow-up studies indicate a superior survival for patients undergoing D2 lymph node dissection.³³ Therefore, this more extensive surgery is recommended for gastric cancer. In contrast, extending resection to include an even more extensive lymph node dissection or D3 retroperitoneal lymph nodes has not been shown to improve survival.

Preoperative Chemotherapy for Gastric Cancer

Adjuvant chemotherapy for resected or resectable gastric cancer has become standard of care. Neoadjuvant chemotherapy has several advantages over adjuvant chemotherapy, including better tolerance of drug toxicity and improved drug delivery. There is also the potential for tumor down-staging and treatment of micro-metastatic tumor deposits. Moreover, it allows pathological assessment of therapeutic efficacy of the treatment regimen. The counter argument against preoperative chemotherapy is disease progression and development of an unresectable tumor. The first large study of preoperative chemotherapy was the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial that was reported in 2006.³⁴ Of the 503 patients enrolled in this study, 74% had gastric cancers and the remainder had gastroesophageal junction (GEJ) cancers. Upfront chemotherapy with epirubicin, cisplatin and 5-fluorouracil (5-FU) followed by surgery to remove residual disease was compared to surgery alone (standard of care). Progression-free survival (PFS) and overall survival (OS) was better for the chemotherapy arm and translated to a 25% reduction in risk of death with preoperative chemotherapy (Table 2). Additional

evidence for a benefit of preoperative chemotherapy for gastric and esophageal adenocarcinoma came from the French trial by the Federation National.³⁵ In this trial, 75% of patients had adenocarcinoma of the distal esophagus and the remainder had gastric cancer. The curative resection rate was improved from 74% to 84% with preoperative chemotherapy. The 5-year OS was similar to the results in the MAGIC trial and led to a 31% reduction in the risk of death (Table 2). Finally, another more recent study of 700 patients with gastric or GEJ cancers showed that a regimen combining docetaxel with infusional 5-FU and oxaliplatin had a significant rate of chemotherapy-induced complete tumor regression (16%).³⁶

Postoperative Chemotherapy for Resected Gastric Cancer

Postoperative adjuvant chemotherapy had not shown a benefit until large trials from Asia mandated a complete D2 lymphadenectomy for patients entering the trial. Over 1,000 patients were randomized to receive S-1 and surgery versus surgery alone.³⁷ S-1 combines an oral 5-FU prodrug, tegafur, with a dihydropyrimidine dehydrogenase inhibitor, gimeracil, and a bowel protectant, oteracil. Overall survival was significantly improved with S-1, and there was a 35% reduction in the risk of death with its use. The CLASSIC trial also entered over 1,000 patients with stage II/III gastric cancer undergoing surgical resection with D2 lymph node dissection. Patients received either oxaliplatin and capecitabine plus surgery versus surgery alone.³⁸ The 5-year OS with surgery alone was 69% versus 78% with surgery plus chemotherapy. The results demonstrated a 31% reduction in risk of death with chemotherapy following curative surgery for stage II/III gastric cancer (Table 3).

Recent genomic profile studies of gastric cancer indicate that tumors are the same in eastern and western countries; however, immune signatures appear to be different.³² Moreover, certain genes are commonly amplified in gastric cancer, and can serve as a target for systemic treatment. One such target is HER2, the product of the *ERBB2* gene, that is amplified in approximately 20% of gastric cancers. The HER2 targeted antibody Trastuzumab was shown to improve response rates, PFS and OS in the landmark ToGA trial when combined with chemotherapy in patients with HER2-positive gastric or esophageal cancers.³⁹ Resected gastric cancers should have immunohistochemical (IHC) studies to determine if the tumor expresses HER2, and therefore may serve as a target for treatment.

Hereditary Diffuse Gastric Cancer

Approximately 10% of gastric cancer cases demonstrate familial clustering, and 1–3% meet the criteria for hereditary diffuse gastric cancer (HDGC). HDGC is a genetic cancer susceptibility syndrome diagnosed by one of the following: (1) two or more documented cases of diffuse gastric cancer in first- or second-degree relatives, with at least one diagnosed before the age of 50 years; or (2) three or more cases of diffuse gastric cancer in first- or second-degree relatives, independent of age of onset.

