

# Gastric Cancer

Gauri R. Varadhachary, MD, and Jaffer A. Ajani, MD

Dr. Varadhachary is Assistant Professor in the Department of Gastrointestinal Medical Oncology at the University of Texas M. D. Anderson Cancer Center in Houston, where Dr. Ajani is Professor of Gastrointestinal Medical Oncology.

## Address correspondence to:

Gauri Varadhachary, MD, Department of Gastrointestinal Medical Oncology, M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Box 426, Houston, TX 77030; E-mail: gvaradha@mdanderson.org.

**Abstract:** Gastric cancer is a very challenging malignancy given that it presents late, has complex pathogenetic mechanisms with multiple carcinogenic processes implicated, and is only moderately sensitive to chemotherapy and radiation. Accurate staging for gastric cancer is possible with the availability of sophisticated imaging studies, endoscopic ultrasound, and laparoscopy. Postoperative chemoradiation is the standard of care in high-risk patients with resected primary disease. Recent encouraging results with the preoperative approach need to be studied further and prospectively compared to postoperative chemoradiation. Chemotherapy has yielded better results than best supportive care for metastatic gastric cancer and also improves quality of life, although all of these studies included a small number of patients. The last decade has seen newer agents used alone or in combination, with promising results. We anticipate that improved trial design, availability of molecular techniques, and continued search for better cytotoxic and targeted agents will help develop better treatments for patients with advanced gastric cancer.

**G**astric cancer presents mostly in an advanced stage and is lethal unless diagnosed early. High incidence of gastric cancer is seen in Japan, South America, and Eastern European countries, and the incidence is low in the United States and Southeast Asia. According to Surveillance, Epidemiology, and End Results (SEER) data, an estimated 22,700 new cases of gastric cancer were diagnosed in the United States in 2004, and an estimated 11,700 patients died of gastric cancer.<sup>1</sup> The incidence of gastric cancer involving body and antrum is decreasing but that of the fundus and gastroesophageal junction is increasing with increase in body mass index.<sup>2</sup> The treatment options for advanced gastric cancer are mainly palliative given that the median survival is less than 9 months. Most patients present with advanced disease and more than 50% of the patients who undergo resection with a curative potential relapse either locally or with distant metastases. Chemotherapy has shown to be better than best supportive care for metastatic gastric cancer and also improves quality of life. In the United States, 5-fluorouracil (5-FU) and cisplatin is the preferred combination reference regimen (although 5-FU alone is also accepted). In Japan, 5-FU alone is accepted for clinical trials (after the Japan Clinical Oncology Group [JCOG] study 9205). This article discusses recent advances in understanding the molecular basis of gastric cancer, novel agents introduced over the last decade (including taxanes, camptothecins, third-generation platinum agents, and novel oral fluoropyrimidines), and issues pertaining to surgery, postoperative adjuvant therapy as well as preoperative therapy.

## Keywords

Gastric cancer, staging, chemotherapy

## Epidemiology and Molecular Events in Gastric Cancer

Several environmental and genetic risk factors are associated with risk for gastric cancer. Studies have shown that diets rich in salted, pickled, or smoked foods have an increased risk and fresh fruits, vegetables, and cereal fiber show a decreased risk.<sup>3,4</sup> There is also some epidemiologic data available on consumption of green tea and an inverse association with the risk of distal gastric cancer.<sup>5</sup> One study published in 1990 discusses the use of electric refrigerators as a link to decreasing incidence of gastric cancer in developing countries.<sup>6,7</sup> Correa was the first to describe the model of carcinogenesis in gastric cancer suggesting that it goes through the sequential stages of chronic gastritis, atrophy, intestinal metaplasia, and dysplasia.<sup>8</sup> This model has been challenged and it is not clear if these molecular events occur in a stepwise manner at each stage.

