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AN UPDATE in the NON-ENDOSCOPIC treatment of Gastric Cancer

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Abstract

Purpose—To review recent seminal studies in esophagogastric cancer.

Recent Findings—Regular low aspirin use may reduce the risk of esophagogastric cancer. Laparoscopic resection of locally advanced gastric cancer appears equivalent to open resection. There is no survival benefit for the addition of postoperative radiation therapy to adjuvant chemotherapy after primary gastric cancer resection. For tumors of the esophagus and gastroesophageal junction, the combination of preoperative radiation therapy with concurrent chemotherapy may be required to ensure achievement of a negative surgical margin and to reduce local tumor recurrence. Epirubicin may not add benefit to fluorinated pyrimidine and platinum based chemotherapy, either in the preoperative setting or in the treatment of metastatic disease. The Her2 targeted agents lapatinib and trastuzumab emtansine failed to improve outcome when either added to or compared to chemotherapy. Immune checkpoint inhibition appears to be active in metastatic gastric cancer.

Summary—Recent studies in esophagogastric cancer help clarify the role of radiation therapy in surgical management, as well as the role of chemotherapeutic and targeted agents.

Keywords

Gastric cancer; radiation therapy; aspirin; laparoscopy; immune checkpoint inhibitors; epirubicin

INTRODUCTION

Gastric cancer is the third leading cause of cancer-related death globally, with a particular high incidence in East Asia, Eastern Europe, and tropical South America (1). There is a survival benefit for adding either preoperative or postoperative adjuvant chemotherapy to surgery. The need to include postoperative adjuvant radiation therapy appears dependent on the adequacy of the surgery performed. The optimal chemotherapy regimen to give as preoperative therapy, or to use in the treatment of metastatic disease, continues to be clarified in controlled studies. New agents, including HER2 targeted therapy and immune checkpoint inhibitors, are under active clinical trial evaluation.

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ESOPHAGASTRIC CANCER PREVENTION

Both retrospective and prospective studies have suggested that aspirin use reduces the risk of developing colorectal cancer. The impact of aspirin use on other cancer types has not been clearly established. Investigators reported long-term follow-up from a pooled cohort analysis of over 135,000 health care professionals assessed on the Nurses' Health Study and the Health Care Professionals Follow-up Study (2). Subjects were studied for dose, frequency, and duration of aspirin use. Regular aspirin use resulted in a slight reduction in overall risk for cancer (RR 0.97) primarily due to gastrointestinal cancer reduction (RR 0.85) and colorectal cancer in particular (RR 0.81), and a trend toward a reduced risk of gastroesophageal (GE) cancer (RR 0.85). Risk reduction was independent of sex and appeared dose dependent at 0.5 to 1.5 standard tablets or more weekly, and significant only appeared after 5 years of aspirin use.

SURGICAL MANAGEMENT AND THE ROLE OF ADJUVANT RADIATION THERAPY

Surgical resection employing a D2 lymphadenectomy is the global standard for locally advanced gastric cancer. Investigators from China reported results of a large, randomized trial in locally advanced gastric cancer comparing laparoscopic versus open gastric resection (3). Of the more than one thousand patients randomized, 41% had node negative disease, 75% had T2-T4a disease, and 30% had poorly differentiated tumors. The mean surgical time was 31 minutes longer on the laparoscopic arm (217 vs 186 minutes, $P < 0.001$), and blood loss was slightly lower on the laparoscopic arm (117 vs 106 ml). Equal numbers of patients had distal gastrectomy (98%) and nearly 100% of patients with either approach achieved a D2 resection. Conversion to open gastrectomy was only required in 6% of laparoscopically treated patients. Intraoperative complication rates were similar for laparoscopic (4.8%) vs the open approach (3.5%, $P = 0.281$). There was no difference in rates of anastomotic leak (1.9% vs 0.6%) and there was no difference in operative mortality. Survival data and longer follow are pending, but the results support greater utilization of laparoscopic resection of gastric cancer.

