The majority of patients who undergo resection for gastric cancer experience relapse and ultimately die of their disease. Therefore, considerable attention has been paid to neoadjuvant and adjuvant strategies to improve surgical outcomes. Two different approaches have been tested in major clinical trials conducted in the past several years: Postoperative chemoradiotherapy was assessed in a US Southwest Oncology Group/Intergroup study (SWOG 9008/INT 0116), and perioperative chemotherapy was studied in a UK Medical Research Council (MRC) randomized trial (the MRC Adjuvant Gastric Infusional Chemotherapy [MAGIC] trial). These trials demonstrated statistically significant survival benefits in patients with resectable gastric cancer. This review will consider these trials and their implications for clinical practice.

Dr. Jackson and colleagues have provided a concise and cogent review of the state of the art of therapies adjunctive to surgery in patients with resectable gastric and gastroesophageal adenocarcinomas. It is essential for clinicians to be aware of the applicable therapeutic strategies that may increase survival in patients with gastric and gastroesophageal cancers, since these tumors occur in over 900,000 people throughout the world each year. As with most gastrointestinal cancers, the cornerstone of successful therapy for stomach cancer is complete surgical resection of the primary tumor. A core question that must be addressed is whether there are proven techniques in addition to surgery that will improve cure rates in patients with resectable gastroesophageal cancers? The nuances surrounding the answer to this question are discussed by Jackson et al.

Postoperative Chemotherapy
In many neoplasms such as breast cancer, lung cancer, and colon cancer, cytotoxic chemotherapy given as adjuvant therapy after resection of the primary tumor has been shown to improve disease-free and overall survival. It is reasonable to ask whether this strategy has proven effective in gastric cancer. As described by Jackson et al, postoperative cytotoxic chemotherapy may result in small improvements in patient outcome, but the level of benefit—typically, far less than a 10% increase in survival—is not considered to be clinically significant. As a result, clinicians have not adopted adjuvant chemotherapy as a standard of care. I do not doubt that at some point in the future, improved cytotoxic and/or targeted therapies will prove beneficial in cases of resected gastroesophageal cancers, but we are not there yet.

If postoperative chemotherapy is not helpful, what are the acceptable strategies to improving outcome in cases with adenocarcinoma of the stomach/distal esophagus? Jackson and colleagues discuss the two therapeutic strategies supported by data from well powered phase III clinical trials that show improvement of outcome in surgically resected patients with gastroesophageal cancer.

Perioperative Chemotherapy
In 2006, Cunningham and colleagues presented the results of a well designed and executed phase III trial evaluating the role of perioperative chemotherapy in the management of resectable gastric cancer. Patients with resectable gastric cancer were randomly allocated to a combination of chemotherapy and gastric resection or to gastric resection alone. The cases allocated to the chemotherapy-and-surgery treatment arm were to receive both pre- and postoperative therapy with ECF (epirubicin [Ellence], cisplatin, fluorouracil [5-FU]). The surgery-alone cases underwent curative-intent gastrectomy and received no adjuvant therapy. The major outcomes evaluated by Cunningham and colleagues were progression-free and overall survival. The study enrolled 503 patients, with 250 receiving perioperative chemotherapy and 253 being treated with surgical resection alone.

Analysis of the trial, as noted by Jackson et al, showed convincing benefit from the use of ECF chemotherapy.[5] The 5-year overall survival rate was 36% for the chemotherapy-treated patients...
and 23% for those receiving surgical resection alone (log rank P = .008). This 13% improvement in survival corresponds with a 25% reduction in risk of death. Progression-free survival was also improved by chemotherapy (log rank P = .001). In the chemotherapy/surgery/chemotherapy cases, there were also encouraging trends in other outcomes such as decreased tumor size and reduction in the extent of nodal metastases. Toxicity of perioperative chemotherapy was manageable. If perioperative chemotherapy with ECF improves survival, downstages tumors, and is reasonably safe, should it be considered a standard of care in the management of resectable gastric cancer? There are several aspects to this question. First, is ECF the “best” chemotherapy? Cunningham and colleagues note that ECF is a chemotherapy program developed in the early 1990s[6] and that there are newer, less complex chemotherapy programs now available that are active in advanced gastric cancer.[7,8] Are these more recently developed treatment programs better than ECF? The answer to this question is becoming available. As Jackson et al point out, the oral fluorinated pyrimidine capecitabine (Xeloda) may be substituted for 5-FU in ECF-like regimens, and it is highly likely that oxaliplatin (Eloxatin) will replace cisplatin in these regimens.[8]

Timing of Treatment

Although there undoubtedly will be debate among oncologists as to which chemotherapy regimen is most appropriate in gastric cancer, a more important question is whether any sort of perioperative chemotherapy represents the best strategy to improve the cure rate in patients with resectable gastric adenocarcinoma? Part of the answer to this question hinges on when in the treatment course clinicians see cases of resectable gastric cancer. Although perioperative chemotherapy may be reasonable for patients seen prior to gastrectomy, patients who have already undergone gastric resection are not candidates for this treatment.

