# Approach to the Medical Management of Surgically Resectable Gastric Cancer

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**Abstract:** The optimal adjuvant management of patients with resectable gastric cancer remains a therapeutic challenge. Although the benefit of adjuvant therapy for these patients is clearly established, recurrence and mortality rates remain high despite such treatment. Moreover, surgical comorbidities and treatment toxicities result in high rates of failure to complete treatment after surgery. Two divergent approaches to adjuvant treatment have emerged as standard: postoperative chemoradiotherapy and perioperative chemotherapy. Because these approaches have never been compared directly, recommendations for adjuvant treatment require multidisciplinary discussion. During this discussion, the characteristics of the symptoms, the histology, location, and stage of the tumor, and the feasibility of the patient's completing all recommended therapy may be considered. In our own practice, we favor perioperative chemotherapy for patients with asymptomatic, proximal, higher-stage disease and adjuvant chemoradiotherapy for patients with symptomatic, distal, lower-stage disease. Herein, we summarize the available data for approaches to the adjuvant treatment of gastric cancer, with special consideration of the characteristics of the patients enrolled in the various studies. We also describe how we developed our paradigm for recommending a particular approach to adjuvant treatment for each patient.

## Introduction

### *Epidemiology*

Gastric and gastroesophageal carcinomas constitute a complex and important global cause of morbidity and mortality.[1] A unique feature of these cancers is the considerable geographic variation in their incidence. The rates are highest in eastern Asia, South America, and central and eastern Europe, and lowest in North America, most parts of Africa, and northern and western Europe. It has been suggested

that this geographic variation reflects differences in the prevalence of several possible etiologic factors, such as *Helicobacter pylori* infection, dietary patterns, and food storage methods.[2] Although the prevalence of this disease is highest in parts of Asia,[1] it remains a major health concern in the western world as well. In its annual update, the Global Burden of Cancer reported 984,000 new cases of stomach cancer in 2013, with 841,000 deaths. Globally, stomach cancer ranked fifth for cancer incidence and second for cancer deaths[3] in 2013. In 2015, there were an estimated 24,590 new cases of gastric cancer in the United States, causing approximately 10,720 deaths.[4]

### *Pathology*

Although other histologic types exist, 90% of gastric cancers are adenocarcinomas,[5] which are subclassified into 3 histologic subtypes: intestinal, diffuse, and mixed variants.[6]

The well-differentiated intestinal subtype is the major variant of gastric adenocarcinoma and predominates in the geographic areas described as high risk.[2] This variant has been linked to environmental factors such as *H pylori* infection and diet.[5,7] It has been suggested that the carcinogenesis of this subtype typically follows the sequence of chronic atrophic gastritis to intestinal metaplasia to dysplasia.[8] The incidence of the intestinal subtype is in steady decline, likely owing to improvements in dietary factors and effective therapies for *H pylori* eradication.[9-11]

The diffuse, undifferentiated subtype, unlike the intestinal subtype, does not seem to have the same relationship to environmental factors and usually originates from a healthy gastric mucosa or against a background of non-atrophic gastritis. Unlike the intestinal subtype, the diffuse subtype has no known precursor lesion. More than 50% of gastric carcinomas of the diffuse subtype have been associated with epigenetic silencing of the E-cadherin gene (*CDH1*), which is a tumor suppressor gene. The loss of function of this gene leads to the dissociation of cells from their matrix, marking their malignant behavior.[5]

These different subtypes may be said to represent different diseases. Therefore, the global health burden of gastric cancer reflects changes in the incidence of specific subtypes, which in turn is affected by environmental and genetic etiologic factors. An overall global decline in the incidence of gastric cancer has corresponded to a decreasing incidence of the intestinal subtype, whereas the diffuse subtype has increased.[10] Epidemiologic studies have shown that the incidence of gastric cancer in the United States decreased by 34% between the period from 1978 to 1983 and the period from 2001 to 2005. A US study based on Surveillance, Epidemiology, and End Results (SEER) data showed that the intestinal subtype declined by 44% between 1973 and 2000, whereas the diffuse subtype increased by 62% during the same period.[12]

The intestinal subtype usually carries a better prognosis than the diffuse subtype, and this may be one of the reasons that treatment outcomes are better in geographical areas where the disease burden is high than in areas with less disease.[13] The diffuse subtype tends to be more aggressive than the intestinal subtype. It has been shown to be associated with a higher risk for lymph node metastases than the intestinal subtype in early gastric cancer.[14] The diffuse subtype also shows a marked tendency for local infiltration, with reactive fibrosis and subsequent stiffening of the gastric wall causing linitis plastica in the most advanced stage.

