MINIREVIEWS

Multimodality management of resectable gastric cancer: A review

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Abstract

Adenocarcinoma of the stomach carries a poor prognosis and is the second most common cause of cancer death worldwide. It is recommended that surgical resection with a D1 or a modified D2 gastrectomy (with at least 15 lymph nodes removed for examination) be performed in the United States, though D2 lymphadenectomies should be performed at experienced centers. A D2 lymphadenectomy is the recommended procedure in Asia. Although surgical resection is considered the definitive treatment, rates of recurrences are high, necessitating the need for neoadjuvant or adjuvant therapy. This review article aims to outline and summarize some of the pivotal trials that have defined optimal treatment options for non-metastatic non-cardia gastric cancer. Some of the most notable trials include the INT-0116 trial, which established a benefit in concurrent chemoradiation and adjuvant chemotherapy. This was again confirmed in the ARTIST trial, especially in patients with nodal involvement. Later, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial provided evidence for the use of perioperative chemotherapy. Targeted agents such as ramucirumab and trastuzumab are also being investigated for use in locally advanced gastric cancers after demonstrating a benefit in the metastatic setting. Given the poor response rate of this difficult disease to various treatment modalities, numerous studies are currently ongoing in an attempt to define a more effective therapy, some of which are briefly introduced in this review as well.

Key words: Neoadjuvant chemotherapy; Adjuvant chemotherapy; Adjuvant chemoradiation; Gastric cancer; Gastric adenocarcinoma

Core tip: Gastric adenocarcinoma is a difficult disease to treat. Surgical resection is the definitive therapy but recurrences are frequent. The use of a multidisciplinary approach to treatment decision-making is imperative. Surgical resection should be an R0 resection (with clear macroscopic and microscopic margins) and at least a D1 lymphadenectomy with a minimum of 15 lymph nodes sampled in the United States and a D2 lymphadenectomy elsewhere. Perioperative chemotherapy is a reasonable option based on the Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial. In patients who are evaluated after resection, adjuvant chemoradiation adds important survival benefit. Other options include adjuvant S-1 in Asian patients, capecitabine/oxaliplatin, and capecitabine/cisplatin.

INTRODUCTION

Adenocarcinoma of the stomach is one of the most common malignancies in the world, ranking fifth after

lung, breast, colorectal, and prostate. According to the World Health Organization, 952000 new cases were diagnosed in 2012 alone, with more than 70% of all cases occurring in developing countries[1]. In the United States, an analysis using the Surveillance Epidemiology and End Results database of the National Cancer Institute found an increase in overall incidence of adenocarcinoma of the esophagus and the gastric cardia from 13.4 per million in 1973 to 51.4 per million in 2009[2]. It is also the second most common cause of cancer death as of 2010. There is a significant disparity in the incidence and survival rates between the Asian and Western countries. For example, the overall 5-year survival worldwide was about 20% according to a report in 2008 but more than 70% in Japan for resectable disease. Such a dramatic difference maybe due to the implementation of screening programs in Japan where there is a higher incidence of gastriccancer resulting in detection of disease at earlier stages. In contrast, patients in the United States are usually diagnosed later in stage as routine screening for gastric cancer is not recommended owing to cost ineffectiveness[3]. The survival benefit may also be related to a more frequent use of second-line chemotherapy in Asian countries, most commonly irinotecans and taxanes, compared to the West[4, 5].

While gastric adenocarcinoma obviously includes tumors arising from the stomach, the classification of tumors of the gastroesophageal junction (GEJ) has been a topic of debate. The most widely used classification was proposed by Rüdiger Siewert *et al*[6] in 2000: type I tumors are tumors in the distal esophagus and may extend to the GEJ from above, type II tumors are adenocarcinomas of the cardia, arising at the GEJ, and type III tumors are cancers that originated from below the cardia and extend to the GEJ and distal esophagus from below. It is also noted that the biologies of these distinct types of GEJ tumors are very different. Type I cancers are mostly associated with intestinal metaplasia and history of gastroesophageal reflux disease. On the other hand, types II and III cancers resemble proximal gastric cancer and have lymphatic spread preferentially to the celiac axis[6,7]. The American Joint Committee on Cancer (AJCC) updated the staging of stomach adenocarcinoma in the 7th edition to include cancers of the GEJ arising more than 5 cm distally of the GEJ or within 5 cm of the GEJ but without extension to the esophagus or GEJ[8]. This distinction is important because many of the clinical trials included cancers of the GEJ in addition to cancers of the stomach. More importantly, cancers of the GEJ as described above behave similarly compared to gastric cancer and are treated as such.

