

# Multimodality Approaches to Localized Gastric Cancer

Prajnan Das, MD, MS, MPH;<sup>a\*</sup> Yixing Jiang, MD, PhD;<sup>b\*</sup> Jeffrey H. Lee, MD;<sup>c</sup> Manoop S. Bhutani, MD;<sup>c</sup> William A. Ross, MD;<sup>c</sup> Paul F. Mansfield, MD;<sup>d</sup> and Jaffer A. Ajani, MD;<sup>e</sup> *Houston, Texas, and Hershey, Pennsylvania*

## Key Words

Gastric cancer, surgery, radiation therapy, chemotherapy

## Abstract

Most patients with localized gastric cancer require multimodality therapy. Surgery is the primary treatment for localized gastric cancer, although controversy exists about the optimal extent of lymphadenectomy in these patients. Recent studies have evaluated the role of laparoscopic surgery and endoscopic mucosal resection in selected patients. Multimodality treatment options for these patients include post-operative chemoradiation and perioperative chemotherapy. The Intergroup 0116 trial demonstrated that patients treated with surgery and post-operative chemoradiation had significantly higher overall survival compared to patients treated with surgery alone. The MAGIC trial showed that patients treated with perioperative epirubicin, cisplatin, and 5-fluorouracil had significantly higher overall survival compared to patients treated with surgery alone. Other recent trials have evaluated the roles of preoperative chemoradiation and adjuvant chemotherapy. Multidisciplinary evaluation plays a crucial role in the management of these patients. (*JNCCN* 2010;8:417–425)

The incidence and mortality of gastric cancer in the United States in 2009 was estimated to be 21,100 and 10,600, respectively.<sup>1</sup> The overall incidence of gastric cancer has decreased during the past several decades,

although the incidence of gastroesophageal junction and proximal gastric cancers has increased, especially in some groups such as white men and women.<sup>2,3</sup> Globally, gastric cancer continues to be one of the most common cancers and causes of cancer death. The estimated worldwide incidence of gastric cancer in 2002 was approximately 934,000, with more than 700,000 deaths.<sup>4</sup>

Because of the relatively poor survival of patients with anything more advanced than early gastric cancer, most patients with localized gastric cancer require multimodality therapy. Hence, multidisciplinary evaluation plays a crucial role in the management of these patients. Multidisciplinary evaluation ideally should involve surgical oncology, medical oncology, radiation oncology, gastroenterology, pathology, and radiology, along with support from nutritionists and social workers.

## Staging

Appropriate staging evaluation represents the first step in the management of patients with localized gastric cancer. In the American Joint Committee on Cancer (AJCC) and International Union Against Cancer staging system, the T classification is based on depth of tumor invasion into the gastric wall and involvement of adjacent structures, whereas the N classification is based on the number of involved lymph nodes. The number of involved nodes seems to be a more important prognostic factor than their location.<sup>5,6</sup>

Patient evaluation includes physical examination and laboratory studies, including blood counts and chemistry profiles. Esophagogastroduodenoscopy (EGD) plays a critical role in the diagnosis and assessment of patients with gastric cancer, and enables visualization of the upper gastrointestinal tract; helps determine the size, extent, and location of the gastric tumor; and allows biopsy of the tumor for pathologic diagnosis.

From the <sup>a</sup>Department of Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas; <sup>b</sup>Department of Medical Oncology, Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania; and <sup>c</sup>Department of Gastroenterology, Hepatology and Nutrition, <sup>d</sup>Department of Surgical Oncology, and <sup>e</sup>Department of Gastrointestinal Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

\*Made equal contributions to the manuscript.

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Correspondence: Prajnan Das, MD, MS, MPH, Department of Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 97, Houston, TX 77030. E-mail: PrajDas@mdanderson.org

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Moreover, EGD helps evaluate presence of *Helicobacter pylori* infection and associated conditions such as Barrett's esophagus and atrophic gastritis.