The incidence of gastric cancer has been changing based on anatomical location of the tumors as well as histologic subtype. A correlation exists between subtype and location; the intestinal subtype tends to occur distally in the stomach, whereas the diffuse subtype tends to occur proximally, toward the cardia. The incidence of gastric cancer in the non-cardia location of the stomach has decreased significantly in multiple population-based studies, and this decrease is likely the cause of the decline in the incidence of gastric cancer in general. A SEER-based epidemiologic study showed that the incidence of non-cardia tumors declined between the period from 1978 to 1983 and the period from 2001 to 2005.[12] The Italian Research Group for Gastric Cancer (GIRCG) has provided further evidence of this trend, reporting that the proportion of gastric cancers in the proximal one-third of the stomach increased between 1991 and 2005, whereas the proportion of gastric cancers in the distal one-third decreased during that time.[15]

### *Clinical Presentation*

More than half of patients who have gastric cancer present with weight loss and abdominal pain. Other common symptoms include nausea, anorexia, melena, and early satiety. In advanced stages, patients may have symptoms related to metastatic disease, especially peritoneal carcinomatosis. On presentation, approximately 70% of patients in the United States have locoregional disease (stages I-III).[16] It has been proposed that the presence of "alarm" symptoms be used to aid in the selection of patients for endoscopic evaluation. These include weight loss, dysphagia, upper gastrointestinal bleeding, and persistent vomiting.[17]

In addition to the features previously described, gastric cancers may exhibit unique symptoms depending on the part of the stomach from which they arise. Cancer arising in the proximal part of the stomach may present with nonspecific symptoms, such as dysphagia and pseudoachalasia.[18] Early satiety may be indicative of a diffusely infiltrative tumor that has resulted in loss of distensibility of the gastric wall. Delayed satiety, vomiting, and gastric

outlet obstruction may indicate a tumor arising from the distal part of the stomach. Bleeding, typically seen with distal tumors, occurs in 10% to 15% of patients. Because of these symptoms, a distal tumor may present at an earlier stage than a more proximally located, otherwise asymptomatic tumor.

## Treatment of Localized Gastric Cancer

### *Surgery*

Surgical resection of the gastric tumor combined with lymphadenectomy remains the only potentially curative option for gastric adenocarcinoma. The optimal extent of lymphadenectomy has been a topic of debate, with significant geographical variations in practice and outcomes. More extensive lymphadenectomy (D2, resection of all regional lymph nodes) has been shown to achieve higher cure rates in the eastern hemisphere (eg, Japan and South Korea), even though the same results could not be replicated in Europe and North America.[19,20] The variation in the success and complication rates of D2 lymphadenectomy may be a reflection of possible geographic variations in technical expertise. After a median follow-up of 15 years, the rate of gastric cancer–related death was lower among patients who underwent D2 resection than among those who underwent D1 resection (37% vs 48%; *P*=.01). However, patients who underwent D2 resection had a higher perioperative mortality rate (10% vs 4%) and a higher morbidity rate (43% vs 25%) compared with those who underwent D1 resection. Patients who underwent D2 resection also had a lower locoregional recurrence rate (25%) compared with those who underwent D1 resection (41%).[21] Therefore, although D2 lymphadenectomy is the accepted surgical standard of care based upon maximal patient benefit, this complex operation requires the technique of a skilled surgeon, given the risk for complications and the requisite knowledge of lymphatic anatomy.

Studies have shown a risk for locoregional and systemic recurrence of approximately 40% in patients treated only with surgical resection of their tumor. The majority of these recurrences take place in the first 2 years after diagnosis. The studies have shown that patients who undergo limited lymphadenectomy tend to have a higher rate of peritoneal and locoregional recurrence, and patients who have the diffuse, undifferentiated histologic subtype with more extensive nodal disease appear to have a higher rate of systemic metastases.[22,23]

### *Medical Therapy for Resectable Gastric Cancer*

Given the high risk for the recurrence of gastric cancer after surgical resection alone, adjuvant treatments with chemotherapy and radiation therapy have been studied in an effort to improve outcomes. A meta-analysis from the GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, which analyzed data from 3838 patients in 17 different trials with a median follow-up longer than 7 years, has shown that the use of any form of adjuvant chemotherapy following surgical resection in a patient with resectable gastric cancer reduces the risk for gastric cancer recurrence by approximately 18%. The estimated median overall survival (OS) was 4.9 years (95% CI, 4.4-5.5) in the surgery-only group vs 7.8 years (95% CI, 6.5-8.7) in the group receiving any form of adjuvant chemotherapy. Beyond this, there were no differences in disease-free survival (DFS) or OS for the different chemotherapy regimens studied.[24]