*Helicobacter pylori* has been recognized as a definite cause of gastric adenocarcinoma based on epidemiologic observational studies and pathogenesis data. Bacteria-specific factors include neutrophil activation, hypochlorhydria as well as presence of virulent strains including cytotoxin-associated gene (cag) A+. Cag A+ *H. pylori* has been associated with more p53 mutations. Host factors hypothesized in leading to gastric cancer include genetic polymorphisms in *IL1-B* and *NAT1*.<sup>9-11</sup> Polymorphisms in the *IL-1 B* gene allow increased production of interleukin -1, which results in hypochlorhydria and possibly makes the gastric mucosa more susceptible to inflammatory changes secondary to *H. pylori* infection, leading to cancer.

Other molecular events have been recently evaluated in gastric cancer. In one study, microsatellite instability (MSI) was noted to be present in 13–44% of gastric cancer with 10–16% of cancers showing MSI-H (high) status.<sup>12</sup> One frequent reason for MSI-H status is hypermethylation of CpG islands in the promoter region of the *hMLH1* gene. Inactivation of tumor suppressor genes including p53, p16, fragile histidine triad (FHIT) and deleted in colon cancer (DCC) have also been recently studied and have a role in gastric carcinogenesis. Oncogenes including c-erbB2 and c-met proto-oncogene, which encodes a tyrosine kinase receptor for hepatocyte growth factor, are overexpressed in gastric cancer.

About 10% of gastric cancers show familial clustering. Guildford et al<sup>13</sup> first described the presence of E-cadherin germline mutation as a cause of early onset, poorly differentiated high-grade, and diffuse gastric cancer in a New Zealand family. They sequenced the E-cadherin gene (E-cadherin protein mediates intracellular adhesion), which revealed a G→T nucleotide substitution in the donor splice consensus sequence of exon 7, leading to a truncated gene product. This pathogenic role of E-cad-

herin germline mutation as a cause of hereditary gastric cancer was confirmed with identification of inactivating mutations in other gastric cancer families. The risk of cancer is high enough to warrant genetic counseling for consideration of prophylactic total gastrectomy, which may be the treatment of choice in mutation carriers.

## Staging and Prognosis of Gastric Cancer

The American Joint Committee on Cancer staging system for gastric cancer is described in Table 1. In gastric cancer, the number of nodal metastasis is more important than the region of nodal involvement for predicting outcome. Patients with more than 15 positive lymph nodes have a survival comparable to those with metastatic disease and staging is considered suboptimal if less than 10 lymph nodes are retrieved during surgery.<sup>14</sup> Accurate pretreatment staging is now possible with newer imaging and surgical techniques including high-resolution computerized tomography, positron emission tomography (PET), endoscopic ultrasound (EUS), and better laparoscopic techniques (with intraoperative ultrasound). Early gastric cancer is diagnosed mainly in patients who are getting endoscopy for other reasons, or for surveillance as high-risk candidates.

Various prognostic factors have been studied in gastric cancer. Green et al<sup>15</sup> studied 150 patients retrospectively and found that on univariate analysis, significant prognostic factors were TNM stage, chemotherapy, surgical attempt, performance status, histology, and tumor site ( $P < .001$ ). On multivariate analysis, independent factors were TNM stage, histology, tumor site, surgical attempt, and chemotherapy ( $P < .01$ ). Tas et al found chemoresponsiveness, high Ca19-9 level (in nonmetastatic disease), high serum lactate dehydrogenase, high carcinoembryonic antigen level, lower albumin levels, older age, and male gender all predicted poorer survival.

## Surgical Issues

Debate regarding the extent of lymphadenectomy in gastric cancer surgery continues. D1 lymphadenectomy involves dissection of only the perigastric lymph nodes. D2 lymphadenectomy includes removal of nodes along the hepatic, left gastric, celiac, and splenic arteries as well as those in the splenic hilum and D3 dissection includes removal of all D1/D2 nodes plus those within the porta hepatis and periaortic nodes. In a study conducted by the Dutch Gastric Cancer Group by Bonenkamp and colleagues,<sup>16</sup> 711 patients were involved in a randomized trial in 80 Dutch hospitals in which D1 lymph node dissection was compared with D2 lymph node dissection for gastric cancer to study morbidity, postoperative mortality, long-term survival, and