Adjuvant therapy improves survival after curative resection in gastric cancer. While U.S. practice combines postoperative chemotherapy and radiation therapy, trials from Europe and Asia support the use of pre and postoperative chemotherapy without radiation. The quality of surgical resection appears to impact on the need for postoperative radiotherapy. Investigators from Korea now report updated results at 7 years of follow up for the Adjuvant Chemoradiation Therapy in Stomach Cancer Trial (ARTIST), a multicenter phase III randomized trial comparing adjuvant chemotherapy with or without radiotherapy after D2 resection in gastric cancer (4). All patients were required to undergo D2 resection. Half of the 458 patients were treated with 6 months of chemotherapy with capecitabine and cisplatin, and half received 4 cycles of chemotherapy sandwiched with treatment with 45 Gy of radiotherapy (1.8 Gy daily fractions 5 days per week for 5 weeks) administered concurrently with capecitabine. Stage Ib/II disease accounted for 58–59% and Stage III/IV disease for 41–42%, and the majority had diffuse histology (57–63%). As shown in Figure 1,

overall survival at 5 years was not improved with the addition of radiotherapy to chemotherapy (75 vs 73%, HR 1.13, $P = 0.484$), although local recurrence was reduced from 13% to 7% with radiation therapy ($p = 0.003$). Disease free survival was improved with radiotherapy for the subsets of patients with node positive (76 vs 72%, $p = 0.04$) and with intestinal histology (94 vs 83%, $P = 0.01$). Immunohistochemistry analyses for EGFR, HER2, MET, p53, FGFR2, MLH1 and E-cadherin failed to be prognostic for disease free survival. The ARTIST trial indicates that adding radiation therapy to adjuvant chemotherapy fails to improve overall survival in gastric cancer if a D2 resection is performed. The study also failed to identify a prognostic biomarker by immunohistochemistry. The ongoing Korean ARTIST 2 trial is evaluating the addition of radiation therapy to adjuvant chemotherapy only in node positive patients.

Results from the European ChemoRadiotherapy after Induction chemotherapy in Cancer of the Stomach (CRITICS) trial were recently presented, comparing perioperative chemotherapy in gastric and GEJ cancer with or without the addition of postoperative radiation therapy in nearly 800 patients (5). Patients with predominantly gastric cancer were treated with 3 cycles of preoperative epirubicin/cisplatin/capecitabine (ECX) or epirubicin/oxaliplatin/capecitabine (EOX) chemotherapy followed by surgery, and then either 3 more cycles of chemotherapy or postoperative capecitabine/cisplatin combined with 45 Gy of radiotherapy. Patients were required to undergo a D1 or D2 resection. R0 resection was achieved in 80–84% of patients, D1 resection was documented in 49% and D2 resection in 37%. Three quarters of resected patients completed their assigned postoperative treatment. There was no difference in 5 year overall survival with the inclusion of radiotherapy (40.9%) compared to chemotherapy alone (40.8%). These results further question the contribution of radiotherapy in the postoperative adjuvant treatment of gastric cancer where adequate surgical resection is performed.

For more proximal adenocarcinomas of the distal esophagus and GE junction, radiation therapy may be required as part of preoperative chemotherapy. Investigators reported follow up from the Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study (CROSS) trial at a median follow up of 84 months for surviving patients (6). On this randomized trial, 368 patients with esophageal and GE junction cancer underwent surgery alone or preoperative treatment with weekly paclitaxel and carboplatin for 5 weeks administered with concurrent 41.4 Gy of radiotherapy in 1.8 Gy daily fractions. The majority of patients treated had clinical stage T3 (78–84%) and node positive (64–65%) disease and adenocarcinoma was the predominant histology (75%). Median overall survival was superior for the chemoradiotherapy arm in all patients (48.6 vs 24 months, HR 0.68), with a significant improvement in adenocarcinoma (43.2 vs 27.1 months, HR 0.73, $p = 0.038$). At long term follow up, local disease recurrence was significantly reduced in patients treated with chemoradiotherapy (38% vs 22%, HR 0.45, $p < 0.0001$), as was distant disease recurrence (48% vs 39%, HR 0.63, $p < 0.0040$). Curative or R0 resection rates were higher with preoperative chemoradiotherapy compared to surgery alone (92% vs 69%).

The need to include radiation therapy as part of preoperative chemotherapy for esophageal and GE junction adenocarcinoma was underscored by abstract presentations of two large randomized trials, OEO5 and STO3, employing preoperative chemotherapy alone reported

from the United Kingdom. OEO5 was presented by investigators from the U.K (7). In the OEO5 trial performed in the U.K. (7), nearly 900 patients with endoscopic ultrasound staged T2–3 or node positive esophageal and GEJ junction adenocarcinoma were treated with the standard of 2 cycles of cisplatin and 5-FU (CF) given preoperatively or with epirubicin, cisplatin, and capecitabine (ECX) for 4 preoperative cycles followed by surgery. Three-year overall survival did not differ for the two approaches (39% for CF vs 42% for ECX, HR 0.92, $p = 0.3017$). Rates of R0 resection were poor in both arms (60% for CF and 66% for ECX). This large trial raises important practice questions, including the failure of epirubicin to contribute to preoperative chemotherapy, and more than 2 cycles of therapy also failing to improve outcome. Given the poor rates of R0 resection, the combined use of preoperative chemoradiotherapy with carboplatin and paclitaxel, as used in the CROSS Trial, may be the preferred treatment approach given the high rate (92%) of R0 resection reported in this trial using combined chemoradiotherapy. The potential failure of preoperative chemotherapy alone to ensure achievement of an R0 resection was also reinforced by the same group's presentation of results from their STO3 trial (8). In this trial, over 1000 patients with esophageal, GE junction, and gastric cancer, received perioperative chemotherapy with ECX with or without the addition of the anti VEGF agent bevacizumab. Bevacizumab failed to improve outcome. Poor rates of R0 resection were also reported (57–59%), particularly in patients with esophageal or GE junction primary tumors.