A wide variation between adjuvant approaches to gastric cancer exists, posing a therapeutic challenge to clinicians. In the western hemisphere, 2 landmark studies have largely streamlined recommendations for the adjuvant care of patients with gastric cancer into 2 rather different approaches. The INT-0116 trial (US Gastric Surgical Adjuvant Trial), published in 2001, established the benefit of postoperative chemotherapy and radiation therapy.[25] The United Kingdom's MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) trial, published in 2006, established the benefit of perioperative chemotherapy without radiation.[26] These 2 adjuvant approaches have never been directly compared, and thus the superiority of one over the other has not been established. Moreover, they remain the model for adjuvant treatment despite the fact that they were initially published at least a decade ago.

### *Postoperative Adjuvant Chemoradiotherapy*

**The INT-0116 Trial.** This trial randomly assigned 556 patients to either observation or postoperative adjuvant chemoradiotherapy after they had undergone resection of gastric or gastroesophageal junction (GEJ) cancer. Patients were eligible if their cancer was between stage Ib and stage IV (M0). In the adjuvant treatment arm, patients received 1 cycle of a continuous infusion of 5-fluorouracil (5-FU; 425 mg/m$^2$/d) and leucovorin (LV) calcium (20 mg/m$^2$/d) for 5 days. This was followed by radiation therapy, with a total of 45 Gy administered in daily fractions of 1.8 Gy, 28 days after the start of the initial cycle of chemotherapy. Concurrently with the radiation, 5-FU (400 mg/m$^2$/d) and LV (20 mg/m$^2$/d) were administered on radiation days 1 through 4 and again on the last 3 days of radiation. At 1 month after the completion of chemoradiotherapy, two 5-day cycles of 5-FU and LV were given, 1 month apart.

In the INT-0116 trial, the majority of the patients (77%) in the chemoradiotherapy arm had tumors in the distal stomach (antrum 53%, corpus 24%). Approximately 20% of the patients had tumors in the cardia. The

tumor histologic subtypes were not reported. The patients were at high risk for relapse; more than two-thirds had T3 or T4 tumors (68%), and 85% had nodal metastases. Of the 281 patients who were assigned to chemoradiotherapy, only 181 (64%) were able to complete the preplanned treatment, emphasizing the toxicity of this therapy, especially after resection for gastric cancer.[25]

The 3-year DFS (48% vs 31%) and OS rates (50% vs 41%) were significantly improved with adjuvant therapy in the INT-0116 trial, and median OS was significantly longer (36 vs 27 months).[25] These benefits were maintained during long-term follow-up: 5-year OS was 43% in the adjuvant arm vs 28% in the control arm (hazard ratio [HR] for survival, 1.32; 95% CI, 1.10-1.60). On long-term follow-up, the rates of distant metastatic recurrence were similar in the 2 arms, whereas there were fewer local and regional recurrences in the chemoradiotherapy arm.[27] Notably, the rate of D2 lymphadenectomy, which is the current standard, was only approximately 10%. The low rate of D2 lymphadenectomy in the INT-0116 trial suggests that these adjuvant data may be out of date with regard to this current standard of care.

**The ARTIST Trial.** The ARTIST (Adjuvant Chemoradiation Therapy in Stomach Cancer) trial, conducted in South Korea, evaluated whether the addition of radiotherapy to adjuvant chemotherapy improved DFS in patients with D2-resected gastric cancer. A total of 458 patients with gastric cancer who had undergone gastrectomy with D2 lymph node dissection were randomly assigned to either 6 cycles of adjuvant chemotherapy with capecitabine and cisplatin (XP) or to 2 cycles of XP followed by chemoradiotherapy and then 2 additional cycles of XP (XPRT). On initial reporting, the 3-year DFS rates were similar in the 2 groups, except in an unplanned subgroup analysis of patients with node-positive disease, which reported favorable outcomes with chemoradiotherapy ($P$=.0365).[28] In a 2015 report on 7-year follow-up data, DFS and OS rates remained similar in the 2 treatment arms. Subgroup analyses demonstrated that chemoradiotherapy significantly improved DFS in patients with node-positive disease.[29]