**Table 1.** American Joint Committee on Cancer Staging for Gastric Cancer

<b>Tumor (T) Stage</b>	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1s	Carcinoma in situ: intra-epithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria or subserosa
T2a	Tumor invades muscularis propria
T2b	Tumor invades subserosa
T3	Tumor penetrates serosa (visceral peritoneum) without invasion of adjacent structures
T4	Tumor invades adjacent structures
<b>Nodal (N) Stage</b>	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–6 regional lymph nodes
N2	Metastasis in 7–15 regional lymph nodes
N3	Metastasis in more than 15 regional lymph nodes
<b>Metastasis (M) Stage</b>	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
<b>Stage Grouping</b>	
Stage 0	Tis N0 M0
Stage IA	T1 N0 M0
Stage IB	T1 N1 M0, T2a/b N0 M0
Stage II	T1 N2 M0 T2a/b N1 M0 T3 N0 M0
Stage IIIA	T2a/b N2 M0 T3 N1 M0 T4 N0 M0
Stage IIIB	T3 N2 M0
Stage IV	T1-3 N3 M0 T4 N1-3 M0 Any T Any N M1

cumulative risk of relapse after surgery. Patients in the D2 group had a significantly higher rate of complications and more postoperative deaths. Five-year survival rates were similar in the 2 groups and the authors concluded that there is currently no role for D2 lymphadenectomy in gastric cancer surgery. D2 lymphadenectomy is not practiced in the western countries.

The JCOG recently reported their morbidity and mortality data from study 9501, a prospective randomized controlled trial comparing D2 with D2 + extended para-aortic lymphadenectomy.<sup>17</sup> A total of 523 patients were randomized over approximately 6 years. The mortality rate was similar in both groups and reported at 0.80% (1 patient in each group died of operative complications, and 1 from each group died of rapid progressive cancer after surgery). Postoperative complications were reported in 24.5% of all patients. Morbidity in the D2 arm was 20.9% and in the D2 plus para-aortic lymphadenectomy arm was 28.1% with no difference in the incidence of major complications. Survival results will be available in the next few years.

### Preoperative Approaches

Preoperative chemoradiation is practiced in many other gastrointestinal primaries. This approach is standard for T3 or N(+) rectal cancer and has shown to decrease local recurrence rate. Approximately half of the patients undergoing gastric cancer surgery manage to get an R0 resection and more than half of them (60%) still succumb to the disease because of locoregional or distant spread. Radiation, chemotherapy, and chemoradiation have been tried preoperatively in gastric cancer. The MAGIC trial, presented last year, evaluated 503 patients in a randomized study of perioperative chemotherapy versus surgery alone for operable gastric and lower esophageal cancers. One arm received 3 cycles of chemotherapy with epirubicin, cisplatin, and infused 5-FU (ECF) preoperatively and 3 cycles postoperatively; the other arm received surgery alone. The chemotherapy arm demonstrated an increased curative resection rate (with histopathologic downstaging), and there are some early data suggesting survival benefit, although mature results are awaited.<sup>18,19</sup>

Ajani et al<sup>20</sup> recently published a multi-institutional study of preoperative chemoradiotherapy in patients with resectable gastric carcinoma. Stringent staging criteria were used including imaging, laparoscopy, and endoscopic ultrasonography (EUS). Thirty-four patients were registered and 28 underwent surgery. Patients were treated with 2 cycles of 5-FU, leucovorin, and cisplatin (28-day cycles) followed by 45 Gy of radiation with concurrent 5-FU. The R0 resection rate was 70%, pathologic complete response rate was 30%, and pathologic partial

response (<10% residual carcinoma in the primary) occurred in 24% of the patients. The median survival time for 33 patients was 33.7 months. Patients achieving a pathologic complete response or pathologic partial response had a significantly longer median survival time of about 64 months compared to those achieving less than pathPR, which was 12.6 months ( $P=.03$ ). It will be useful to compare preoperative chemoradiation to postoperative chemoradiation in a prospective trial.

