Management of gastric cancer
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Purpose of review
Gastric cancer is an uncommon cancer in the United States but is a very common cancer globally and is endemic in East Asia. It is a virulent cancer that presents with metastatic disease in about one half of United States patients.

Recent findings
In this review article, we discuss palliative chemotherapy options as well as validated preoperative, perioperative and postoperative strategies for locally advanced disease, which include chemotherapy and/or chemoradiation.

Summary
In the metastatic setting, there has been incremental improvement in cytotoxic chemotherapy combinations in the past 2 decades. Two targeted agents – trastuzumab and ramucirumab – are now approved. In the locally advanced setting, perioperative chemotherapy or postoperative chemotherapy or chemoradiation improves outcomes relative to surgery alone.

Keywords
adjuvant, chemoradiation, chemotherapy, gastric cancer, preoperative

INTRODUCTION
Gastric cancer, an uncommon but highly virulent malignancy in the United States, will be diagnosed in 22,220 patients in 2014, with 10,990 deaths [1]. In comparison to its relative rarity in the United States, gastric cancer is endemic in parts of East Asia, which account for more than half of the approximately 1 million cases that develop per year globally [2].

In the United States, the incidence of gastric cancer has decreased significantly in the past 50 years, but the location of the primary tumor has also changed. Distal gastric cancer, which previously predominated, has become uncommon, whereas the incidence of tumors of the gastric cardia and gastroesophageal junction have increased 4–10% per year among United States men since 1976 [3,4].

Changing epidemiologic factors account for the increasing incidence of proximal tumors. Chronic infection with Helicobacter pylori has been implicated in the development of gastric cancer on the basis of epidemiological evidence [5]. A decline in H. pylori infection in the United States has led to an overall decrease in the number of gastric cancer cases. On the other hand, proximal and gastroesophageal junction tumors are now more common because of an increased incidence of gastroesophageal reflux disease [6] and obesity [7].

In the metastatic setting, chemotherapy is the mainstay of treatment. Although there have been incremental improvements in terms of efficacy and tolerability, outcomes remain poor.

For locally advanced gastric cancer, surgery remains the most important component of curative therapy. Numerous studies have evaluated preoperative and postoperative strategies for locally advanced disease, including chemotherapy or chemoradiation. As a whole, these studies show that some treatment in addition to surgery clearly improves outcomes.

These studies have variously enrolled purely gastric cancers (especially distal tumors, which is the predominant location in Asia) or have also included tumors that involve the gastroesophageal junction or even lower esophagus. Consistent with guidelines from the National Comprehensive Cancer Network, our practice pattern is to apply the conclusions of these studies based on the Siewert classification of...
In the metastatic setting, standard treatment for gastric cancer consists of a fluoropyrimidine/platinum doublet.

In the United Kingdom, the addition of epirubicin to this doublet is standard, but there are no randomized data to support this. The only validated three-drug regimen, which adds docetaxel to the doublet, is toxic. Several modifications have been developed but remain suitable only for fit and motivated patients.

Two targeted therapies – trastuzumab for Her2-positive gastric cancer and ramucirumab as second-line therapy – are now available.

For resectable gastric cancers, perioperative chemotherapy with ECF or 5-FU/cisplatin improves survival vs. surgery alone.

For patients who undergo upfront surgery, adjuvant chemotherapy (with a fluoropyrimidine alone or with a fluoropyrimidine/platinum doublet) or chemoradiation with a fluoropyrimidine also improves outcomes.

PALLIATIVE CHEMOTHERAPY

Approximately 50% of patients diagnosed with gastric cancer present with overt metastatic disease and chemotherapy is the mainstay of palliation in this setting. With the high likelihood that patients with initial locoregional disease will eventually develop metastatic disease as well as the incorporation of chemotherapy into validated perioperative strategies, systemic chemotherapy will ultimately be used in the large majority of patients.

Given the modest activity of single agents, combination chemotherapy of two and even three drugs has been extensively studied and is the standard-of-care for medically fit patients. Despite incremental advances, the duration of response to both modern single agents and combination regimens is only generally 4–6 months, with median overall survival (OS) of 10–12 months.