A possible interpretation of the ARTIST trial results is that radiation therapy may be beneficial for locoregional control and that perhaps only patients with node-positive disease may benefit from adjuvant chemoradiotherapy. The generalizability of this interpretation is open to scrutiny. The Korean population has a comparatively small body habitus, which minimizes surgical complications and allows high rates of successful adjuvant therapy. ARTIST-II, in which patients with node-positive disease are being randomly assigned to either of 2 adjuvant chemotherapy arms or to a third arm that includes adjuvant chemoradiotherapy, is recruiting patients.[30]

***Perioperative Chemotherapy***

**The MAGIC Trial.** An alternative to postoperative chemoradiotherapy was reported in 2006 after completion of the MAGIC trial, which enrolled 503 patients with potentially resectable gastric (74%), GEJ (15%), or distal esophageal (11%) adenocarcinomas. The patients were randomly assigned either to surgery alone or to surgery plus perioperative chemotherapy. Planned perioperative chemotherapy consisted of 3 preoperative and 3 postoperative cycles of epirubicin, cisplatin, and 5-FU (ECF). One 3-week cycle of chemotherapy consisted of epirubicin (50 mg/m$^2$) given by intravenous bolus on day 1, cisplatin (60 mg/m$^2$) given intravenously with hydration on day 1, and a continuous intravenous infusion of 5-FU (200 mg/m$^2$) for 21 days.

Although 90% of those patients assigned to receive preoperative chemotherapy completed all 3 cycles, only 57% began postoperative chemotherapy and only 43% completed it. These findings again highlight the challenge of administering adjuvant therapy after surgery for gastric cancer. However, it also highlights the relatively consistent ability to administer neoadjuvant therapy.

Just 40% of patients in the MAGIC trial underwent D2 lymphadenectomy. Although this percentage is higher than that in the INT-0116 trial, the relatively low rate limits the generalizability of the study results to the current standard-of-care operation. More than two-thirds of the patients had positive lymph nodes (69%). The 5-year survival of the patients randomly assigned to perioperative ECF was significantly better than that of the patients undergoing surgery alone (36% vs 23%; $P$=.009). The local recurrence rates were 14.4% in the perioperative chemotherapy group and 20.6% in the surgery-alone group. In addition, the rates of distant metastases were 24.4% in the perioperative chemotherapy group and 36.8% in the surgery-alone group.[26]

In 2008, modifications of the ECF regimen in patients with previously untreated esophagogastric cancer were studied in the REAL-2 (Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer) trial. Cisplatin was replaced with oxaliplatin, and 5-FU was replaced with capecitabine. The study showed that oxaliplatin and capecitabine can be used as alternatives to cisplatin and 5-FU, respectively, with less toxicity and no sacrifice of benefit.[31]

**The FNCLCC/FFCD Trial.** In 2011, the French Fédération Nationale des Centres de Lutte Contre le Cancer/Fédération Francophone de Cancérologie Digestive (FNCLCC/FFCD) study demonstrated significant survival benefit for perioperative adjuvant chemotherapy with cisplatin and 5-FU in patients with completely resected lower esophageal, GEJ, or gastric cancer. Chemotherapy consisted of 2 or 3 preoperative cycles of

intravenous cisplatin (100 mg/m$^2$) on day 1 and a continuous intravenous infusion of 5-FU (800 mg/m$^2$/d) for 5 consecutive days (days 1-5) every 28 days and 3 or 4 postoperative cycles. Only 50% of the patients who received at least 1 cycle of preoperative chemotherapy and underwent surgery received postoperative chemotherapy. The patients who received perioperative chemotherapy had better rates of 5-year OS (38% vs 24%; *P*=.02) and 5-year DFS (34% vs 19%; *P*=.003) than the patients who were treated with surgery alone.[32]

The FNCLCC/FFCD trial, although smaller than the MAGIC study, showed comparable benefit with the use of only 2 drugs: cisplatin and 5-FU. This raises the question of whether epirubicin needs to be included in the chemotherapy regimen. However, this question cannot be answered without a head-to-head comparison.

Based on the 2 trials, the benefit of chemotherapy is apparent, even if fewer than 50% of the patients in both studies completed the full preplanned postoperative chemotherapy. In both studies, postoperative morbidity was the main reason for not being able to complete the preplanned postoperative chemotherapy. This naturally raises the question of whether administering all the chemotherapy in the neoadjuvant setting is preferable to reserving half of the therapy for after surgery, as nearly half of the patients were not able to receive further chemotherapy after surgery. Currently, no high-quality data are available to answer this question.