### Postoperative Adjuvant Therapy

The fact that most patients relapse after a curative resection indicates the need for postoperative adjuvant therapy. The pattern of relapse is locoregional or distant, which includes mainly liver and peritoneum. Adjuvant chemotherapy, radiotherapy, and chemoradiotherapy have been studied in gastric cancer. Adjuvant chemotherapy alone has shown disappointing results and is not considered standard. Coombe et al<sup>21</sup> studied the role of 5-FU, doxorubicin, and mitomycin (FAM) as adjuvant therapy versus no adjuvant treatment. Two hundred eighty-one patients were included in the analysis. There was no significant difference in disease-free or overall survival between the 2 groups ( $P=.21$ ). Retrospective subgroup analysis suggested a possible benefit in patients with T3-T4 cancer ( $P=.04$ ) and the authors concluded that further evaluation is needed regarding the role of adjuvant chemotherapy for T3-T4 staged patients. Lise et al<sup>22</sup> from the European Organization for the Research and Treatment of Cancer group presented their data on FAM adjuvant chemotherapy versus surgery alone in 314 patients and concluded that adjuvant FAM chemotherapy delayed time to recurrence but did not improve overall survival. A Southwest Oncology Group study published by MacDonald and colleagues<sup>23</sup> randomized 193 patients in a phase III trial comparing 6 cycles of postoperative FAM chemotherapy with observation only. No difference in disease-free survival and overall survival found between FAM adjuvant therapy and surgery. Retrospective review of pathology showed that the quality of surgical resection affected survival (irrespective of FAM use) and it is possible that poor surgical quality control may have contributed in a negative study.

The role of radiation alone, given as intraoperative radiotherapy (IORT) or external beam adjuvant therapy has shown to reduce locoregional relapse but does not improve survival. Avizonis et al<sup>24</sup> presented a phase II study (RTOG 85-04) with 27 patients who had undergone maximal resection and were treated with IORT and adjuvant external beam radiation (23 of 27 patients, 24–50 Gy). Median survival was 19.3 months. In a prospective, randomized trial of preoperative and intraoperative radio-

therapy versus surgery alone in resectable gastric cancer led by Skoropad et al<sup>25</sup> showed no significant difference in overall survival in the 2 groups.

The only phase III trial that has shown an improvement in overall survival is Intergroup 0116 which has made chemoradiation the standard of care in the United States for patients with resected, high-risk gastric cancer or gastroesophageal junction carcinoma.<sup>26</sup> In this study, 556 patients with resected adenocarcinoma of the stomach or gastroesophageal junction were randomly assigned to surgery plus postoperative chemoradiotherapy or surgery alone. The adjuvant treatment consisted of 5-FU 425 mg/m<sup>2</sup>/day and leucovorin 20 mg/m<sup>2</sup>/day for 5 days, followed by 4,500 cGy of radiation at 180 cGy per day, given 5 days per week for 5 weeks, with modified doses of 5-FU and leucovorin on the first 4 and the last 3 days of radiation. One month after the completion of radiotherapy, 2 5-day cycles of 5-FU plus leucovorin were given 1 month apart. The median overall survival in the surgery-only group was 27 months and 36 months in the chemoradiotherapy group. Disease-free survival at 3 years was 31% versus 48%, respectively ( $P < .001$ ). Three-year overall survival was 41% for the surgery arm and 50% for the chemoradiotherapy arm ( $P = .005$ ).