The combination of infusional 5-FU/cisplatin has been studied extensively since the 1980s, and the doublet of a fluoropyrimidine with a platinum compound remains a reference regimen in many contemporary trials. More contemporary trials have evaluated substitutions of both of these drugs with either an oral 5-FU prodrug (capecitabine [10] or S-1 [11]) and/or the newer platinum compound oxaliplatin [10,12]. Regimens such as S-1/cisplatin [11], capecitabine/cisplatin [13], infusional 5-FU/oxaliplatin [12] and capecitabine/oxaliplatin (along with the anthracycline epirubicin) [10] appear to have at least comparable efficacy compared to 5-FU/cisplatin and are also mostly associated with decreased toxicity and increased ease of administration. In fact, an individual patient data meta-analysis of two randomized trials that compared capecitabine-based with infusional 5-FU-based regimens – the capecitabine/cisplatin vs. 5-FU/cisplatin trial [13] and the Randomized epirubicin, cisplatin, 5-fluorouracil (ECF) for Advanced and Locally Advanced Esophagogastric Cancer 2 study [10] discussed in more detail below – suggested that capecitabine-based treatments are associated with superior response rates (RRs) and OS than infusional 5-FU regimens [14].

THREE-DRUG REGIMENS

In the United Kingdom, the addition of the anthracycline epirubicin to cisplatin/5-FU (ECF regimen) is standard. The Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 study compared the ECF regimen with the ECX (which involves the substitution of S-1 with capecitabine), the EOF (substitution of oxaliplatin for cisplatin) and the EOX regimen (a double substitution of both capecitabine and oxaliplatin) in patients with locally advanced or metastatic esophagogastric adenocarcinomas or squamous cell carcinoma [10]. All the combinations had similar RRs (40–48%) and toxicities, and the EOX regimen was associated with improved median OS compared to the ECF regimen (11.2 vs. 9.9 months, \( P = 0.02 \)), leading the authors to propose that the EOX regimen could replace ECF in future trials.

Despite the standard use of ECF or one of its derivatives in the United Kingdom, the clear superiority of this triplet over a fluoropyrimidine/platinum doublet has never been demonstrated in a randomized fashion. One piece of evidence frequently cited to support the incorporation of an anthracycline comes from Cochrane meta-analysis by Wagner et al. [15], which analyzed three individually negative trials. Combining all three trials revealed a survival benefit for the addition of epirubicin [hazard ratio...
In comparison to the unclear benefit of adding an anthracycline, there are randomized data to support the addition of a taxane. The phase III V325 randomized trial in junction and gastric adenocarcinomas compared the docetaxel/cisplatin/infusional 5-FU regimen (DCF) with infusional 5-FU/cisplatin [17]. The addition of docetaxel improved RRs (37 vs. 25%, \( P = 0.01 \)) and time-to-progression (5.6 vs. 3.7 months, \( P < 0.001 \)), but OS was only slightly improved (median OS 9.2 vs. 8.6 months, 2-year OS 18 vs. 9%, \( P = 0.02 \)). In addition, the three-drug regimen was associated with significantly more toxicity, including a grade 3/4 neutropenia rate of 82% (vs. 57%) and febrile neutropenia in 29% of patients (vs. 12%). Fifty percent of patients came off treatment either because of severe adverse events or consent withdrawal. Despite these significant toxicities, the authors reported a slower decrement in quality-of-life measurements in the DCF arm [18]. On the basis of this study, docetaxel was approved by the United States Food and Drug Administration in 2006 for use with 5-FU/cisplatin in this context.

As the toxicities seen with the parent DCF regimen are significant and may outweigh its small survival advantage over 5-FU/cisplatin, it has not been widely adopted. It is also unclear whether similar survival benefits would be accrued by the sequential use of first-line 5-FU/cisplatin followed by subsequent docetaxel at progression.