Currently, surgical resection is the only curative mode of treatment for non-metastatic gastric adenocarcinoma. However, median survival with surgery alone, historically, was poor. Patients who had undergone resection are prone to suffer from locoregional or distant recurrences of their disease. As a result, neoadjuvant and adjuvant therapies aimed at the eradication of micrometastases

were studied in an attempt to reduce recurrence and prolong survival. This review article aims to outline some of the pivotal data that led to current clinical practices in resectable gastric cancer. It also briefly introduces ongoing trials in a global effort to improve overall survival for this difficult disease. Data presented in this review article were retrieved using a PubMed search with the key words "adjuvant," "neoadjuvant," "perioperative therapy," and "resectable gastric cancer."

CURATIVE RESECTION

Though this review aims to summarize available data in medical treatment of resectable gastric cancer, it is important to discuss surgical management given its central role in overall management. Controversies surround the surgical management of gastric cancer. In 1999, Bozzetti *et al*[9] found no difference in survival between total and subtotal gastrectomies but that subtotal gastrectomy was associated with improved nutritional status and quality of life. With the advancement of laparoscopic techniques, laparoscopic gastrectomy was found to have similar outcomes but with fewer complications compared to open gastrectomy in meta-analyses and case-control studies[10-13]. Furthermore, a resection margin of 1 mm was found to be sufficient as long as the resection margins were free of tumor[12].

The depth of lymphadenectomy has been a topic of debate as well. A D1 dissection involves a gastrectomy and the removal of the greater and lesser omental lymph nodes. A D2 dissection involves the above plus the removal of all lymph nodes along the left gastric artery, common hepatic artery, celiac artery, splenic hilum and splenic artery. The D1 dissection was traditionally favored in the West, specifically in the United States, whereas D2 resection was preferred in the East[14] and Europe. This discrepancy was based on early randomized trials that failed to show a survival benefit with D2 lymphadenectomy[15,16]. Subsequent studies showed that D2 resection indeed offered a survival benefit, prompting a change in practice. Recently, Shrikhande *et al*[17] established the non-inferiority of perioperative gastrectomy with D2 lymphadenectomy for locally advanced resectable gastric adenocarcinoma when combined with neaoadjuvant chemotherapy. More importantly, half of those patients who achieved a pathologic response were found to have lymph node involvements, arguing for the necessity of D2 gastrectomy[17]. A randomized trial comparing D1 and D2 dissections found that there was no difference in overall 5-year survival between the two practices. However, subgroup analyses suggest that D1 resection may be beneficial for those with pT1 disease while a trend towards improved survival was seen with D2 lymphadenectomy in patients with nodal involvement[18]. Based on some of these trials in addition to other clinical data, the National Comprehensive Cancer Network guidelines currently recommends a D1 or a modified D2 gastrectomy with at least 15 lymph nodes removed for examination in

the United States, though noting that D2 lymphadenectomies should be performed at experienced centers[19].

NEOADJUVANT CHEMOTHERAPY

Neoadjuvant treatment has the appeal of allowing for a more complete surgical resection while assessing for response to chemotherapy and risk for recurrence. However, robust data to support use of neoadjuvant therapy are limited at this time. Schuhmacher *et al*[20] reported data from the European Organisation for Research and Treatment of Cancer 40954 trial comparing neoadjuvant cisplatin, folinic acid, and infusional fluorouracil with surgery alone. A total of 144 patients with locally advanced adenocarcinoma of the stomach and GEJ were recruited and randomized. Those assigned to chemotherapy received 48-d cycles of neoadjuvant biweekly cisplatin, weekly L-folinic acid and fluorouracil for 2 cycles. The study was closed prematurely due to poor accrual. Only 62.5% of patients assigned to the chemotherapy arm completed 2 cycles of treatment.

Median follow-up was about 4 years. Preoperative chemotherapy reduced tumor size and nodal involvement compared to surgery alone. Given the low accrual, this study was ultimately underpowered at 25%. Progression-free survival had a hazard ratio of 0.76 but was not statistically significant (95%CI: 0.49 to 1.16, *P* = 0.2). The 2-year survival rates were 72.7% in the chemotherapy arm and 69.9% in the surgery only arm. The hazard ratio for overall survival was 0.84 in favor of chemotherapy, though it was not a statistically significant finding (95%CI: 0.52 to 1.35, *P* = 0.466). The authors noted that while this was a negative study with a small sample size, the rate of R0 resection was higher in the group that received neoadjuvant chemotherapy at 81.9%, compared to 66.7% in the group that did not (*P* = 0.036)[20]. Whether this difference would have translated into a benefit in progression-free survival or overall survival remains unanswered.