### *Utilization of Adjuvant Radiation and Chemotherapy*

Despite these practice-changing studies, the rate of utilization of the regimens in appropriate patients is reportedly low in the community. A study of the SEER-Medicare database looked at the utilization of adjuvant chemoradiotherapy and perioperative chemotherapy after publication of the landmark INT-0016 and MAGIC trials in 2001 and 2006, respectively. From 2002 to 2009, only 25% of eligible patients received adjuvant chemoradiotherapy, and only 3% received perioperative chemotherapy. Patients who saw a medical oncologist as part of their treatment were more likely to receive adjuvant or perioperative chemotherapy with or without radiation.[33] These numbers may not truly reflect reality, especially in high-volume centers. Regardless, they underscore the importance of treating patients up front in a multidisciplinary approach for better planning and possibly better outcomes of treatment.

### *Adjuvant Clinical Paradigm*

At our institution, potential candidates for curative surgical resection of a gastric cancer are discussed in a multidisciplinary setting before a treatment plan is recommended. This approach allows each patient's disease to be considered in terms of extent, location, biology, and symptoms, so that the adjuvant recommendation of either up-front surgery followed by chemoradiotherapy or perioperative chemotherapy can be tailored to the individual circumstances.

In our practice, we typically recommend perioperative chemotherapy, akin to the MAGIC trial, for those patients who have a greater tumor burden (ie, T3-T4 or nodal disease) or more proximal disease. The biology of tumors in the proximal part of the stomach has been observed to be unique in comparison with that of tumors in the distal location, with a greater propensity to spread regionally, as evidenced by the often higher stage of proximal tumors at diagnosis in comparison with distal cancers. The unique biology of this disease favors the perioperative adjuvant approach in order to achieve better local control before surgery, an approach that limits the scope of the surgery that may be necessary in order to achieve complete resection and increase the likelihood of a margin-free resection. This is consistent with the finding that the majority of patients enrolled in the perioperative MAGIC trial had proximally located disease, including esophageal and junctional tumors.

As noted, a significant percentage of patients are not able to receive the postoperative component of the recommended perioperative chemotherapy. Given the poor outcomes of gastric cancer even with adequate surgical resection, some form of adjuvant therapy is clearly required in order to maximize patient outcomes. The added benefit of the perioperative approach in the MAGIC trial is that because most patients complete their preoperative chemotherapy, most are able to receive at least half of the recommended therapy, regardless of their postoperative performance and recovery.

The EORTC (European Organisation for Research and Treatment of Cancer) trial 40954 attempted to compare neoadjuvant chemotherapy followed by surgery with surgery alone in patients who had locally advanced cancer of the stomach and cardia, but it was closed early owing to poor accrual. Although the 2 treatment arms were well balanced in terms of baseline and disease-related characteristics, a number of important findings significantly favored neoadjuvant chemotherapy: a higher complete resection rate, smaller primary tumor size, and less lymph node metastasis compared with surgery alone. However, this study did not demonstrate a statistically significant survival benefit for neoadjuvant therapy in locally advanced gastric cancer. Unlike the landmark trials that have guided our current treatment paradigm, the majority of the patients in this trial had high-quality surgery, with more than 94% undergoing D2 lymphadenectomy.[34] The question of whether the lack of a survival difference was due to poor accrual or to the uniformly high quality of the surgery in the 2 treatment arms remains unanswered. The

favorable features seen in the neoadjuvant chemotherapy arm, however, may suggest the former.

Since the publication of the INT-0116 and MAGIC trials, D2 lymphadenectomy has become widely accepted as a standard of care. The majority of patients in both studies had D1 lymphadenectomy, which is now considered inadequate. The question of whether the additional chemotherapy or radiation therapy made up for the inadequate surgery, or if these therapies had real benefits, cannot be answered at this point owing to inadequate data.

For perioperative chemotherapy, we favor the modified ECF regimen of epirubicin, oxaliplatin, and capecitabine (EOX), which the REAL-2 trial proved to be noninferior but better tolerated.[31] For patients who are unlikely to tolerate the triplet chemotherapy regimen, a doublet combination of a fluoropyrimidine with a platinum agent is alternatively recommended, given the positive survival outcome reported in the FNCLCC/FFCD perioperative chemotherapy trial with a similar regimen. In the absence of a head-to-head comparison of triplet and doublet regimens, expectations regarding tolerance guide the decision to include or exclude the anthracycline.