Abdominal CT scan is used to determine the locoregional extent of disease, nodal involvement, and presence of ascites or hepatic metastasis. Chest imaging with CT scan or plain radiographs is also needed to evaluate for thoracic metastasis. In women, pelvic CT or ultrasound can help evaluate for ovarian metastasis. Endoscopic ultrasonography (EUS) is being increasingly used for the clinical staging of gastric cancer patients because of its superior accuracy for T and N staging, compared with CT scans.<sup>7,8</sup> The use of fine needle aspiration under EUS guidance has increased the accuracy of nodal staging with EUS, as has been shown with other cancers.<sup>9</sup> PET and PET-CT scans are also frequently being used for gastric cancer staging. PET scan can help in nodal staging and detecting distant metastasis.<sup>10,11</sup> However, approximately 40% of gastric carcinomas may not be detected with PET scan, especially those with diffuse growth pattern or mucinous histology, for which the likelihood of detecting even the primary tumor is extremely low.<sup>12</sup> Staging laparoscopy can help identify patients with positive peritoneal cytology, who represent a high-risk subgroup, and identify the 20% to 30% of patients with presumed localized cancer who in fact have low-volume peritoneal disease.<sup>13,14</sup>

## Surgery

Surgery is the primary treatment for localized gastric cancer; however, surgery alone may not be sufficient to produce long-term survival in patients with locally advanced tumors. For patients with gastroesophageal junction or proximal gastric cancer, surgical options include transthoracic esophagogastrectomy, transhiatal esophagectomy, and transabdominal surgery with either resection of the lower esophagus and proximal stomach or total gastrectomy.<sup>15</sup> For patients with distal gastric cancer, surgical options include total and subtotal gastrectomy.<sup>15</sup> Randomized trials have shown that subtotal gastrectomy produces oncologic outcomes similar to those of total gastrectomy in patients with distal gastric cancer.<sup>16–18</sup> The key goals of surgery are to achieve a microscopically negative primary tumor resection (R0) and grossly negative margins of at least 5-cm.<sup>15</sup>

Controversy persists regarding the optimal extent of lymphadenectomy. The current AJCC stag-

ing system requires pathologic assessment of at least 15 regional nodes for gastric cancer.<sup>19</sup> Retrospective studies indicate that more extensive lymph node dissection improves outcomes over less extensive nodal dissection.<sup>20,21</sup> However, randomized trials comparing patients undergoing D1 lymphadenectomy (dissection of perigastric lymph nodes) with those undergoing D2 lymphadenectomy (dissection of perigastric lymph nodes and nodes along the celiac, left gastric, hepatic, and splenic vessels) have not shown a significant difference in survival, perhaps because patients treated with D2 lymphadenectomy have much higher rates of postoperative morbidity and mortality.<sup>22,23</sup> These randomized trials had certain limitations, such as the frequent incorporation of splenectomy and partial pancreatectomy with D2 dissection, which may have been the source of the increased morbidity and mortality associated with D2 lymphadenectomy.

In a randomized trial from Taiwan, 221 patients underwent either D3 lymphadenectomy (dissection of levels D1, D2, and D3) or D1 lymphadenectomy.<sup>24</sup> The 5-year overall survival was significantly higher in the D3 group than the D1 group (60% vs. 54%;  $P = .04$ ). A recent larger randomized trial from Japan evaluated extensive nodal dissection similar to the Taiwan study. This study compared D2 dissection with D2 plus para-aortic lymphadenectomy, and showed no differences in overall or recurrence-free survival between these groups.<sup>25</sup> Many institutions currently regard D2 dissection as a standard of care for gastric cancer provided that it can be performed with low operative morbidity and mortality.<sup>15</sup> The extent of lymph node dissection can also be assessed by Maruyama index, which provides a quantitative estimate of residual nodal disease after surgery.<sup>20</sup> An analysis of the Dutch D1-D2 randomized trial showed that the Maruyama index served as an independent predictor of overall survival and relapse risk.<sup>26</sup>