HDGC is inherited in an autosomal dominant pattern⁴⁰ and caused by truncating mutations in the *CDH1* gene located on chromosome 16q22.1. This gene encodes for E-cadherin, a calcium-dependent cell adhesion glycoprotein. Functionally, E-cadherin impacts maintenance of normal tissue morphology and cellular differentiation. *CDH1* acts as a tumor

suppressor gene in HDGC, with loss of function leading to loss of cell adhesion and subsequent proliferation, invasion, and metastasis. In contrast to truncating mutations, missense mutations have been reported, but they are not functionally significant.

The average age of onset of HDGC is 38 years old. Among individuals found to carry a germline *CDHI* mutation, the sensitivity of radiographic and endoscopic screening for gastric cancer has been poor. Histologically, in early stages, HDGC is characterized by multiple microscopic infiltrates of malignant signet ring cells that may underlie normal mucosa. Because these malignant foci are small (typically <4 mm) and diffusely distributed throughout the stomach, they are difficult to identify via random endoscopic biopsy. Endoscopic surveillance for HDGC has been reported previously to be ineffective. In one large series, preoperative endoscopy failed to detect HDGC in 21/23 (91%) patients.⁴¹ Unfortunately, by the time patients are symptomatic and present for treatment, they usually have locally advanced gastric cancer, and their prognosis is poor (Table 4).⁴² Published case reports describe patients who have multifocal diffuse gastric cancer despite normal preoperative endoscopy with random biopsies. Although asymptomatic *CDHI* carriers who undergo prophylactic gastrectomy are typically cured, the 5-year survival rate for individuals who develop clinically apparent diffuse gastric cancer is only 10%, with the majority dying before age 40.⁴² The optimal timing of prophylactic gastrectomy in individuals with *CDHI* mutations is unknown, but most recommend that it be performed 5 years earlier than the youngest patient in the family with HDGC.⁴³

Although potentially lifesaving, prophylactic total gastrectomy for *CDHI* mutation carriers is associated with significant risks. Overall mortality for total gastrectomy is estimated to be between 2% and 4%. Furthermore, there is long-term morbidity including diarrhea, dumping, weight loss, and difficulty eating. A recent prospective quality-of-life study of the effects of prophylactic gastrectomy for HDGC patients demonstrated that physical and mental function recovers to baseline 9–12 months postoperatively.⁴⁴ However, 70% of patients had diarrhea, 63% fatigue, 81% eating discomfort, 63% reflux, 45% eating restrictions and 44% altered body image, which persisted beyond this time point.

Additionally, because women with *CDHI* mutations have a nearly 40% lifetime risk of developing lobular breast carcinoma, they should be carefully screened with annual mammography and breast MRI starting at age 35.⁴⁵ They should also perform monthly self-examinations and undergo breast examination by a physician every 6 months.

The emergence of gene-directed total gastrectomy as a treatment strategy for patients with HDGC represents the culmination of a successful collaboration between molecular biologists, geneticists, oncologists, gastroenterologists, and surgeons. It is anticipated that the recognition of similar molecular markers in other familial cancer syndromes will transform the approach to the early diagnosis and treatment of a variety of tumors.

Summary

Gastric cancer is the third most common world-wide cause of cancer-related deaths. Without the use of screening, most patients present with advanced disease and 40% have distant metastases. Diagnosis is usually made by endoscopy and staging based upon a combination

of CT, PET, EUS, and laparoscopy. Surgical resection is an integral part of a curative treatment and D2 lymph node dissection ensures adequate nodal sampling. Preoperative or postoperative chemotherapy improves outcomes and prolongs patient survival. While most gastric adenocarcinomas are sporadic, 1–3% of hereditary diffuse gastric cancer due to germline alterations in the *CDH1* gene that encodes for E-cadherin. This syndrome is characterized by signet ring cell adenocarcinoma that is typically multifocal and more prevalent in the proximal stomach. When diagnosed by genetic testing, these patients can be cured by total gastrectomy and this is recommended even when endoscopy is negative for identifying malignancy. In addition, germline mutations in *CDH1* are also associated with lobular breast cancer in 40% of female patients. In conclusion, the management of sporadic and hereditary gastric cancer continues to evolve in terms of treatments and our understanding of the underlying biology of the disease.