TREATMENT OF METASTATIC DISEASE

There is ongoing controversy regarding the role of gastrectomy in the setting of metastatic disease, or whether chemotherapy alone should be used to treat metastatic disease. Investigators from Asia reported results of the REGATTA Trial (9). This ambitious trial conducted in Japan and Korea evaluated patients with low volume metastatic gastric cancer defined as a single non curable factor, including four or fewer small liver metastases, small volume peritoneal disease, or low volume M1 abdominal nodal metastatic disease. All patients were treated with S-1 (an oral fluoropyrimidine) and cisplatin cycled every 5 weeks. Patients were randomized to chemotherapy alone or to upfront gastrectomy followed by chemotherapy to start within 8 weeks of surgery. Of the 175 patients randomized, the majority had peritoneal metastases (73–77%), intestinal histology (75–76%), middle third tumors (24–33%), T3 disease (90–91%), and N0–1 disease (51–55%). The trial was closed at the first interim analysis given the low probability of demonstrating a survival benefit for gastrectomy, with 2 year overall survival of 25.7% for gastrectomy compared to 31.4% for chemotherapy alone (HR 1.08, $p = 0.66$). Median overall survival for chemotherapy was 16.6 months compared to 14.3 months for the surgery arm (HR 1.09, $p = 0.70$). Surgery had a particularly negative impact on patients with N0–1 disease and with upper third tumors. Higher rates of chemotherapy related adverse events were also seen in the gastrectomy arm. Retrospective, uncontrolled trials evaluating a benefit for surgery in metastatic gastric cancer have sometimes suggested a survival benefit for the addition of surgery, but such studies are open to severe selection bias. Whether or not surgery later in the course of the disease improves survival, including potentially gastrectomy or metastatectomy, also remains unproven.

Although standard chemotherapy for metastatic gastric cancer combines a fluorinated pyrimidine (usually fluorouracil [5-FU] or capecitabine) with either cisplatin or oxaliplatin, there is controversy as to whether or not adding other chemotherapy agents improves outcome. French investigators reported results of a phase III trial comparing first line chemotherapy treatment with FOLFIRI (folinic acid, fluorouracil, and irinotecan) or ECX (epirubicin, cisplatin and capecitabine) in metastatic gastric cancer (10). The trial indicated no difference in response rate for FOLFIRI compared to ECX (39.2% vs 37.8%), and no difference in either progression free survival (5.3 vs 5.8 months) or overall survival (9.5 vs 9.7 months). FOLFIRI seemed to have less toxicity and superior time to treatment failure (which factors in patients coming off therapy for toxicity) compared to ECX (see Figure 2). There also appeared to be no contribution of epirubicin to improved outcome in the recently reported CALGB 80403/E1206 trial (11), a randomized trial comparing FOLFOX (folinic acid, fluorouracil, and oxiplatin), ECF (epirubicin, cisplatin, and fluorouracil), and a third regimen irinotecan plus cisplatin in metastatic GE junction and esophageal cancer. All therapy arms also had the inclusion of the epidermal growth factor receptor targeted agent cetuximab. Comparing FOLFOX and ECF, there was no difference in response (53% vs 60%), progression free survival (6.8 vs 7.1 months), or overall survival (11.6 vs 11.8 months). There were more therapy related deaths on the ECF arm.