Laparoscopic gastrectomy may have certain potential benefits over open gastrectomy, such as reduced pain, shorter duration of hospitalization, and lower blood loss.<sup>27</sup> Outcomes of a retrospective multicenter study involving 1294 patients treated with laparoscopic gastrectomy in Japan were comparable to those of open surgery.<sup>28</sup> Multiple other prospective and retrospective studies of laparoscopic gastrectomy for gastric cancer indicate acceptable oncologic outcomes.<sup>27,29</sup> However, most studies on laparoscopic gastrectomy have been from Asia, and clinical experience with this technique

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remains limited in the United States. Further studies are warranted to establish the safety and efficacy of laparoscopic gastrectomy in the Western population. Ideally, large randomized trials should be performed to compare the surgical and oncologic outcomes of laparoscopic and open gastrectomy.

Patients with superficial early gastric cancer (T1a) should ideally be treated with endoscopic mucosal resection (EMR).<sup>30,31</sup> Appropriate candidates for EMR are those with adenocarcinoma confined to the mucosa, less than 2 cm in diameter, low or moderate degree of differentiation, without evidence of ulcer, and with no lymphovascular involvement.<sup>30</sup> These selected patients have minimal risk for nodal involvement and are therefore amenable to endoscopic resection. Some studies have suggested that small undifferentiated gastric cancers can also be treated with EMR, although no clear consensus exists.<sup>32,33</sup>

Surgical and institutional expertise and volume can influence outcomes in patients with gastric cancer. A study based on the Medicare database showed that patients who underwent gastrectomy at National Cancer Institute–designated cancer centers had significantly lower surgical mortality rates than those treated at control hospitals.<sup>34</sup> Similar results were found in a study of all gastrectomies performed in Texas over a 3-year period.<sup>35</sup> Multidisciplinary evaluation plays an important role in the management of most gastric cancer patients. Patients at high-volume hospitals are significantly more likely to be seen by radiation and medical oncologists preoperatively than those treated at low-volume hospitals.<sup>36</sup> Therefore, optimal care for patients with gastric cancer could be facilitated by referral to high-volume centers.

### Postoperative Chemoradiation

The Intergroup 0116 trial showed a benefit to postoperative chemoradiation for patients with gastric cancer.<sup>37</sup> In this landmark study, 556 patients with stage IB to IV, nonmetastatic gastric or gastroesophageal junction adenocarcinoma were randomized after surgery to undergo either observation or adjuvant chemoradiation therapy. Chemoradiation consisted of 1 cycle of 5-fluorouracil (5-FU) and leucovorin, followed by radiation therapy (45 Gy) with concurrent bolus 5-FU and leucovorin, followed by 2 more cycles of 5-FU and leucovorin. Patients in the chemoradiation arm had a 3-year overall survival of 50% and median survival

of 36 months, whereas those in the control arm had a 3-year overall survival of 41% and median survival of 27 months ( $P = .005$ ). Moreover, patients in the chemoradiation arm had 3-year relapse-free survival of 48%, whereas those in the control arm had 3-year relapse survival of 31% ( $P < .001$ ). This trial established postoperative chemoradiation as a standard of care for localized gastric cancer in patients with stage IB–IV nonmetastatic disease.

The Intergroup 0116 trial had several limitations. Although D2 dissection was recommended, 54% of patients were believed to have had D0 dissection (less than complete removal of perigastric lymph nodes), 36% had D1 dissection, and 10% had D2 dissection.<sup>37</sup> Because more than half of the patients had limited surgery and/or lymph node assessment, whether adjuvant chemoradiation benefits patients undergoing more extensive surgeries remains unclear, although the benefits of adjuvant therapy were seen in all lymph node dissection groups. A subsequent analysis showed that the Maruyama Index was an independent predictor of survival for the patients in this trial.<sup>38</sup> Hence, the survival outcomes of the trial may have been different if all patients had undergone appropriate nodal dissection.

Notably, patients were not considered for enrollment into this study until after recovery from surgery, and therefore prospective evaluation of the surgery was not part of the study. Moreover, as many as 35% of radiation treatment plans in the trial had major or minor protocol violations.<sup>37</sup> The trial incorporated radiotherapy quality assurance, which allowed most of the radiation protocol violations to be corrected before the start of radiotherapy.