Systematic Approach to Minimally Invasive Distal Gastrectomy

The introduction of advanced surgical technologies has changed the methods that surgeons use to perform operations for many cancers. In select cancers, there are clear outcomes advantages when using advanced minimally invasive surgical (MIS) techniques. With respect to radical gastrectomy for patients with gastric adenocarcinoma, prospective studies have demonstrated superior short-term and equivalent long-term outcomes for MIS techniques when compared to open approaches.^{46,47,48} However, the utilization of smaller incisions and instruments that are extensions of fingers and hands engenders new dilemmas. It is unclear whether MIS techniques adequately maintain the integrity of cancer operations, especially when surgeons are early in their learning curve. Furthermore, it is unclear what impact the growing utilization of MIS techniques may have on teaching surgical trainees the standard open techniques.

These concerns are particularly important to address when considering gastric cancer surgery in Western countries, where the incidence of gastric cancer is relatively low and the prevalence of morbid obesity is high, leading to greater difficulties in developing and maintaining surgical expertise. Worldwide gastric cancer remains one of the most common malignancies.^{49, 50} However, in Western countries gastric cancer incidence has declined considerably over the past several decades and in the United States, it is not within the top 10 list of most common cancers. In Eastern nations where the incidence is higher, there has been greater acceptance and mastery of MIS techniques for gastrectomy. Based on our experience, we present a systematic approach to teaching and mastering MIS gastrectomy despite the challenges faced by Western surgeons.

Parallels in MIS versus Open Technique

When performing distal gastrectomy (open or MIS), we propose using the same or similar type of instruments for all key steps.⁵¹ This consistent approach facilitates a smooth transition between open and MIS cases, wherein the only difference becomes the size of the incision rather than the technical performance of the operation. For example, energy devices should be used to divide small and large tissues; and small and medium-sized clips should be used to ligate blood vessels. Endoscopic linear staplers should be used to transect small

intestine and stomach. The major difference in our approach between open and MIS techniques is the creation of the gastrojejunal anastomosis. For the open approach, we employ hand sewn two-layer anastomoses. For the MIS approach, an endoscopic or robotic linear stapler is used to create the anastomosis; and the common enterotomy is sutured closed either with the Endostitch or robotic suturing technique.

Systematic Clockwise Approach

It is important to develop a standardized and easy-to-remember series of steps that are followed for both open or MIS approaches. Distal gastrectomy with lymphadenectomy can be performed in a clockwise series of key steps with harvesting of nodal tissues along each of the major vessels ligated at its origin: (1) Enter the lesser space by dividing the gastrocolic ligament. (2) Ligate the right gastroepiploic vessels. (3) Transect the duodenum. (4) Ligate the right gastric artery. (5) Divide the gastrohepatic ligament to the right crus and along the lesser curvature of the stomach. (6) Ligate the left gastric vessels. (7) Transect the stomach and perform gastrojejunal anastomosis using Billroth II reconstruction.

Conclusions

MIS distal gastrectomy requires advanced surgical technique and skill, which are difficult to develop and teach in the setting of low volume related to the low incidence of gastric cancer in the US. However, a programmatic effort to use similar instruments and steps for open or MIS gastrectomy, such as the approach described above, can facilitate the adoption of such operative strategies while maintaining oncologic outcomes and adequate education of surgical trainees.

Is There a Role for Cytoreductive Surgery and HIPEC for Gastric Cancer?

Cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC) have been an established modality of treatment for various abdominal pathologies, including appendiceal and colorectal cancers; however, its application in the setting of gastric cancer with peritoneal metastases (PM) has only recently been considered. Because gastric cancer often disseminates into the peritoneal cavity, CRS with HIPEC has been investigated as an adjunct treatment, although this modality may only be applicable to a specific subset of patients. At present, CRS/HIPEC is only investigational, and standard treatment for metastatic gastric carcinoma is palliative-intent systemic chemotherapy.

Emerging Evidence for CRS and HIPEC in Selected Patients

The first report of CRS and HIPEC for gastric cancer came from Japan in the 1980s, where mitomycin C was utilized in a prophylactic intent in gastric cancer patients with serosal involvement.⁵² This study observed a survival benefit in those undergoing HIPEC; since then, multiple studies, largely from Asia and Europe, have emerged studying the role of CRS/HIPEC in gastric cancer. Retrospective studies from France have observed an association with improved survival, particularly in those with limited PM. In a recent analysis from Lyon Sud Hospital in France, 127 patients (1989–2015) with PM were treated with CRS/HIPEC. The study observed a median OS of 13 months, with a 14% 5-year OS and 10% 10-year OS, which compared favorably to historic controls.⁵³ However, the rate of

major complications was 50%, and did not change with experience; this rate is higher than other institutional reports, although most report upwards of 15% morbidity.