Several investigators have attempted to modify the regimen to increase tolerability. For example, our group performed a randomized phase II trial of parent DCF (with prophylactic growth factor support) vs. a modified DCF (mDCF) regimen (consisting of reduced doses of docetaxel and cisplatin administered with bolus and 2-day infusional 5-FU and leucovorin) [19]. mDCF was associated with decreased toxicity compared to parent DCF (neutropenic fever rate 6 vs. 17%, grade 3/4 nausea/vomiting rate 3 vs. 20%), although activity appeared comparable or even superior in the mDCF arm. Nevertheless, 30% of the patients receiving mDCF (who had a median age of 56 years) required hospitalization for treatment-related toxicities, reinforcing the notion that this remains a relatively difficult regimen to administer. Our practice is to reserve triplet chemotherapy with a taxane for younger patients without medical comorbidities, who have access to frequent toxicity assessments when on treatment.

**TARGETED THERAPIES**

There are now two targeted therapies that are approved by the United States Food and Drug Administration for advanced esophagogastric cancer. The first drug approved in 2010 was trastuzumab, a monoclonal antibody against Her2, which is overexpressed in approximately 20% of gastric cancers. In the pivotal Trastuzumab for Gastric Cancer (ToGA) trial, the addition of trastuzumab to fluoropyrimidine/cisplatin for patients with gastroesophageal junction and gastric adenocarcinomas, whose tumors were Her2 positive by immunohistochemistry (IHC) (3+) or fluorescent in-situ hybridization (Her2/CEP17 ratio \( \geq 2 \)), improved outcomes [20]. RRs (47 vs. 35%, \( P = 0.0017 \)), median progression-free survival (6.7 vs. 5.5 months, \( P = 0.0002 \)) and OS (13.8 vs. 11.1 months, \( P = 0.0046 \)) were all improved with the addition of trastuzumab. The greatest benefit seen for the addition of trastuzumab was in high Her2 overexpressers with IHC 3+ or fluorescent in-situ hybridization-positive/IHC 2+ patients.

Ramucirumab, an antibody against vascular endothelial growth factor receptor 2, was approved in April 2014 on the basis of the phase III REGARD study that evaluated second-line ramucirumab vs. placebo [21**]. This study revealed an improvement in median OS by 1.4 months for the ramucirumab arm. Treatment was well tolerated and the only significant grade 3 toxicity was hypertension in 8% of patients.

In addition, a second phase III study of second-line paclitaxel with or without ramucirumab (the RAINBOW study [22*]) has been presented in abstract form. Median OS was improved by 2.2 months for ramucirumab/paclitaxel vs. paclitaxel alone. When combined with paclitaxel, there was a higher incidence of grade 3/4 neutropenia (41 vs. 19%) but not a higher rate of neutropenic fever (3.1 vs. 2.4%).

**PREOPERATIVE CHEMOTHERAPY**

A strategy of perioperative chemotherapy is the predominant approach in Europe and increasingly
in the United States based primarily on the phase III Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial performed in the United Kingdom [23]. This trial randomized 503 patients with gastric cancer to three cycles each of preoperative and postoperative ECF and surgery or surgery alone. Perioperative chemotherapy resulted in significant improvement in 5-year OS (36 vs. 23%, \( P = 0.009 \)), establishing this regimen as a standard-of-care.

A similar degree of benefit was also noted in the contemporaneous French Federation Francophone de Cancerologie Digestive (FFCD) 9703 trial of 224 patients with esophagogastric adenocarcinoma [24]. Patients were randomized to six cycles of perioperative 5-FU/cisplatin followed by surgery vs. surgery alone. Perioperative chemotherapy on this trial was associated with a significant improvement in 5-year disease-free survival (DFS; 34 vs. 19%, \( P = 0.003 \)) and OS (38 vs. 24%, \( P = 0.02 \)). Although comparisons between different clinical trials must be made cautiously, the survival benefit seen with 5-FU/cisplatin on this trial appears to be nearly identical to that seen with ECF in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial.

On the other hand and most recently, the European organization for Research and Treatment of Cancer 40954 trial evaluated a strategy of perioperative 5-FU/leucovorin/cisplatin in 144 patients with gastroesophageal junction and gastric adenocarcinoma [25]. The trial was stopped because of poor accrual, which limits the power of the study, and no differences in survival were detected.

These data are summarized in Table 1.