### Chemotherapy for Metastatic Gastric Cancer

Chemotherapy improves survival and quality of life in selected patients with advanced gastric cancer compared to best supportive care. In the 1980s and early 1990s, 5-FU, doxorubicin, mitomycin-C, methotrexate, and etoposide were the drugs used in various combinations as chemotherapeutic regimens for metastatic gastric cancer. MacDonald and colleagues<sup>27</sup> presented data on 62 patients

treated with FAM, and 42% achieved an objective partial response. Later, a randomized phase III trial compared FAMTX (5-FU, doxorubicin, and methotrexate) to FAM and showed a response rate of 41% for FAMTX versus 9% for FAM; survival was 42 weeks versus 29 weeks, respectively.<sup>28</sup> Van Cutsem et al<sup>29</sup> studied etoposide, leucovorin, and 5-FU (ELF) in advanced gastric cancer and reported a 27% PR; 33% of the patients showed an improvement in their performance status. The mean survival was 8 months and the authors concluded that ELF was an active and safe regimen for the treatment of gastric cancer. More recently, there is renewed interest with the availability of newer agents including taxanes, camptothecins, oxaliplatin, and S1. The role of targeted agents alone and in combination with cytotoxic therapy is currently being defined.

Taxanes have been studied in advanced gastric cancer for over 5 years in first-, second-, and third-line setting. Paclitaxel and docetaxel have been combined with cisplatin and 5-FU; rationale being their nonoverlapping side effects profiles and lack of cross-resistance. Docetaxel has been studied as a single agent in at least 8 phase II trials and the mean response rate reported is 19%. Irinotecan has been studied alone as well as in combination with taxanes and cisplatin. S1 is a new oral fluorinated pyrimidine derivative, in which the oral 5-FU prodrug, tegafur, is combined with 2 5-FU-modulating substances, 5-chloro-2, 4-dihydropyridine (gimeracil), and potassium oxonate (oteracil), at a molar ratio of 1:0.4:1. Early small-study phase II data on these agents are discussed in Table 2. It is noteworthy that an increase in response rate with the best of combination therapies has so far not translated to increased survival.

There are 4 large phase III trials ongoing (1 is completed with interim data available) in advanced gastric and

**Table 2.** Selected Phase II Chemotherapeutic Trials with Newer Agents in Advanced Gastric Cancer

Regimen	Patients, N	Response Rate, %	Overall Survival, mo	Reference
Docetaxel + cisplatin (first line)	45	56	9	Roth <sup>30</sup>
Docetaxel + cisplatin + PI 5-FU (first line)	41	51	9.3	Roth <sup>31</sup>
Irinotecan + cisplatin (first line)	36	58	9	Ajani <sup>32</sup>
Irinotecan + cisplatin (one prior therapy)	29	31	5	Ajani <sup>33</sup>
Irinotecan + docetaxel	46	26	7.3	Jatoi <sup>34</sup>
5-FU + oxaliplatin	37	43	9.6	Al-Batran <sup>35</sup>
S1 + cisplatin	19	74	12.7	Koizumi <sup>36</sup>

5-FU = 5-fluorouracil; PI = protracted infusion.

**Table 3.** Ongoing Phase III Chemotherapeutic Trials for Advanced Gastric Cancer

Docetaxel + Cisplatin + 5-FU vs 5-FU + Cisplatin
ECF (epirubicin + cisplatin + 5-FU) vs EOF (epirubicin + oxaliplatin + 5-FU) vs ECX (epirubicin + cisplatin + capecitabine) vs EOX (epirubicin + oxaliplatin + capecitabine)
Irinotecan + 5-FU + leucovorin vs 5-FU + cisplatin
5-FU vs 5-FU + cisplatin vs uracil + tegafur + mitomycin (completed)

PI = protracted infusion; 5-FU = 5-fluorouracil.