Dr. Yutaka Yonemura is credited with being one of the pioneers of CRS/HIPEC in gastric cancer. He has reported improved survival in patients with PM randomized to CRS/HIPEC compared to those undergoing CRS without HIPEC; systemic chemotherapy >6 cycles was also shown to be an independent factor for survival.⁵⁴ Dr. Yonemura also proposed a strategy of neoadjuvant intraperitoneal (IP) and systemic chemotherapy (NIPS) comprised of oral S-1 combined with IP Taxotere and cisplatin, also known as bidirectional chemotherapy, as an aggressive and safe means to treat PM.

In the United States, the GYMSSA trial, a prospective randomized trial comparing CRS/HIPEC/FOLFOXIRI chemotherapy to FOLFOXIRI alone showed no survival difference between those undergoing CRS/HIPEC/systemic chemotherapy versus systemic therapy alone. However, meaningful statistical comparisons could not be made and no definite conclusions drawn because the study was severely limited by poor accrual (i.e., only 17 patients).⁵⁵ On the other hand, the complication rate was very high with nearly every patient experiencing a grade 3 complication or higher; reoperation was performed in four (44%) patients, for hemorrhage and anastomotic leak. Like other published reports, however, this study found that a lower peritoneal carcinomatosis index and achievement of complete cytoreduction of disease were favorable prognostic factors. Another larger phase III randomized trial from China compared 68 patients undergoing CRS versus CRS plus HIPEC with Mitomycin C and Cisplatin. This trial observed a survival improvement in those undergoing CRS plus HIPEC versus CRS alone, as well as identified complete cytoreduction and exposure to >6 cycles of chemotherapy as additional factors associated with improved survival.⁵⁴ Although retrospective, a multi-center French group also observed 5-year survival in patients with a peritoneal cancer index <7 and complete cytoreduction, again suggesting that CRS/HIPEC may improve survival in highly select patients.⁵⁶

Looking to the future, the GASTRICHIP Trial, a randomized, open, multicenter phase III trial, with a design to understand the role of HIPEC in the setting of locally advanced gastric cancer and/or positive peritoneal cytology, will attempt to evaluate the role of HIPEC in a prophylactic fashion. This trial is currently accruing; however, these patients have a lower disease burden than those with macroscopic PM, and the results may not be broadly applicable. The GASTRIPEC Trial, also currently accruing, is a prospective multicenter phase III trial that will evaluate survival in patients with gastric PC randomized to CRS versus CRS and HIPEC following 3 cycles of preoperative chemotherapy. These trials may help identify in further detail which patients may benefit from CRS/HIPEC and elucidate the role of HIPEC in addition to CRS alone.

Summary

Given the heterogeneity within available studies, it is difficult to determine the best standard of care for any patient presenting with PM. While the results of prospective, randomized studies suggest a potential for improved survival in highly selected patients who undergo CRS/HIPEC, the morbidity of these procedures ranges from 20 to 40% in most reported series, and the overall complication rates are up to 50%.⁵³ Additionally, the impact of

neoadjuvant systemic chemotherapy, the type of IP chemotherapy agent, the utility of NIPS, and the role of adjuvant chemotherapy remains to be elucidated for broad application to patients with gastric cancer and PM. Enthusiasm for CRS/HIPEC for gastric cancer PM must be tempered by the understanding that only a highly select patient population may qualify for this aggressive treatment. These patients must have an excellent performance status to tolerate CRS/HIPEC, a low tumor burden, and should demonstrate lack of disease progression while receiving systemic chemotherapy. Moreover, CRS and HIPEC are not exclusive of systemic treatment. Thus, this approach should only be considered as an adjunct in the multidisciplinary care of the appropriately selected patients and ideally should be performed in the setting of a clinical trial. Further collaborative studies, perhaps across countries, and multi-institutional clinical trials may allow for improved understanding of the timing and role of CRS/HIPEC.