A retrospective study from Korea evaluated the role of adjuvant chemoradiation for treating gastric cancer in patients undergoing D2 dissection—a group that was not adequately addressed in the Intergroup trial.<sup>39</sup> This study compared 544 patients treated with D2 dissection and postoperative chemoradiation and 446 patients with similar characteristics treated with D2 dissection alone in the same period. Adjuvant chemoradiation was similar to that administered in the Intergroup trial. Patients were treated with 1 cycle of 5-FU and leucovorin, followed by radiation therapy (45 Gy) with concurrent bolus 5-FU and leucovorin, followed by 2 more cycles of 5-FU and leucovorin. Overall survival was significantly higher in patients treated with surgery and chemoradiation than in those treated with surgery alone (median survival, 95 vs. 63 months;  $P$

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= .02). The relapse-free survival was also significantly higher in patients treated with surgery and chemoradiation than with surgery alone (median relapse-free survival, 76 vs. 53 months;  $P = .016$ ). This study supports the use of postoperative chemoradiation even among patients treated with D2 dissection. However, the retrospective nature of this study limits the conclusions that can be drawn.

Population-based studies have also shown benefits with postoperative chemoradiation. A study based on the Surveillance, Epidemiology, and End Results (SEER) database showed that postoperative irradiation significantly increased survival in patients with stage III and IV M0 gastric cancer compared with surgery alone.<sup>40</sup> Another study based on the SEER database showed that the use of radiotherapy significantly increased in the period after publication of the Intergroup study compared with the period before publication.<sup>41</sup> Correspondingly, overall survival significantly increased in the period after publication of the Intergroup study compared with the prior period.<sup>41</sup>

Appropriate radiation treatment planning is critical to cover the areas at risk for locoregional recurrence, while reducing the risk for acute and late toxicity. Consensus guidelines have been published on radiation treatment planning for patients with gastric cancer.<sup>42</sup> Advanced techniques for radiation therapy, such as 3-dimensional conformal radiotherapy and intensity modulated radiation therapy, may help reduce the risk for acute and late toxicity.<sup>43</sup> However, when using these advanced techniques, particular care needs to be taken to ensure that the targets are adequately covered and also to take into account other factors, such as organ motion and variations in gastric filling. Because patients with gastric cancer may experience significant acute toxicity during chemoradiation, supportive care and symptom management play critical roles in the management of these patients. Given the complexities of radiation treatment planning, the need for multidisciplinary management and supportive care, and the protocol violations seen in the Intergroup 0116 trial, patients may benefit from referral to high-volume centers specializing in radiation oncology.

## Preoperative Chemoradiation

Preoperative therapy has certain potential advantages over postoperative therapy. Preoperative therapy may shrink the tumor and potentially increase the rate of

resectability, and may also sterilize the operative field, thereby reducing the risk for tumor seeding. Another advantage is superior tissue perfusion in this setting, which can lead to better drug delivery and increased oxygenation, therefore augmenting the effects of chemotherapy and radiation.

The role of preoperative radiotherapy without concurrent chemotherapy was evaluated in a large randomized trial from China.<sup>44</sup> In this study, 370 patients with adenocarcinoma of the gastric cardia were randomized to receive either surgery alone or preoperative radiotherapy (40 Gy) followed by surgery. Patients in the preoperative radiotherapy arm had significantly higher rates of resection and overall survival. A meta-analysis of 4 randomized trials also indicated a survival benefit with preoperative radiotherapy compared with surgery alone.<sup>45</sup>