Additional albeit limited trial data emerged recently in attempts to further characterize the use and benefits of neoadjuvant chemotherapy. A small randomized, double-blinded controlled trial from Tehran found similar survival rates after a follow-up period of about 10 mo when comparing use of preoperative docetaxel, cisplatin, and 5-fluorouracil (DCF) followed by surgery with surgery alone[21]. In a recent phase Ⅱ study, the use of neoadjuvant paclitaxel and cisplatin was found to provide a pathologic response of 34.6% and a 3-year overall survival of 41.5% (95%CI: 27.4% to 55.0%)[22]. A small non-randomized study from China compared the use of epirubicin, oxaliplatin, and capecitabine (EOX) with 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX). An improved pathologic response was found with use of EOX. This study, however, enrolled 87 patients in the FOLFOX arm and only 26 patients in the EOX arm[23].

Given the paucity and variability of information, systemic reviews were conducted to attempt to clarify the role of neoadjuvant chemotherapy. A meta-analysis

was performed investigating the effectiveness of 5-fluorouracil-based chemotherapy in the neoadjuvant setting. Seven randomized controlled trials were included for analysis with a total of 1249 patients. The results showed that neoadjuvant chemotherapy improved overall survival with an odds ratio of 1.40 (95%CI: 1.11 to 1.76, *P* = 0.0005). The 3-year progression-free survival was also higher in the chemotherapy group at 37.7% compared to 27.3% in the control group, odds ratio of which was 1.62 (95%CI: 1.21 to 2.15, *P* = 0.001). There was no difference in perioperative mortality or complication rates between the two groups. Combination chemotherapy was superior to monotherapy. Additionally, intravenous administration of chemotherapy was found to have a greater impact than oral administration. Finally, it demonstrated a preference in Western countries for neoadjuvant treatment compared to Asian countries[24].

On the other hand, Liao *et al*[25] did not find an improvement in overall survival or R0 resection with use of neoadjuvant therapy. A meta-analysis of 6 randomized, controlled trials with 781 patients was conducted. The odds ratio was 1.16 for overall survival with use of neoadjuvant chemotherapy (95%CI: 0.85 to 1.58, *P* = 0.36) and 1.24 for R0 resection (95%CI: 0.78 to 1.96, *P* = 0.36)[25], neither of which were statistically significant. Currently, available data further illustrates the controversy in defining the optimal neoadjuvant treatment.

PERIOPERATIVE CHEMOTHERAPY

The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial in 2006 established the role of perioperative chemotherapy for resectable gastroesophageal cancer as the standard of care. A total of 503 treatment-naïve patients with adenocarcinoma of the stomach or lower third of the esophagus were randomized to receive perioperative epirubicin, cisplatin, and infused fluorouracil (ECF) or surgery alone. The trial was initially designed to recruit gastric adenocarcinomas but was extended to include tumors of the GEJ due to its increased incidence. Patients had stage Ⅱ and Ⅲ disease or locally advanced but inoperable disease.

Two hundred and fifty patients were randomized to receive 3 cycles of preoperative epirubicin (50 mg/m^2 on day 1), cisplatin (60 mg/m^2 on day 1), and fluorouracil (200 mg/m^2 daily) for 21 d, followed by surgical resection and 3 additional cycles of ECF. A total of 215 patients, 86% of those randomized to the perioperative chemotherapy arm, completed chemotherapy; 41.6% of these patients completed all 6 cycles of chemotherapy. Median follow-up was about 4 years. Preoperative chemotherapy significantly reduced tumor size at time of resection with a median maximum diameter of 3 cm (compared to 5 cm in those without chemotherapy, *P* < 0.001). There was also more T1 and T2 tumors as well as N0 and N1 disease in the group exposed to chemotherapy. Five-year survival rates were 36.3% in the perioperative chemotherapy arm and 23% in the surgery arm with an overall sur-

vival hazard ratio of 0.75 (95%CI: 0.60 to 0.93, *P* = 0.009). Progression-free survival was also improved with chemotherapy with a hazard ratio of 0.66 (95%CI: 0.53 to 0.81, *P* < 0.0019). Local recurrence was noted in 14.4% of patients in the perioperative chemotherapy group and in 20.6% in the surgery group. Distant metastases were also less frequent in those who received chemotherapy (24.4% *vs* 36.8%)[26]. The benefits of this regimen was confirmed in 2013 when Mirza *et al*[27] found an improvement in survival when patients completed both the pre- and postoperative cycles.

In 2007, the results for the FNLCC ACCORD07-FFCD 9703 trial were presented at the annual American Society of Clinical Oncology meeting and later published in 2011. A total of 224 patients with adenocarcinoma of the stomach or GEJ were randomized to receive 2-3 cycles of fluorouracil at 800 mg/m^2 for days 1-5 and cisplatin 100 mg/m^2 on day 1, for a 28-d cycle followed by surgery and postoperative chemotherapy for an additional 3-4 cycles or surgery alone. The planned maximum cycles were set at 6. The trial was closed early as a result of accrural difficulties.