gastroesophageal junction cancer as depicted in Table 3. TAX 325 trial is an ongoing international trial comparing docetaxel, cisplatin, and 5-FU to the reference regimen of cisplatin and 5-FU in patients with untreated inoperable locally advanced or metastatic gastric carcinoma.<sup>37</sup> In the first stage of this study, docetaxel and cisplatin combination was compared to docetaxel, cisplatin, and 5-FU (DCF), with the objective being to identify which combination is more effective, based on safety and efficacy data. In the second stage of this 2-stage design, the better of those 2 treatment arms was to be compared to cisplatin/5-FU in the phase III portion of the trial. One hundred fifty-eight patients were accrued to the phase II randomized portion of the trial. Results showed that docetaxel/cisplatin showed a response rate of 28% and docetaxel/cisplatin/5-FU response rate was 43%. Based on these results, the independent data monitoring committee (IDMC) selected DCF as the experimental arm for the phase III stage. Target accrual goal is 462 patients. Results for 232 patients, presented in 2003, show that the time to progression (TTP) is statistically superior for docetaxel/cisplatin/5-FU (5.2 months;  $P=.0008$ ) compared with cisplatin/5-FU (3.7 months). The response rate was 39% for docetaxel/cisplatin/5-FU and 23% for cisplatin/5-FU, which was also statistically superior ( $P=.012$ ). DCF had more hematologic toxicities and nonhematologic toxicities (mainly diarrhea) but the first 30-day mortality was similar in both arms.

Another large phase III study with mature data expected soon is the V306 trial, which compares irinotecan, 5-FU, and leucovorin to 5-FU and cisplatin. Pozzo et al<sup>38</sup> presented the data from the randomized phase II portion of this study in which irinotecan/cisplatin was compared with irinotecan, infusional 5-FU, and folinic acid with about 40 patients in each arm. The overall response rates were 28% and 42%, respectively. Besides an increase in the response rate, irinotecan with 5-FU was less toxic; this

regimen was chosen as the experimental arm for the phase III portion of the V306 study.

The third phase III trial is a randomized 4-arm trial evaluating the efficacy of oxaliplatin, epirubicin, and capecitabine.<sup>39</sup> Six hundred patients will be randomized to one of these 4 arms: ECF (epirubicin/cisplatin/fluorouracil), EOF (epirubicin/oxaliplatin/fluorouracil), ECX (epirubicin/cisplatin/capecitabine), and EOX (epirubicin/oxaliplatin/capecitabine). Preliminary results for 176 patients were presented in 2003, showing a combined PR and CR rate of 31% for ECF, 33% for EOF, 35% for ECX, and 52% for EOX. The target accrual for this trial has now been increased from 600 to 1,000 patients.

The recently completed prospective randomized phase III trial (JCOG 9205) by Ohtsu et al<sup>40</sup> yielded negative results for the experimental arm. The purpose of the study was to compare 5-FU alone, 5-FU plus cisplatin, and uracil and tegafur plus mitomycin (UFTM) in patients with advanced gastric cancer. Two hundred eighty patients were accrued between these 3 arms. At the interim analysis, the UFTM arm showed a significantly inferior survival with higher hematologic toxicity than did control arm 5-FU alone, and the registration to UFTM was terminated. The overall response rates of the 5-FU alone, 5-FU plus cisplatin, and UFTM arms were 11%, 34%, and 9%, respectively. Although 5-FU plus cisplatin showed a higher response rate and longer progression-free survival than did 5-FU alone, there was no difference in overall survival. The median survival was 7.1 months with 5-FU, 7.3 months with 5-FU plus cisplatin, and 6.0 months with UFTM, respectively. The authors concluded that 5-FU alone would remain a reference arm in future Japanese trials for advanced gastric cancer.

## Conclusions

Overall survival is the gold-standard primary endpoint for phase III trials, whether they involve chemotherapy for metastatic disease or chemoradiation in a perioperative setting. There is no consensus that tumor response rate is an accurate surrogate that can translate into a survival benefit. The role of progression-free survival is not clear and would require adequately powered studies (as in colon cancer adjuvant trials). Accurate staging of gastric cancer as well as quality control in surgical methods allow proper analysis of the results and should be reinforced for all large phase III trials for operable gastric cancer. Better understanding of molecular profiles and pathogenesis of gastric cancer will allow us to develop better therapies. Trials with targeted agents including epidermal growth factor receptor antibodies, tyrosine kinase inhibitors, antivascular endothelial growth factor antibodies, and COX-2 inhibitors are currently in development.

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