Several recent prospective trials have investigated the role of preoperative chemoradiation for gastric cancer.<sup>46-50</sup> In one trial, 41 patients were treated with 2 cycles of 5-FU, paclitaxel, and cisplatin, followed by radiotherapy with concurrent paclitaxel and infusional 5-FU, with 40 patients then undergoing surgery.<sup>47</sup> This study showed a pathologic complete response rate of 20%, R0 resection rate of 78%, and median survival beyond 36 months. In a phase II trial conducted by the Radiation Therapy Oncology Group, 49 patients were treated with 2 cycles of induction chemotherapy with 5-FU, leucovorin, and cisplatin, followed by radiation therapy with concurrent 5-FU and paclitaxel, followed by surgery.<sup>48</sup> Grade 4 toxicity occurred in 21% of patients. Among 43 evaluable patients, the pathologic complete response rate was 27% and the R0 resection rate was 77%. The results of these prospective studies of preoperative chemoradiation are promising. Preoperative chemoradiation may play a particularly important role in patients with localized unresectable or borderline resectable gastric cancer by increasing the rates of resectability in these patients. Given the high rate of completion of preoperative therapy relative to postoperative therapy, and the demonstrated benefit of postoperative therapy, randomized trials are warranted to compare preoperative and postoperative chemoradiation.

A recent randomized trial from Germany compared preoperative chemotherapy and preoperative chemoradiation.<sup>51</sup> This study randomized 126 patients with adenocarcinoma of the lower esophagus or gastric cardia to undergo either induction chemo-

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therapy with 5-FU, leucovorin, and cisplatin, or the same chemotherapy followed by radiation therapy (30 Gy) with concurrent cisplatin and etoposide, followed by surgery in both groups. The study was closed early because of slow accrual. The pathologic complete response rate was 16% in the chemoradiation group and 2% in the chemotherapy group ( $P = .03$ ). The 3-year overall survival rate was higher in the chemoradiation group (47%) compared with the chemotherapy group (28%), but this difference did not reach statistical significance ( $P = .07$ ).

Because of early closure and lower than planned accrual, this study had limited power to detect a survival difference. Additionally, the dose of radiotherapy was substantially less than in other studies, which may have further impacted results. Although results from this trial are not definitive, this study suggests a survival benefit for preoperative chemoradiation compared with preoperative chemotherapy in patients with gastroesophageal junction adenocarcinoma.

### Perioperative Chemotherapy

The premise behind perioperative chemotherapy is very similar to that for preoperative chemoradiation: downstage the primary tumor and eliminate micrometastases. The benefit of perioperative chemotherapy has been shown in other solid tumors, such as metastatic colon cancer.<sup>52</sup> Similar benefit was observed in squamous cell carcinoma of the esophagus.<sup>53</sup>

The most compelling evidence for perioperative chemotherapy is the phase III United Kingdom Medical Research Council Adjuvant Gastric (MAGIC) trial.<sup>54</sup> In this trial, 503 patients with potentially resectable gastric cancer were randomized to undergo surgery with pre- and postoperative epirubicin, cisplatin, and 5-FU or surgery alone. The perioperative chemotherapy group showed a significantly better overall survival (hazard ratio [HR], 0.75; 95% CI, 0.60–0.93;  $P = .009$ ; 5-year survival rate of 36% vs. 23%) and progression-free survival (HR, 0.66; 95% CI, 0.53–0.81;  $P < .001$ ). However, the trial was criticized for its nonstandardized surgery, potentially inaccurate preoperative staging from the absence of laparoscopy, and what some consider a relatively poor outcome in the surgery-alone group.

Because the MAGIC trial showed a survival advantage associated with perioperative chemotherapy, this approach could be adopted in certain clinical set-

tings. Cross-trial comparisons between the MAGIC trial and INT-0116 could potentially be misleading. For example, INT-0116 had 85% nodal positivity whereas MAGIC had only 72% nodal positivity. Many factors could have influenced nodal assessment in these trials, such as surgical approach. Moreover, these trials could have potentially had other differences in patient characteristics. Thus, whether perioperative or postoperative chemoradiation leads to better outcomes in patients with gastric cancer remains unknown. Current data cannot be used to recommend one approach over the other. Ongoing phase III trials will address the role of chemotherapy in the preoperative versus the postoperative setting (Table 1). In addition, the role of radiation in this disease is being further evaluated.