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References

1. Joensuu H, DeMatteo RP. The management of gastrointestinal stromal tumors: a model for targeted and multidisciplinary therapy of malignancy. *Annual review of medicine*. 2012; 63:247–58. DOI: 10.1146/annurev-med-043010-091813
2. Keung EZ, Raut CP. Management of Gastrointestinal Stromal Tumors. *The Surgical clinics of North America*. 2017; 97(2):437–52. DOI: 10.1016/j.suc.2016.12.001 [PubMed: 28325196]
3. Bannon AE, Klug LR, Corless CL, Heinrich MC. Using molecular diagnostic testing to personalize the treatment of patients with gastrointestinal stromal tumors. *Expert review of molecular diagnostics*. 2017; 17(5):445–57. DOI: 10.1080/14737159.2017.1308826 [PubMed: 28317407]
4. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Annals of surgery*. 2000; 231(1):51–8. [PubMed: 10636102]
5. Shi E, Chmielecki J, Tang CM, Wang K, Heinrich MC, Kang G, et al. FGFR1 and NTRK3 actionable alterations in “Wild-Type” gastrointestinal stromal tumors. *Journal of translational medicine*. 2016; 14(1):339.doi: 10.1186/s12967-016-1075-6 [PubMed: 27974047]
6. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Archives of pathology & laboratory medicine*. 2006; 130(10):1466–78. RA-5–1116 [pii]. [PubMed: 17090188]
7. Fero KE, Coe TM, Fanta PT, Tang CM, Murphy JD, Sicklick JK. Surgical Management of Adolescents and Young Adults With Gastrointestinal Stromal Tumors: A US Population-Based Analysis. *JAMA surgery*. 2017; doi: 10.1001/jamasurg.2016.5047
8. Gold JS, Gonen M, Gutierrez A, Broto JM, Garcia-del-Muro X, Smyrk TC, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. *The lancet oncology*. 2009; 10(11):1045–52. S1470-2045(09)70242-6 [pii]. DOI: 10.1016/S1470-2045(09)70242-6 [PubMed: 19793678]
9. Joensuu H, Vehtari A, Riihimäki J, Nishida T, Steigen SE, Brabec P, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. *The lancet oncology*. 2012; 13(3):265–74. DOI: 10.1016/S1470-2045(11)70299-6 [PubMed: 22153892]
10. Joensuu H, Rutkowski P, Nishida T, Steigen SE, Brabec P, Plank L, et al. KIT and PDGFRA mutations and the risk of GI stromal tumor recurrence. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015; 33(6):634–42. DOI: 10.1200/JCO.2014.57.4970 [PubMed: 25605837]