The median follow-up was 5.7 years. In the chemotherapy arm, 97% of patients received at least 1 cycle of preoperative chemotherapy, 87% received at least 2 cycles. Of these, 50% went on to receive post-operative chemotherapy. R0 resection rate was 84% in the chemotherapy group compared to 74% in the surgery group (*P* = 0.04). There was a trend towards less nodal involvement at time of surgery in the chemotherapy group (67% *vs* 80%, *P* = 0.054) but the sizes of tumors at resection were similar in both groups. Five-year survival was 38% (95%CI: 29% to 47%) in the chemotherapy group and 24% (95%CI: 17% to 33%) in the surgery group. Five-year disease-free survival was also significantly improved with chemotherapy at a rate of 34% (95%CI: 26% to 44%) compared to 19% (95%CI: 13% to 28%). Furthermore, the chemotherapy arm also offered improved overall survival with a hazard ratio of 0.69 (95%CI: 0.50 to 0.95, *P* = 0.02) and disease-free survival with a hazard ratio of 0.65 (95%CI: 0.48 to 0.89, *P* = 0.003).

It is important to note, however, that this study was originally designed to include patients with cancer of the esophagus and was only extended to include cancer of the stomach in 1998. Consequently, 64% of accrued patients had disease of the GEJ while only 25% had gastric carcinoma. In a multivariate analysis, it was noted that preoperative chemotherapy and tumor site at the GEJ were significant prognostic factors for overall survival, *P* = 0.01 and *P* < 0.01, respectively. The other pathologies were not noted to have a statistically significant benefit when analyzed separately because of small sample sizes[28,29].

In a small non-randomized study, the use of perioperative FOLFOX was compared with adjuvant FOLFOX. A total of 73 patients with resectable T3 and T4 gastric adenocarcinoma were recruited between December 2001 and September 2005, 33 of which were assigned to the perioperative arm while 37 patients were assigned to the adjuvant arm. Those receiving perioperative chemotherapy received 3-wk cycles of FOLFOX for 2-4 cycles, followed by surgery and further chemotherapy for a total of 6 cycles. Those allocated to the adjuvant arm received the same FOLFOX regimen for a total of 6 cycles. The median follow-up duration was 53 mo. The 4-year overall survival was 78% (95%CI: 64% to 92%) in the perioperative chemotherapy group compared to 51% (95%CI: 35% to 67%, *P* = 0.031) in the adjuvant group. The 4-year disease-free survival was 78% (95%CI: 64% to 92%) and 48% (95%CI: 32% to 64%, *P* = 0.022), respectively[30]. While this was a very small, non-randomized study, it provided evidence for further investigational efforts to evaluate the role of FOLFOX in a perioperative setting.

Finally, the use of perioperative chemotherapy, with or without radiation, was confirmed as advantageous compared to surgery alone in a Cochrane database meta-analysis of randomized controlled trials. The hazard ratio with use of chemotherapy was 0.81 (95%CI: 0.73 to 0.89), which corresponded to a 5-year relative survival increase of 19% and an absolute increase of 9%[31].

ADJUVANT CHEMORADIATION

In 2001, Macdonald *et al*[32] published clinical results from the INT-0116 (Intergroup 0116) study evaluating effects of adjuvant chemoradiation using concurrent fluorouracil and leucovorin followed by 2 cycles of fluorouracil and leucovorin after completion of radiation as compared to surgery alone. The regimen used is now commonly known as the Macdonald regimen. This study also changed the standard of care for gastric adenocarcinoma. It recruited 603 patients between 1991 and 1998 with stages IB to IV(M0) gastric or gastroesophageal adenocarcinoma. Gastric primaries comprised of about 80% of total recruited patients. Sixty-four percent of those randomized to chemoradiation completed treatment. Median follow-up was 5 years with median survival of 36 mo in the chemoradiation group and 27 mo in the control group. Three-year survival rates were 50% in the chemoradiation arm and 41% in the surgery arm, with a hazard ratio of 1.35 (95%CI: 1.09 to 1.66, *P* = 0.005) in the surgery arm. The median progression-free survival was 30 mo with adjuvant treatment compared to 19 mo without, which translated to three-year rate of progression-free survival of 48% and 31%, respectively. One of the criticisms of this trial was that more than half of the patients had less than D1 resections. It was possible that the adjuvant treatment acted to compensate for the suboptimal surgery. The effect of adjuvant radiotherapy in setting of D2 resections remains unclear from this data set[32].