### Adjuvant Chemotherapy

Adjuvant chemotherapy has not consistently been shown to improve overall survival in gastric cancer; Table 2 summarizes some of the early adjuvant studies that showed survival benefit. Meta-analyses of adjuvant gastric cancer trials have also shown an inconsistent benefit of adjuvant chemotherapy, with some showing a relative risk reduction of 20% to 28%,<sup>55–59</sup> and others reporting no difference.<sup>60</sup> In the meta-analysis by Janunger et al.,<sup>57</sup> although overall odds ratios (ORs) favored adjuvant chemotherapy (OR, 0.84; 95% CI, 0.74–0.96), a survival benefit was no longer seen in Western trials (OR, 0.96; 95% CI, 0.83–1.12) when separated from Asian studies. This may be partly because of differences in the vigorousness of pathologic assessment or lymph node dissections performed in the United States and Europe compared with Asian countries.

The results from a Japanese adjuvant trial are perhaps most intriguing,<sup>61</sup> which randomized 1059 patients with stage II or III gastric cancer who underwent D2 surgical resection to either observation or 1 year of oral S-1 adjuvant therapy. S-1 is an orally active combination of tegafur (i.e., a prodrug converted by cells to FU), gimeracil (i.e., an inhibitor of dihydropyrimidine dehydrogenase that degrades FU), and oteracil (i.e., an inhibitor of FU phosphorylation in the gastrointestinal tract). The 3-year overall survival was improved in the S-1 group (80.1% vs. 70.1% in the observation group;  $P = .003$ ). The toxicity profile was very favorable. Although S-1 may impact the clinical practice in Asian population, the results of this agent in the Western population are rather disappointing, as shown in the First

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**Table 1 Ongoing Phase III Trials in Localized Gastric Cancer**

Study	Intervention	Number of Patients	End Point
Dutch Colorectal Cancer Group (CRITICS)	Arm 1: Preoperative 3x ECC followed by D1 surgery followed by postoperative cisplatin + capecitabine with 45 Gy radiation Arm 2: Preoperative 3x ECC followed by D1 surgery followed by 3x ECC	788	OS
EORTC	Arm 1: Preoperative 2x cisplatin + 5-FU + LV followed by surgery Arm 2: Surgery alone	360	OS
Kyoto University Japan (completed)	Arm 1: D2 surgery followed by S-1 Arm 2: Preoperative 2x S-1 + cisplatin followed by surgery	100	OS
Swiss Group for Clinical Cancer Research	Arm 1: Preoperative 4x DCF followed by surgery Arm 2: Surgery followed by 4x DCF	240	OS
Samsung Medical Center (ARTIST) Korea	Arm 1: Surgery followed by capecitabine and cisplatin Arm 2: Surgery followed by capecitabine + cisplatin + radiation	490	DFS
CALGB/NCCTG/ ECOG	Arm 1: Surgery followed by INT-0116 chemoradiation regimen Arm 2: Surgery followed by 1x ECF followed by 5-FU daily CI with radiotherapy followed by 2x ECF	824	OS
sanofi-aventis Asia	Arm 1: Surgery followed by capecitabine and oxaliplatin Arm 2: Surgery alone	1024	DFS
JCOG9206-2 Japan (Serosa-positive; completed)	Arm 1: D2 surgery followed by intraoperative intraperitoneal cisplatin followed by postoperative cisplatin and UFT Arm 2: D2 surgery alone	280	OS

Abbreviations: 5-FU, 5-fluorouracil; CI, continuous infusion; DCF, docetaxel, cisplatin, and 5-FU; DFS, disease-free survival, ECC, epirubicin, cisplatin, and capecitabine; ECF, epirubicin, cisplatin, and 5-FU; LV, leucovorin; OS, overall survival; UFT, oral 5-FU.

Line Advanced Gastric Cancer Study (FLAGS).<sup>62</sup> This may be because of biologic differences among patient populations regarding how the drug is metabolized.