### POSTOPERATIVE CHEMORADIATION

In the United States, a standard-of-care is postoperative chemoradiation for resected gastroesophageal junction and gastric cancers based primarily on the results of the Intergroup 116 trial [26]. This trial randomized 556 patients to adjuvant chemotherapy and chemoradiation with bolus 5-FU/leucovorin vs. observation alone following surgery. Patients who received adjuvant chemoradiation had an improvement in 3-year OS (51 vs. 40%, \( P = 0.005 \)).

Despite this positive result, this trial is frequently criticized because of the relatively suboptimal surgical resections that were performed – 54% of patients had less than a D1 or D2 resection, which is less than a complete dissection of the involved lymph nodes (a D1 dissection is a complete dissection of local lymph nodes, whereas a D2 dissection comprises an extended lymph node dissection). It has been argued that radiation in this setting compensated for inadequate surgery because the greatest impact of adjuvant chemoradiation was a reduction in local recurrence of cancer. Such benefits may not be seen for radiotherapy if a more complete D1 or D2 surgical resection is undertaken.

On the basis of the results of the Intergroup trial, the Cancer and Leukemia Group B launched and completed the 80101 trial. Five hundred and forty-six gastric cancer patients were enrolled. The standard arm consisted of systemic bolus 5-FU/leucovorin preceding and following chemoradiation with infusional 5-FU, whereas the experimental arm intensified the systemic chemotherapy by replacing the bolus 5-FU/leucovorin with the ECF regimen. Results have been presented in abstract form and reveal no improvement in 3-year DFS (47 vs. 46%) or OS (52 vs. 50%) with the addition of an anthracycline and platinum compound to 5-FU [27]. These results are also virtually identical to the outcomes in the adjuvant chemoradiation arm of the Intergroup 116 trial. These results indicate that 5-FU monotherapy, combined with radiation, remains a standard-of-care, in particular in patients who have undergone less than a D1 or D2 resection. Adding cisplatin and epirubicin to adjuvant chemotherapy failed to improve survival. ECF should not be used as

### Table 1. Results of phase III preoperative or perioperative chemotherapy trials in gastric and gastroesophageal junction cancer

| Treatment                     | Number of patients | R0 resection rate | Pathologic CR rate | Survival | Local failure* | Reference |
|-------------------------------|--------------------|-------------------|--------------------|----------|----------------|-----------|
| Perioperative ECF + surgery   | 250                | 69%               | 0%                 | 24 months| 5-year 36%    | 14%       | Cunningham et al. [23] |
| Surgery                       | 253                | 66%               | N/A                | 20 months| 5-year 23%    | 21%       |                     |
| Perioperative 5FU/Cis + surgery| 109               | 87%               | NS                 | NS       | 5-year 38%    | 24%       | Ychou et al. [24]    |
| Surgery                       | 110                | 74%               | N/A                | NS       | 5-year 24%    | 26%       |                     |
| Preoperative 5FU/LV/Cis + surgery| 72                | 82%               | 7.1%               | 64.6 months| 2-year 73%    | NS        | Schumacher et al. [25] |
| Surgery                       | 72                 | 67%               | N/A                | 52.5 months| 2-year 70%    | NS        |                     |

Cis, cisplatin; CR, complete response; ECF, epirubicin, cisplatin, 5-fluorouracil; LV, leucovorin; N/A, not applicable; NS, not stated.

*Local failure with or without distant recurrence.
an adjuvant chemotherapy regimen, although preoperative and postoperative ECF without radiation therapy remains a care standard.

These results are summarized in Table 2.

**RADIATION AFTER D2 GASTRECTOMY**

An attempt to answer the question of whether there is a benefit for postoperative radiation in patients who have undergone a D2 gastrectomy was made by investigators of the Korean Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial. This recently published study randomized 458 patients with stage IB-IV gastric cancer who had undergone D2 resections to either six cycles of adjuvant capecitabine/cisplatin or two cycles of capecitabine/cisplatin before and after chemoradiation with capecitabine (Table 2) [28]. In the overall population, patients in the chemoradiation arm had a nonstatistically significant trend toward improved 3-year DFS (78.2 vs. 74.2%, \( P = 0.09 \)). In a subgroup analysis of 396 patients with lymph node-positive disease, there was a statistically significant improvement in 3-year DFS in the chemoradiation arm (77.5 vs. 72.3%, \( P = 0.04 \)). There was no difference in the rate of locoregional or metastatic recurrence in either arm. On the basis of these results, a follow-up study (ARTIST-II, NCT 01761461) is ongoing for patients with lymph node-positive disease; in addition to being randomized to receive chemoradiation or chemotherapy alone, the systemic chemotherapy will consist of either S-1 alone or with oxaliplatin.