After median follow-up of 10.3 years, an update to the INT-0116 trial was presented in 2012. The hazard ratio for progression-free survival was 1.51 (95%CI: 1.25 to 1.83, *P* < 0.001) and 1.32 (95%CI: 1.10 to 1.60, *P* = 0.0046) for overall survival without the addition of

chemoradiation. Median progression-free survival was 27 mo for adjuvant therapy compared to 19 mo without (P < 0.001). Median overall survival was 35 mo with additional treatment compared to 27 mo without (P = 0.0046). There was no notable long term adverse effect found. This update confirmed earlier findings that additional adjuvant chemoradiation offered significant benefit in gastric cancer[33].

With the approval of capecitabine in 1998 for breast cancer and subsequently colorectal cancer, a new oral option became available. Using this new oral fluorouracil prodrug, the ARTIST (Adjuvant Chemoradiation Therapy in Stomach Cancer) trial expanded on the idea of adjuvant chemoradiation. It compared adjuvant capecitabine and cisplatin with capecitabine, cisplatin and concurrent capecitabine chemoradiation. From 2004 to 2008, 458 patients with adenocarcinoma of the stomach who had undergone an R0 gastrectomy with at least D2 lymph node dissection were randomized. Those assigned to the chemotherapy arm received 6 cycles of capecitabine (1000 mg/m^2 twice daily on days 1-14) and cisplatin (60 mg/m^2 on day 1) every 3 wk. Those assigned to the chemoradiation received 2 cycles of the same doses of capecitabine and cisplatin, followed by concurrent capecitabine (825 mg/m^2 twice daily) and radiation, followed by 2 additional cycles of capecitabine and cisplatin in 3-wk cycles.

Median duration of follow-up was 53.2 mo. Treatments were completed by 75.4% of those randomized to the chemotherapy arm and 81.7% of those assigned to the chemoradiation arm. Three-year disease-free survival rates were 78.2% in the concurrent chemoradiation group and 74.2% in the chemotherapy alone group (P = 0.0862). While this was not statistically significant, a subgroup analysis found a statistically significant improvement in 3-year disease-free survival in patients with nodal involvement using chemoradiation (77.5% *vs* 72.3%, P = 0.0365), which corresponded to a hazard ratio of 0.6865 (95%CI: 0.4735 to 0.9952, P = 0.0471). Overall survival data had not matured at time of publication. It should be noted that while disease-free survival was improved with the addition of radiation, the rate of locoregional recurrence and distant metastases were not different between the two study groups[34].

CALGB 80101, a US Intergroup study, compared the INT-0116 protocol regimen (bolus FU and leucovorin with FU plus concurrent RT) versus postoperative ECF before and after FU plus concurrent RT in 546 patients with completely resected gastric or GEJ tumors that extended beyond the muscularis propria or were node positive[35]. The fraction of enrolled patients with GEJ versus gastric primary tumors was not reported. In a preliminary report presented at the 2011 meeting of the American Society of Clinical Oncology, patients receiving ECF had lower rates of diarrhea, mucositis, and grade 4 or worse neutropenia. Overall survival, the primary endpoint, was not significantly better with ECF (at three years, 52% *vs* 50% for ECF and FU/LV, respectively). The trial was not adequately powered to assess non-inferiority. The loca-

tion of the primary tumor GEJ *vs* proximal versus distal stomach did not have any effect on treatment outcome.

A meta-analysis also confirmed the utility of adjuvant chemoradiation in resectable gastric adenocarcinoma after an R0 resection[36].

ADJUVANT CHEMOTHERAPY

As perioperative and adjuvant chemoradiation became widely accepted, the benefit of adjuvant chemotherapy was also investigated. The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) trial sought to answer this question. S-1 is an oral dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine combination of tegafur, gimeracil, and oteracil. Once ingested, tegafur is converted *in vivo* to fluorouracil. This was a phase Ⅲ, randomized study that recruited 1059 patients with stage Ⅱ or Ⅲ adenocarcinoma of the stomach from 2001 to 2004. All patients underwent a D2 gastrectomy with an R0 resection. Those patients assigned to adjuvant therapy received S-1 in 80, 100, or 120 mg daily doses, estimated based on body surface area, for 4 wk with 2 wk of rest for 1 year.

The study initially found, after a median follow up of 3 years, that the 3-year overall survival was 80.1% in the S-1 group compared to 70.1% in the surgery alone group. The hazard ratio was 0.68 (95%CI: 0.52 to 0.87, P = 0.003). The investigators performed an updated analysis of the results after 5 years of follow-up in 2011, which found a hazard ratio of 0.669 (95%CI: 0.54 to 0.828). Overall survival was 71.7% (95%CI: 67.8% to 75.7%) and 61.1% (95%CI: 56.8% to 65.3%) in the chemotherapy and observation groups, respectively. The 5-year relapse-free survival was 65.4% (95%CI: 61.2% to 69.5%) in the treatment arm compared to 53.1% (95%CI: 48.7% to 57.4%) in the surgery alone arm; hazard ratio was 0.653 (95%CI: 0.537 to 0.793). This reduction in hazard ratio was seen across all disease stages in subgroup analyses[37].