What then can be concluded from the adjuvant data? First, adjuvant chemotherapy in curatively resected gastric cancer may provide a small overall benefit; however, evidence is currently insufficient to recommend adjuvant chemotherapy alone as part of routine treatment for gastric cancer. In addition, most of the positive adjuvant studies were reported from Asia (Table 1), and the biology of gastric cancer in the Asian population may be different from the Western population. The results of the MAGIC study suggest the benefit of using perioperative chemotherapy in resected gastric cancer. However, more than 50% of the patients did not complete postoperative chemotherapy, underscoring the greater ability of patients to tolerate therapy

before resection rather than after. One could argue that the survival benefit observed in the MAGIC trial is largely attributed to preoperative chemotherapy.

Second, any potential survival benefit of adjuvant chemotherapy in gastric cancer may be confined to patients at greatest risk for relapse (e.g., node-positive or T3–T4 tumors). Finally, further adjuvant studies with newer chemotherapeutic agents known to have clinical activity against gastric cancer (e.g., taxanes, oxaliplatin, irinotecan) are warranted. More consistent survival advantages may be seen in adjuvant trials incorporating these more modern drugs or targeted agents.

One question that remains unanswered is whether any difference in outcomes would be seen in patients treated with postoperative chemotherapy compared with postoperative chemoradiation therapy, after preoperative chemotherapy and surgery. A recently opened

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**Table 2** Adjuvant Gastric Cancer Phase III Trials Reporting a Survival Advantage

Regimen	5-Year Overall Survival	P Value	Study
MMC	68%	.05	Imanaga and Nakazato <sup>64</sup>
Surgery alone	53%		
MMC	41%	< .025	Grau et al. <sup>65</sup>
Surgery alone	26%		
MMC/5-FU/Ara-C/tegafur	36%	.05	Ochiai et al. <sup>66</sup>
MMC/5-FU/Ara-C/tegafur + BCG	18%		
Surgery alone	31%		
Continuous hyperthermic peritoneal perfusion MMC	64.2%	.02	Hamazoe et al. <sup>67</sup>
Surgery alone	52.5%		
MMC	64.3%; ns	.05	Nakajima et al. <sup>68</sup>
MMC/5-FU/Ara-C	66.9%		
Surgery alone	56%		
MMC/5-FU/protein-bound polysaccharide	56.9%	.03	Maehara et al. <sup>69</sup>
Surgery alone	45.7%		
MMC	76%		Estape et al. <sup>70</sup>
Surgery	30%		
ELF	25%	< .01	Neri et al. <sup>71</sup>
Surgery alone	13% (36-mo median follow-up)		
MMC	44%	.04	Grau et al. <sup>65</sup>
MMC/tegafur	67%		
S-1	80.1% (3-yr OS)	.003	Sakuramoto et al. <sup>72</sup>
Surgery alone	70.1%		

Abbreviations: 5-FU, 5-fluorouracil; Ara-C, cytosine arabinoside; BCG, bacillus Calmette-Guerin; ELF, epidoxorubicin, leucovorin, and 5-fluorouracil; MMC, mitomycin; ns, not significant; OS, overall survival.

phase III trial sponsored by the Netherlands Cancer Institute, the CRITICS Study, is investigating whether postoperative chemoradiation (45 Gy) with concurrent cisplatin and capecitabine leads to improved overall survival compared with postoperative chemotherapy (epirubicin, cisplatin, capecitabine [ECC]) in patients treated with preoperative ECC chemotherapy and adequate (D1+) surgery (Table 1). This study is not expected to reach completion until 2014 ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)). Another phase III trial, the ARTIST trial from Korea, is comparing postoperative chemoradiation (45 Gy) and concurrent capecitabine and cisplatin, with postoperative chemotherapy with capecitabine and cisplatin, after D2 dissection.<sup>63</sup>

## Conclusions

Over the past several decades, significant progress has been made in prolonging survival in patients with localized gastric cancer, including improved surgical techniques and incorporation of multimodality approaches. The role of radiotherapy in gastric

cancer will be further assessed in the CRITICS trial. Further improvements in screening methods for early detection, the incorporation of clinically relevant biomarkers, and the use of new chemotherapy regimens and targeted agents may ultimately improve clinical outcomes in gastric cancer.

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