11. Sicklick JK, Lopez NE. Optimizing surgical and imatinib therapy for the treatment of gastrointestinal stromal tumors. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract*. 2013; 17(11):1997–2006. DOI: 10.1007/s11605-013-2243-0 [PubMed: 23775094]
12. Joensuu H, Roberts PJ, Sarlomo-Rikala M, Andersson LC, Tervahartiala P, Tuveson D, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *The New England journal of medicine*. 2001; 344(14):1052–6. DOI: 10.1056/NEJM200104053441404 [PubMed: 11287975]
13. Dematteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009; 373(9669):1097–104. S0140-6736(09)60500-6 [pii]. DOI: 10.1016/S0140-6736(09)60500-6 [PubMed: 19303137]
14. Joensuu H, Eriksson M, Sundby Hall K, Hartmann JT, Pink D, Schutte J, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA : the journal of the American Medical Association*. 2012; 307(12):1265–72. DOI: 10.1001/jama.2012.347 [PubMed: 22453568]
15. Fraenkel M, Kim M, Faggiano A, de Herder WW, Valk GD, Knowledge N. Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. *Endocr Relat Cancer*. 2014; 21(3):R153–63. DOI: 10.1530/ERC-13-0125 [PubMed: 24322304]
16. Modlin IM, Lye KD, Kidd M. Carcinoid tumors of the stomach. *Surg Oncol*. 2003; 12(2):153–72. [PubMed: 12946486]
17. Fendrich V, Bartsch DK. Surgical treatment of gastrointestinal neuroendocrine tumors. *Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie*. 2011; 396(3):299–311. DOI: 10.1007/s00423-011-0741-7
18. Rindi G, Petrone G, Inzani F. 25 Years of neuroendocrine neoplasms of the gastrointestinal tract. *Endocr Pathol*. 2014; 25(1):59–64. DOI: 10.1007/s12022-013-9292-5 [PubMed: 24399298]
19. Corey B, Chen H. Neuroendocrine Tumors of the Stomach. *The Surgical clinics of North America*. 2017; 97(2):333–43. DOI: 10.1016/j.suc.2016.11.008 [PubMed: 28325190]
20. Jenny HE, Ogando PA, Fujitani K, Warner RR, Divino CM. Laparoscopic antrectomy: a safe and definitive treatment in managing type 1 gastric carcinoids. *American journal of surgery*. 2016; 211(4):778–82. DOI: 10.1016/j.amjsurg.2015.08.040 [PubMed: 26992358]
21. Postlewait LM, Baptiste GG, Ethun CG, Le N, Cardona K, Russell MC, et al. A 15-year experience with gastric neuroendocrine tumors: Does type make a difference? *Journal of surgical oncology*. 2016; 114(5):576–80. DOI: 10.1002/jso.24369 [PubMed: 27393718]
22. Mulkeen A, Cha C. Gastric carcinoid. *Curr Opin Oncol*. 2005; 17(1):1–6. [PubMed: 15608504]
23. Ruszniewski P, Delle Fave G, Cadiot G, Komminoth P, Chung D, Kos-Kudla B, et al. Well-differentiated gastric tumors/carcinomas. *Neuroendocrinology*. 2006; 84(3):158–64. DOI: 10.1159/000098007 [PubMed: 17312375]
24. Doherty GM, Olson JA, Frisella MM, Lairmore TC, Wells SA Jr, Norton JA. Lethality of multiple endocrine neoplasia type I. *World J Surg*. 1998; 22(6):581–6. discussion 6–7. [PubMed: 9597932]
25. Ekeblad S, Skogseid B, Dunder K, Oberg K, Eriksson B. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. *Clin Cancer Res*. 2008; 14(23):7798–803. DOI: 10.1158/1078-0432.CCR-08-0734 [PubMed: 19047107]
26. Sato Y, Hashimoto S, Mizuno K, Takeuchi M, Terai S. Management of gastric and duodenal neuroendocrine tumors. *World J Gastroenterol*. 2016; 22(30):6817–28. DOI: 10.3748/wjg.v22.i30.6817 [PubMed: 27570419]
27. Lesurtel M, Nagorney DM, Mazzaferro V, Jensen RT, Poston GJ. When should a liver resection be performed in patients with liver metastases from neuroendocrine tumours? A systematic review with practice recommendations. *HPB (Oxford)*. 2015; 17(1):17–22. DOI: 10.1111/hpb.12225 [PubMed: 24636662]
28. Delle Fave G, Capurso G, Milione M, Panzuto F. Endocrine tumours of the stomach. *Best practice & research Clinical gastroenterology*. 2005; 19(5):659–73. S1521-6918(05)00087-9 [pii]. DOI: 10.1016/j.bpg.2005.05.002 [PubMed: 16253892]

29. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA: a cancer journal for clinicians*. 2015; 65(2):87–108. DOI: 10.3322/caac.21262 [PubMed: 25651787]
30. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA: a cancer journal for clinicians*. 2016; 66(1):7–30. DOI: 10.3322/caac.21332 [PubMed: 26742998]
31. Ilson DH. Current Progress in the Adjuvant Treatment of Gastric Cancer. *Surgical oncology clinics of North America*. 2017; 26(2):225–39. DOI: 10.1016/j.soc.2016.10.008 [PubMed: 28279466]
32. Lin SJ, Gagnon-Bartsch JA, Tan IB, Earle S, Ruff L, Pettinger K, et al. Signatures of tumour immunity distinguish Asian and non-Asian gastric adenocarcinomas. *Gut*. 2015; 64(11):1721–31. DOI: 10.1136/gutjnl-2014-308252 [PubMed: 25385008]
33. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *The lancet oncology*. 2010; 11(5):439–49. DOI: 10.1016/S1470-2045(10)70070-X [PubMed: 20409751]
34. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *The New England journal of medicine*. 2006; 355(1):11–20. DOI: 10.1056/NEJMoa055531 [PubMed: 16822992]
35. Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011; 29(13):1715–21. DOI: 10.1200/JCO.2010.33.0597 [PubMed: 21444866]
36. Al-Batran SE, Hofheinz RD, Pauligk C, Kopp HG, Haag GM, Luley KB, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. *The lancet oncology*. 2016; 17(12):1697–708. DOI: 10.1016/S1470-2045(16)30531-9 [PubMed: 27776843]
37. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011; 29(33):4387–93. DOI: 10.1200/JCO.2011.36.5908 [PubMed: 22010012]
38. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet*. 2012; 379(9813):315–21. DOI: 10.1016/S0140-6736(11)61873-4 [PubMed: 22226517]
39. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010; 376(9742):687–97. DOI: 10.1016/S0140-6736(10)61121-X [PubMed: 20728210]
40. Lynch HT, Grady W, Suriano G, Huntsman D. Gastric cancer: new genetic developments. *Journal of surgical oncology*. 2005; 90(3):114–33. discussion 33. DOI: 10.1002/jso.20214 [PubMed: 15895459]
41. Hebbard PC, Macmillan A, Huntsman D, Kaurah P, Carneiro F, Wen X, et al. Prophylactic total gastrectomy (PTG) for hereditary diffuse gastric cancer (HDGC): the Newfoundland experience with 23 patients. *Annals of surgical oncology*. 2009; 16(7):1890–5. DOI: 10.1245/s10434-009-0471-z [PubMed: 19408054]
42. Chen Y, Kingham K, Ford JM, Rosing J, Van Dam J, Jeffrey RB, et al. A prospective study of total gastrectomy for CDH1-positive hereditary diffuse gastric cancer. *Annals of surgical oncology*. 2011; 18(9):2594–8. DOI: 10.1245/s10434-011-1648-9 [PubMed: 21424370]
43. Bardram L, Hansen TV, Gerdes AM, Timshel S, Friis-Hansen L, Federspiel B. Prophylactic total gastrectomy in hereditary diffuse gastric cancer: identification of two novel CDH1 gene mutations-

- a clinical observational study. *Familial cancer*. 2014; 13(2):231–42. DOI: 10.1007/s10689-013-9698-8 [PubMed: 24389957]
44. Worster E, Liu X, Richardson S, Hardwick RH, Dwerryhouse S, Caldas C, et al. The impact of prophylactic total gastrectomy on health-related quality of life: a prospective cohort study. *Annals of surgery*. 2014; 260(1):87–93. DOI: 10.1097/SLA.0000000000000446 [PubMed: 24424140]
 45. Benusiglio PR, Malka D, Rouleau E, De Pauw A, Buecher B, Nogues C, et al. CDH1 germline mutations and the hereditary diffuse gastric and lobular breast cancer syndrome: a multicentre study. *Journal of medical genetics*. 2013; 50(7):486–9. DOI: 10.1136/jmedgenet-2012-101472 [PubMed: 23709761]
 46. Kelly KJ, Selby L, Chou JF, Dukleska K, Capanu M, Coit DG, et al. Laparoscopic Versus Open Gastrectomy for Gastric Adenocarcinoma in the West: A Case-Control Study. *Annals of surgical oncology*. 2015; 22(11):3590–6. DOI: 10.1245/s10434-015-4381-y [PubMed: 25631063]
 47. Huscher CG, Mingoli A, Sgarzini G, Sansonetti A, Di Paola M, Recher A, et al. Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: five-year results of a randomized prospective trial. *Annals of surgery*. 2005; 241(2):232–7. [PubMed: 15650632]
 48. Vinuela EF, Gonen M, Brennan MF, Coit DG, Strong VE. Laparoscopic versus open distal gastrectomy for gastric cancer: a meta-analysis of randomized controlled trials and high-quality nonrandomized studies. *Annals of surgery*. 2012; 255(3):446–56. DOI: 10.1097/SLA.0b013e31824682f4 [PubMed: 22330034]
 49. Guggenheim DE, Shah MA. Gastric cancer epidemiology and risk factors. *Journal of surgical oncology*. 2013; 107(3):230–6. DOI: 10.1002/jso.23262 [PubMed: 23129495]
 50. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA: a cancer journal for clinicians*. 2011; 61(2):69–90. DOI: 10.3322/caac.20107 [PubMed: 21296855]
 51. Hamner, J., Kim, J. *Surgery for Cancers of the Gastrointestinal Tract*. New York, NY: Springer-Verlag; 2014. p. 75–86.
 52. Koga S, Hamazoe R, Maeta M, Shimizu N, Murakami A, Wakatsuki T. Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with mitomycin C. *Cancer*. 1988; 61(2):232–7. [PubMed: 3121165]
 53. Passot G, Vaudoyer D, Villeneuve L, Kepenekian V, Beaujard AC, Bakrin N, et al. What made hyperthermic intraperitoneal chemotherapy an effective curative treatment for peritoneal surface malignancy: A 25-year experience with 1,125 procedures. *Journal of surgical oncology*. 2016; 113(7):796–803. DOI: 10.1002/jso.24248 [PubMed: 27110915]
 54. Yang XJ, Huang CQ, Suo T, Mei LJ, Yang GL, Cheng FL, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. *Annals of surgical oncology*. 2011; 18(6):1575–81. DOI: 10.1245/s10434-011-1631-5 [PubMed: 21431408]
 55. Rudloff U, Langan RC, Mullinax JE, Beane JD, Steinberg SM, Beresnev T, et al. Impact of maximal cytoreductive surgery plus regional heated intraperitoneal chemotherapy (HIPEC) on outcome of patients with peritoneal carcinomatosis of gastric origin: results of the GYMSSA trial. *Journal of surgical oncology*. 2014; 110(3):275–84. DOI: 10.1002/jso.23633 [PubMed: 25042700]
 56. Chia CS, You B, Decullier E, Vaudoyer D, Lorimier G, Abboud K, et al. Patients with Peritoneal Carcinomatosis from Gastric Cancer Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Is Cure a Possibility? *Annals of surgical oncology*. 2016; 23(6):1971–9. DOI: 10.1245/s10434-015-5081-3 [PubMed: 26753751]