S-1, or tegafur, is not approved for use in the United States by the FDA. Based on pharmacokinetics studies, it has been documented that the drug is metabolized differently between Asians and Caucasians. The difference lies in the presence of CYP2A6, which occurs at a higher frequency in Eastern Asians. This enzyme is associated with reduced activity and subsequently reduced conversion of the prodrug *in vivo* to fluorouracil. Chuah *et al*[38] found that given the same dosing, the exposure to fluorouracil was similar in both ethnic groups. This was suggested by the investigators to be a result of increased renal clearance in Caucasians. Despite the same degree of exposure to the active metabolite, Caucasians were noted to have more grades 3 and 4 gastrointestinal toxicities compared to Asians (21% *vs* 0%)[38]. As a result of this difference, there is concern that tegafur use in the United States population may require dose reductions and efficacy of lower doses for resectable gastric cancer has not been addressed.

The First-Line Advanced Gastric Cancer Study evaluated an international cohort of patients with unresectable,

locally advanced or metastatic gastric and gastroesophageal adenocarcinoma using a protocol that compared S-1 and cisplatin with fluorouracil and cisplatin. It did not find significant differences in efficacy or toxicity profiles between the various ethnic groups[39]. This phase III, randomized trial suggests that tegafur can be effective in Caucasians with advanced gastric cancer; however, further studies for resectable gastric carcinoma are warranted.

In 2012, a Korean group published results of the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) trial, which compared adjuvant capecitabine and oxaliplatin after D2 gastrectomy with R0 resection with surgery alone in stage II and III gastric adenocarcinomas. A total of 1035 patients were recruited between 2006 and 2009 in centers in South Korea, China, and Taiwan. Patients were randomized to either adjuvant chemotherapy or observation alone. Those assigned to chemotherapy received capecitabine (1000 mg/m^2 twice daily on days 1-14) and oxaliplatin (130 mg/m^2 on day 1) of a 3-wk cycle for a total of 8 cycles.

Median duration of follow-up was about 34 mo in both arms and 67% of those receiving chemotherapy completed 8 cycles of treatment. The 3-year disease-free survival was 74% (95%CI: 69% to 79%) and 59% (95%CI: 53% to 64%) in the chemotherapy and surgery alone groups, respectively, with a hazard ratio for chemotherapy of 0.56 (95%CI: 0.44 to 0.72, $P < 0.0001$). The 3-year overall survival was 83% (95%CI: 79% to 87%) in the treatment group compared to 78% (95%CI: 74% to 83%) in the observation group. The hazard ratio for overall survival was 0.72 (95%CI: 0.52 to 1.00, $P = 0.0493$). Estimation of median overall survival was not available at time of publication. In the subgroup analyses, survival benefit was seen in all disease stages and N1 and N2 diseases. There was no significant benefit for those with N0 disease[40].

A small randomized, double-blinded study was conducted to evaluate use of adjuvant FOLFOX4 *vs* fluorouracil/leucovorin in resectable gastric adenocarcinoma. A total of 80 patients were recruited from 2005 to 2009 after D2 gastrectomy with an R0 resection. Median duration of follow-up was about 36 mo. The 3-year overall survival was 36 mo in the FOLFOX4 group compared to 28 mo in the control group ($P < 0.05$). Similarly, the 3-year recurrence-free survival was 30 mo with the addition of oxaliplatin compared to 16 mo without ($P < 0.05$)[41].

Most recently, a phase III study conducted by Kang *et al*[42] found an advantage using adjuvant cisplatin, mitomycin-C, and doxifluridine (iceMFP). Known as AMC 0101 trial, 521 patients were randomly assigned to receive mitomycin-C and doxifluridine (Mf, control) or the study arm, which included use of intraperitoneal cisplatin. The hazard ratio for recurrence in the iceMFP group was 0.70 (95%CI: 0.54 to 0.90, $P = 0.006$) with a 30% risk reduction for recurrence. The recurrence-free survival at 3 years was 60% (95%CI: 54% to 67%) in the study group compared to 50% (95%CI: 43% to 57%) in the

control group. Median recurrence-free survival was not yet reached in the iceMFP arm but was 34.5 mo (95%CI: 24.2 to 63.8) in the Mf arm. Three-year overall survival rates were 71% (95%CI: 65% to 77%) and 60% (95%CI: 53% to 66%) for iceMFP and Mf, respectively[42]. Doxifluridine is another oral prodrug of 5-fluorouracil. Though doxifluridine is not FDA-approved for use in the United States, it is approved for use in Asia, calling into question the efficacy of cisplatin, mitomycin, and 5-fluorouracil (or its equivalent) in the United States.