When doublet therapy is employed, our practice is to recommend modified FOLFOX-6, which is very similar to FLO (5-FU 2600 mg/m$^2$ via 24-hour infusion, LV 200 mg/m$^2$, and oxaliplatin 85 mg/m$^2$ given every 2 weeks), the regimen used in the phase 3 trial for advanced gastric cancer conducted by the German Arbeitsgemeinschaft Internistische Onkologie (AIO) study group. The patients who received FLO had comparable outcomes (even better outcomes in patients older than 65 years) while experiencing fewer side effects than patients receiving FLP (5-FU 2000 mg/m$^2$ via continuous intravenous infusion, LV 200 mg/m$^2$ weekly, and cisplatin 50 mg/m$^2$ every 2 weeks).[35] Alternatively, capecitabine and oxaliplatin can be used, as in the design of the CLASSIC (Adjuvant Capecitabine Plus Oxaliplatin for Gastric Cancer After D2 Gastrectomy) trial.[36]

Conversely, for those patients who have a lower stage of disease at presentation or who have a distally located tumor, we typically favor an up-front surgical approach, to be followed postoperatively with chemotherapy and radiation therapy, akin to the INT-0116 trial. As stated, the biology of distal tumors is different from that of tumors arising proximally, and the lower stage at presentation does seem to correlate with this unique biology. An additional feature of this biological difference is the symptomatic presentation of distal tumors, which tend to present clinically, with either bleeding or obstruction. This clinical declaration by the tumors may be the reason for their generally lower stage at presentation; the more proximally located tumors tend not to be associated with such symptoms.

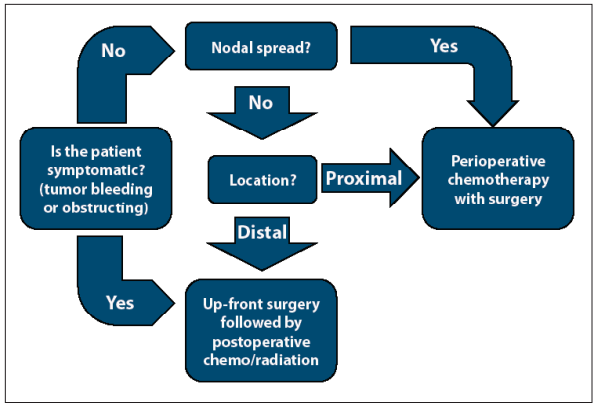


**Figure.** Algorithm for deciding between perioperative chemotherapy and postoperative chemoradiotherapy.

Regardless of location or stage, for patients whose tumors are symptomatic, as with bleeding or obstruction, we always favor an up-front surgical approach. This is driven by the risk that further symptomatic progression will mandate urgent surgery during chemotherapy should the perioperative approach be employed, which carries a greater risk to the patient. The algorithm for our approach is summarized in the Figure.

## Conclusions

At this point, there is a paucity of well-defined clinical guidelines and algorithms to direct the medical management of patients with resectable gastric cancer toward one or the other of the adjuvant treatment options. Lacking these standards, our personalized approach of offering each patient a multidisciplinary consultation up front can help pair the right tumor with the best treatment. Ongoing clinical trials will certainly refine the selection of the best treatment modality for individual patients. One such study, CRITICS (Randomized Phase III Trial of Adjuvant Chemotherapy or Chemoradiotherapy in Resectable Gastric Cancer), is perhaps poised to offer the next such refinement. All patients in this trial underwent preoperative chemotherapy and standardized surgery, and then were randomly assigned postoperatively to either chemotherapy (akin to the MAGIC trial) or chemoradiotherapy (akin to the INT-0116 trial).[37] As we await results, a multidisciplinary approach to each patient up front is recommended in order to synthesize a consensus recommendation regarding the adjuvant approach before surgical resection. It is imperative that patients not undergo surgery until such a discussion takes place.

Gastric cancer is an aggressive malignancy that carries a poor prognosis, even when patients are treated according to existing therapeutic standards. Although gastric cancer is considered to be a single disease entity based on anatomy, it is obvious that this is not the case. Significant

differences in histology most likely reflect variations in disease biology. A better understanding of the biology of this disease may help personalize the treatment approach by optimizing the timing of radiation and choice of chemotherapy and/or molecularly targeted therapy and, it is hoped, increase the likelihood of long-term cure.

### *Disclosures*

*Dr Tesfaye has no relevant disclosures, Dr Smaglo has financial arrangements with Taiho, and Dr Marshall has financial arrangements with Celgene, Genentech, Amgen, and Bayer.*

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