Patients with gastric cancer are commonly seen by oncologists after a gastrectomy with curative intent has been performed. Is there a standard of care for these cases? In 2001, data on a postoperative chemoradiation adjuvant therapy program were published.[9] This study from the US Intergroup GI Cancer Consortium, INT-0116, resulted in a postoperative chemoradiation treatment regimen being adopted as a standard of care for cases of resected gastric cancer. INT-0116 demonstrated that postoperative combined-modality therapy, incorporating 5-FU and leucovorin chemotherapy along with external-beam radiation to the gastric resection site and the draining lymph node areas, was beneficial for patients with resected gastric cancer. INT-0116 enrolled over 550 eligible cases. The patients in this study were randomly allocated to surgery alone or surgery followed by chemoradiation. These cases were generally at significant risk for relapse after gastric resection, with 85% of all cases having lymph node metastases and 65% having primary tumor invading completely through the gastric wall. The major outcomes analyzed were disease-free and overall survival. Chemoradiation significantly improved overall and disease-free survival. Median survival increased from 27 to 36 months (log rank P = .005) for cases receiving the postoperative combined-modality therapy program, and disease-free survival was also improved from 19 to 30 months. This result was highly significant (P < .001). As noted by Jackson et al, with a median follow-up of over 7 years, updated results from INT-0116 showed that the benefits of chemoradiation were maintained.

Interpreting the Data

The most important question for clinicians treating gastric cancer is how should the data from Cunningham et al and INT-0116 influence the management of patients with resectable gastric cancer? Does perioperative chemotherapy represent such an advance in gastric cancer therapy that the standard of care must change? Cunningham and colleagues[5] have presented a clinical trial that is well designed and well executed, and clinicians may have confidence in the results of this phase III trial. The results provide solid evidence that perioperative therapy with ECF improves the outcome for patients with resectable gastric cancer identified before gastrectomy. That said, there are some concerns about the Cunningham perioperative chemotherapy data. For example, will delaying surgery result in some patients not being able to undergo gastrectomy? Jackson and colleagues point out that 21/250 cases (8%) randomized to perioperative chemotherapy were unable to undergo resection and thus lost the opportunity for curative treatment. The major reason for being unable to undergo gastrectomy was disease progression. Would these patients have been able to undergo surgical resection of the primary neoplasm if the operation had not been delayed by up to 3 months for the administration of preoperative chemotherapy? We cannot know, but a potential risk of perioperative therapy is losing the “window” for surgical resection.
Since patients enrolled in INT-0116 were identified postoperatively, there is no concern about the loss of opportunity for gastrectomy. However, in regard to postoperative chemoradiation, there are several considerations. One concern germane to postoperative chemoradiation is the level of toxicity seen in the treatment arm of INT-0116. As noted by Jackson et al, 97% of cases receiving postoperative chemoradiation develop grade 3 or 4 toxicities. Although this is a daunting statistic, it is important to understand that most of this toxicity was easily managed hematologic toxicity. There were only two definitely confirmed treatment-related toxic deaths, so there is no doubt that chemoradiation as delivered in INT-0116 can be given safely.

Another significant factor regarding INT-0116 is the type of surgery performed in these patients. Only 10% of cases had a formal D2 dissection. Since 85% of all cases on the study had lymph node metastases, it is highly likely that many cases had unresected lymph node metastases. Does this mean that postoperative chemoradiation is effective because it controls unresected lymph node metastases? Would chemoradiation be unnecessary in patients undergoing D2 dissection? The answer to this question can only be addressed by a phase III trial carried out in a D2 dissection population. Such a trial has been initiated in Europe. What is known, without doubt, about postoperative chemoradiation is that this strategy is effective in the North American population treated in INT-0116.

Treatment Recommendations
So how should a clinician manage a patient with resectable or resected gastroesophageal cancer at high risk for relapse? Since adequate gastrectomy—defined as a complete resection of the tumor with negative margins and containing at least 15 identifiable lymph nodes (a D2 resection)—is important for both curative intent and adequate staging, the clinician should do everything possible to encourage this level of surgical care.

The results of the UK Medical Research Council (MRC) perioperative chemotherapy study[5] and the US intergroup INT-0116 study[9] give the clinician a choice of options. I agree with the conclusion of Jackson et al that there is no “best” approach to adjunctive therapy in patients with resectable gastroesophageal cancer. Although there is no one best treatment, the good news is that clinicians now have two options for cases with resected or potentially resectable tumors. Just as postoperative chemoradiation is a proven treatment strategy for postgastrectomy cases, perioperative chemotherapy may be considered an appropriate option for patients with localized resectable gastric adenocarcinoma who have been identified preoperatively.

—John S. Macdonald, MD, FACP

Disclosures: The author has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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