ONGOING TRIALS AND FUTURE DIRECTIONS

Given the tenacious natural history of gastric cancer, many trials are currently ongoing to define more optimal treatments. Early phase I and II data found promise in some new regimens, such as perioperative docetaxel, cisplatin, and capecitabine (DCX) and DCF[43,44], neoadjuvant S-1 and cisplatin or paclitaxel and cisplatin[45], and neoadjuvant docetaxel with S-1[46].

Of note, one highly anticipated trial, known as the Chemoradiotherapy after Induction Chemotherapy in Cancer of the Stomach trial, is a phase III, randomized, multicenter trial designed to compare overall survival in patients with resectable gastric cancer when treated with 3 cycles of preoperative epirubicin, cisplatin, and capecitabine (ECC) followed by surgery and either an additional 3 cycles of ECC or concurrent chemoradiation with cisplatin, capecitabine, and 45 Gy. Accrural started in 2007 with results last updated in 2011, having enrolled 350 patients at that time[47].

In the United Kingdom, the MAGICB/ST03 study is exploring epirubicin, cisplatin and capecitabine (ECX) with or without bevacizumab followed by surgery, and adjuvant ECX with and without maintenance bevacizumab.

Neoadjuvant therapy is under study in a European trial comparing preoperative FU and cisplatin *vs* surgery alone and a joint Swiss/Italian trial of preoperative docetaxel, cisplatin and FU compared to surgery alone. Similarly, a Japanese study is evaluating preoperative cisplatin plus S-1 (an oral fluoropyrimidine) followed by surgery and postoperative S-1 *vs* surgery and postoperative S-1 alone (KYUH-UHA-GC04-03).

The Korean ARTIST II trial is comparing adjuvant chemotherapy (S-1 *vs* S-1/oxaliplatin) with or without radiotherapy for completely resected gastric adenocarcinoma.

A randomized trial, the TOPGEAR trial, is underway in Europe and Canada to directly compare preoperative chemotherapy alone (ECF) *vs* chemoradiotherapy (two cycles of ECF followed by concurrent fluoropyrimidine-based chemoradiotherapy) in patients with resectable adenocarcinoma of the stomach and GEJ; both groups will receive three further cycles of ECF postoperatively

Uses of targeted agents are also being actively investigated. Recently, the REGARD trial, which was a random-

Trial	No. of patients	Median survival (mo)	Overall survival	Progression-free survival
Neoadjuvant chemotherapy				
EORTC 40954[20]			(2 yr)	
5FU, cisplatin, folinic acid	72	64.62	72.70%	NR
Surgery alone	72	52.53	69.90%	NR
Perioperative chemotherapy				
MAGIC Trial[26]			(5 yr)	
ECF	250	NR	36.30%	NR
Surgery alone	253	NR	23%	NR
Fnlcc accord07/ffcd 9703[29]			(5 yr)	(5 yr)
5FU, cisplatin	113	NR	38%	34%
Surgery alone	111	NR	24%	19%
Adjuvant chemoradiation				
INT-0116 trial[32]			(3 yr)	(3 yr)
5FU, CRT	281	36	50%	48%
Surgery alone	275	27	41%	31%
Artist trial[34]				(3 yr)
Capecitabine, cisplatin, CRT	230	NR	NR	78.20%
Capecitabine, cisplatin	228	NR	NR	74.20%
Adjuvant chemotherapy				
ACTS-GC Trial[37]			(3, 5 yr)	(5 yr)
S-1	529	NR	80.1%, 71.7%	65.40%
Surgery alone	530	NR	70.1%, 61.1%	53.10%
Classic trial[40]			(3 yr)	(3 yr)
Capecitabine, oxaliplatin	520	NR	83%	74%
Surgery alone	515	NR	78%	59%

Table 1 Notable trial data for neoadjuvant and adjuvant therapies for gastric (or gastroesophageal) adenocarcinoma

NR: Not reported; 5FU: 5-fluorouracil; ECF: Epirubicin/cisplatin/5-fluorouracil; CRT: Chemoradiation therapy.

ized, double-blinded, placebo-controlled, international study, established ramucirumab as an active biologic agent in advanced gastric cancer. Ramucirumab is a fully human IgG monoclonal antibody. It functions as a VEGFR-2 antagonist by preventing ligand binding and subsequent receptor-mediated pathway activation in endothelial cells, thus causing a decrease in tumor growth. Eligible patients had unresectable locally advanced recurrent or metastatic gastric or GEJ adenocarcinoma that progressed after first-line therapy. The majority population in both arms (approximately 75%) were patients with gastric adenocarcinoma. Median overall survival was 5.2 mo with ramucirumab and 3.8 mo with placebo. Hazard ratio was 0.776 (95%CI: 0.603 to 0.998, $P = 0.047$). Estimated overall survival and progression free survival were also improved[48]. This pivotal study established the role of ramucirumab as a single agent in advanced or metastatic gastric cancer. Further studies are sure to follow.