Unfortunately, the results of the ARTIST trial do not provide definitive evidence for incorporating radiation into adjuvant therapy for optimally resected patients, although there may be a small absolute benefit of about 5% in 3-year DFS for radiation. The finding that radiation appears to benefit patients with lymph node-positive disease is somewhat counterintuitive as these patients are presumed to be at greater risk for developing distant metastases than patients with lymph node-negative disease and might, therefore, be expected to derive less benefit from an approach designed to improve locoregional control. Finally, even if one were to adopt a strategy of adjuvant chemoradiation for this population, it is entirely unclear that the systemic chemotherapy should consist of a fluoropyrimidine/platinum doublet as the negative CALGB 80101 study has already shown no benefit to adding cisplatin (and an anthracycline) to a fluoropyrimidine.

**POSTOPERATIVE CHEMOTHERAPY**

In comparison to chemoradiation, trials in East Asia of resectable gastric cancer have frequently focused on postoperative chemotherapy alone. To date, two large phase III trials have demonstrated a benefit for this approach. These data support the use of adjuvant fluoropyrimidines as monotherapy and combination chemotherapy with a fluoropyrimidine plus a platinum agent. The results are summarized in Table 3.

The Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) study was performed in Japan. In this study of 1059 patients with stage II/III gastric cancer who had undergone D2 resections, patients were randomized to 1 year of adjuvant chemotherapy with the oral 5-FU prodrug...
S-1 vs. observation [29]. Five-year outcomes for this trial were recently updated, confirming that adjuvant S-1 is associated with significant improvements in 5-year OS (71.7 vs. 61.1%, HR 0.67, 95% CI 0.54–0.83) compared to observation alone [30].

The second trial is the capecitabine and oxaliplatin adjuvant study in stomach cancer trial (CLASSIC), which was performed in 1035 East Asian patients who had undergone a D2 resection of stage II-IIIB gastric cancer [31]. Patients were randomized to 6 months of adjuvant capecitabine/oxaliplatin vs. observation. Although OS data remain immature, adjuvant chemotherapy was associated with an improvement in 3-year DFS (74 vs. 59%, HR 0.56, 95% CI 0.44–0.72, \(P < 0.0001\)).

A lack of benefit for adding a taxane to a fluoropyrimidine in the adjuvant setting was revealed by the results of the recently published Stomach cancer Adjuvant Multi-Institutional group Trial (SAMIT) study conducted in Japan [32*]. One thousand, four hundred and thirty-three evaluable patients with T4a or T4b tumors who had undergone initial surgery were randomized to receive either an oral fluoropyrimidine alone or paclitaxel preceding it. There was no improvement in 3-year DFS for the group that also received a taxane (57.2 vs. 54.0%, \(P = 0.273\)), suggesting that more chemotherapy in an unselected population may not be a beneficial strategy.

### CONCLUSION

Gastric cancer remains a significant worldwide health problem, with proximal gastric and gastro-esophageal junction tumors an emerging epidemic in Western countries.

In the last decade, there have been incremental improvements in outcomes both in the metastatic and locally advanced setting. Nevertheless, survival remains poor. Although beyond the scope of this review article, experimental approaches being investigated in the metastatic setting include immunotherapy, novel anti-Her2 strategies and therapies directed against such emerging targets as MET and its ligand, hepatocyte growth factor, and against fibroblast growth factor receptor. In the locally advanced setting (and in addition to the ARTIST-II study), several studies – the Dutch CRITICS study (NCT00407186) and the Australian TOPGEAR trial (Trial of preoperative therapy for gastric and esophagogastric junction adenocarcinoma; NCT01924819) – are also trying to definitively address the benefit of adding chemoradiation to perioperative chemotherapy.

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### Conflicts of interest

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Stomach and duodenum

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This study suggests that adding a taxane to a fluoropyrimidine in the adjuvant setting for resected gastric cancer is not beneficial.