Table 1

Characteristics of Gastric Neuroendocrine Subtypes

Features	Type I	Type II	Type III	Type IV
Percentage of all gastric NETs	80 to 100%	5 to 10%	10 to 15%	<5%
Associated syndrome	Pernicious anemia	Zollinger-Ellison (MEN-1)	None	None
Hypergastrinemia	Present	Present	Absent	Absent
Gastric acid level	Low	High	Normal	Normal
Tumor size	<1 cm	>1 cm	> 2 cm	>4 cm
WHO grade	1	1 to 2	2 to 3	3
Primary tumor distribution	Multiple	Multiple	Solitary	Solitary
Propensity for metastasis	Low	Low	High	High
Preferred resection	Endoscopic	Endoscopic	Surgical	Surgical
Prognosis	Excellent	Good	Poor	Poor

Table 2

Preoperative chemotherapy gastroesophageal junction and gastric adenocarcinoma

Trial	Number of patients randomized	Chemotherapy Treatment	5-year Overall Survival
MAGIC ⁶	503	Epirubicin, cisplatin and 5-FU	36.3% (chemotherapy) vs. 23% (surgery)
Federation National ⁷	224	Cisplatin plus 5-FU	38% (chemotherapy) vs. 24% (surgery)

Data are extracted from reference by Ilson.³¹

Table 3

Postoperative chemotherapy in gastric cancer

Trial	Number of patients randomized	Treatment	5-year survival
ACTGS ⁹	515	S-1	72%
	519	Surgery	61%
CLASSIC ¹⁰	520	Capecitabine-Oxaliplatin	78%
	515	Surgery	69%

Data are extracted from reference by Ilson.³¹

Table 4

Outcome of Patients with Hereditary Diffuse Gastric Cancer Based on the Presence of Symptoms at Diagnosis compared to those who underwent prophylactic gastrectomy

n	Symptoms	Age, y (range)	Sensitivity of Endoscopy	4-yr Disease-Specific Survival
13	No	48 (18–70)	15%	100%
5	Yes	40 (23–52)	100%	40%

Patients who were diagnosed by *CDH1* mutation screening and did not have symptoms at diagnosis had an improved long-term outcome. Each patient who underwent prophylactic gastrectomy had a T1N0 gastric cancer and was cured, while only 20% of patients who presented with symptoms were cured by stomach surgery.⁴²