In the United Kingdom, the MAGICB/ST03 study is exploring epirubicin, cisplatin and capecitabine (ECX) with or without bevacizumab followed by surgery, and adjuvant ECX with and without maintenance bevacizumab.

The ToGA trial established use of trastuzumab in HER2-positive metastatic gastric cancer[49]. Similar promise was found with the use of trastuzumab in combination with chemotherapy[50-53] and additional clinical trials are currently underway. For instance, the TOXAG study is a phase II clinical trial looking at the safety profile of adjuvant oxaliplatin, capecitabine, and trastuzumab with radiation. It is currently recruiting patients.

With respect to surgical interventions, new modes of

treatment are being reviewed. A randomized trial known as CCOG 1102 has been planned to study the efficacy of extensive intraoperative peritoneal lavage compared to traditional surgery in resectable advanced gastric cancer with a primary end point of disease-free survival. A total of 300 patients are planned for accrual[54]. And finally, in regards to the controversy surrounding the extent of lymphadenectomy, a prospective randomized trial has been planned to compare D1 and D2 lymphadenectomy with a primary endpoint of 5-year overall survival.

CONCLUSION

Adenocarcinoma of the stomach, unfortunately, carries a poor prognosis and has a high mortality rate despite current available therapies. Most clinicians now treat GEJ and proximal gastric (*i.e.*, cardia) cancers as esophageal cancers, using preoperative chemoradiotherapy. However, it is important to note that tumors arising from within 5 cm of the GEJ without extension into the esophagus are classified in the same category as gastric cancer according to the updated AJCC Staging Manual and should be treated as such. This review outlines evidence-based approaches in the management of this difficult disease.

For patients with non-cardia gastric cancer, randomized trials and meta-analyses provide support for a number of approaches including adjuvant chemoradiotherapy, as shown in the INT-0116 trial, perioperative chemotherapy (preoperative plus postoperative), as was used in the MAGIC trial. Few studies have compared these approaches; however, the optimal way to integrate

combined modality therapy has not been definitively established. Decisions are often made based on institutional and/or patient preference. A major problem, at least in the United States, is that some patients with gastric cancer undergo surgery prior to consultation by medical or radiation oncologists.

Currently, a multidisciplinary approach and definitive surgical resection are recommended for locally advanced, early stage cancer. The gastrectomy should be performed laparoscopically if possible. It should be with negative margins and accompanied by a D1 lymphadenectomy with at least 15 lymph nodes sampled. A D2 lymphadenectomy should be performed in well-experienced centers.

For patients who have already undergone potentially curative gastric resection, we suggest adjuvant chemoradiotherapy rather than surgery alone for patients with N1 disease (which would include T1N1 stage IB), and for patients with T3N0 (stage ⅡA) disease and above, based upon the results of US Intergroup trial INT-0116[22]. For the subgroup of patients with T2N0 disease, either observation or adjuvant treatment is acceptable, and the decision can be based upon individualized patient (such as age, performance status, and motivation for treatment) and disease risk factor (*e.g.*, histologic grade or the presence of lymphovascular or perineural invasion) considerations.

An acceptable alternative approach for patients who are seen prior to resection is perioperative chemotherapy alone (ECF). It is reasonable to select patients utilizing the eligibility criteria for the MAGIC trial (patients of any age with a performance status of 0 or 1), a histologically proven adenocarcinoma of the stomach that was considered to invade through the submucosa (stage T2 or higher), with no evidence of distant metastases or locally advanced inoperable disease, as evaluated by CT, ultrasonography or laparoscopy[17].

East Asian patients with resected node-positive disease or T3N0 (stage ⅡA) disease and above, may take one year of postoperative S-1 chemotherapy. It is difficult to know whether the benefit of adjuvant therapy with S-1, as demonstrated in the Japanese ACTS-GC trial[26], can be extrapolated to other populations, given the markedly better outcomes seen in both the treated and the surgery alone control groups, stage for stage, when compared to outcomes in other non-Japanese populations. Until further information becomes available, we suggest that this approach be limited to East Asian patients. Other alternative chemotherapy regimens for adjuvant therapy include capecitabine plus oxaliplatin, as was used in the CLASSIC trial[29], or capecitabine plus cisplatin, as was used in the ARTIST trial[24]. Table 1 summarizes the available data from pivotal trials.

As technology moves increasingly toward molecular targeted therapy, biologic agents such as trastuzumab and ramucirumab hold great promise in the treatment of this disease as well. Their roles have not yet been defined in locally advanced gastric cancer but they are important new advances in the era of personalized medicine.

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