TARGETED THERAPY

Trastuzumab, an antibody that interferes with the HER2 receptor, improves response and survival when added to chemotherapy in HER2 positive metastatic gastric cancer. Investigators reported the results of the TRIO-013/LOGIC trial, a placebo controlled randomized phase III trial comparing standard chemotherapy with capecitabine and oxaliplatin with or without the addition of the HER2 tyrosine kinase inhibitor lapatinib, in HER2 positive GE junction and gastric adenocarcinoma (12). At the time of the study initiation, trastuzumab had not yet been approved in HER2 positive disease. Tumors had to test positive for HER2 amplification by fluorescence in situ hybridization (FISH) testing. Of the 487 patients treated with confirmed HER2 positive status, the majority had a gastric primary (86–88%) of intestinal subtype (89–90%) and nearly all had metastatic disease (95). Overall survival was not improved with lapatinib compared to placebo (12.2 vs 10.5 months, HR 0.91, $p = 0.3492$). Progression-free survival (PFS) was improved with lapatinib (6.0 vs 5.4 months, HR 0.82, $p = 0.0381$), as was response rate (53% vs 39%, $P = 0.0031$). Higher rates of grade 3 and 4 toxicity were seen with lapatinib (diarrhea 12% vs 3%, nausea 6% vs 2%). Despite the activity for lapatinib in HER2 positive breast cancer, this agent failed to improve survival in the first line chemotherapy treatment of HER2 positive gastric cancer. It is evident that efficacy of HER2 targeted agents in breast cancer will not automatically translate into benefits in gastric cancer. Negative results for the agent trastuzumab emtansine (TDM-1) in the second line treatment of HER2 positive gastric cancer were also recently reported (13). This agent is a conjugate of trastuzumab with an antimicrotubule agent, and it is approved for treatment of HER2 positive breast cancer. Patients who had received prior chemotherapy with or without trastuzumab were assigned to treatment with weekly or every 3 week TDM-1, or to treatment with a physician choice of paclitaxel or docetaxel. Comparing weekly TDM-1 or taxane therapy, there was no difference in overall survival (7.9

vs 8.6 months) and no difference in response (20.6% vs 19.6%) or in progression free survival (2.7 vs 2.9 months). We await results of first line dual targeted therapy with pertuzumab (which targets HER2 and HER3) and trastuzumab in HER2 positive metastatic gastric cancer.

Given the limited benefit of conventional chemotherapy for metastatic gastric cancer, trials are ongoing evaluating immune checkpoint inhibitors, which relieve immunosuppression by blocking either the PD-1 receptor or the ligands that activate this pathway, including PDL-1. Investigators now report the results of an industry sponsored, international, multicenter single arm phase 1b trial of the anti-PD-1 antibody pembrolizumab in metastatic gastric cancer (14). Patients were required to have immunohistochemistry positive staining for PDL-1 in either tumor or stroma. Patients received pembrolizumab 10 mg/kg every 2 weeks. Response rate was the primary endpoint. PDL-1 positivity was seen in 40% of patients screened. Of 39 patients enrolled, equal numbers were treated in Asia and the rest of the world, and most had received 2 or more prior chemotherapy regimens (57%). The GE junction was the primary tumor location in 28%. Partial response by central review was seen in 8 of 36 evaluable patients (22%), with median response duration of 40 weeks. Half of the responses appeared more durable. Progression free survival was 1.9 months and overall survival 11.4 months. A higher interferon γ gene expression signature, and a higher mononuclear inflammatory cell density score, correlated with higher antitumor response. Pembrolizumab has promising activity in patients with gastric cancer positive for PD-L1 expression, and justifies the multiple ongoing phase II and III trials of anti PD-1 and anti PD-L1 therapies in esophagogastric cancer. A clear biomarker to predict response to these agents remains to be identified.

CONCLUSION

Recent studies in gastric cancer have more clearly defined a role for laparoscopic surgery in primary disease, and have questioned whether adding postoperative radiotherapy to adjuvant chemotherapy after gastrectomy adds any benefit as long as adequate D1 or D2 resection is performed. For esophageal and GE junction cancers, adding radiotherapy to preoperative chemotherapy results in higher rates of curative resection and a potentially lower rate of local tumor recurrence. In the treatment of metastatic disease, there is no role for routine upfront gastrectomy prior to chemotherapy, and chemotherapy regimens such as FOLFIRI or FOLFOX may be preferable to adding epirubicin to 5-FU/platinum based therapy. The HER2 targeted agents lapatinib and TDM-1 will not likely move forward in clinical development. Study of immune checkpoint inhibitors is moving forward given promising data from early phase trials.

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Key points

- Regular aspirin use may reduce the risk of gastric cancer.
- Laparoscopic resection is acceptable for locally advanced gastric cancer.
- Postoperative radiation therapy does not improve survival with either perioperative or postoperative adjuvant chemotherapy after D1-2 gastrectomy.
- Poor rates of R0 resection occur with preoperative chemotherapy alone for distal esophageal and GE junction adenocarcinoma, and combined preoperative chemoradiotherapy is preferred for this tumor location.
- Epirubicin may not improve outcome added to two drug chemotherapy either in the preoperative or metastatic disease setting.
- Neither lapatinib added to chemotherapy, nor trastuzumab emtansine, improved outcome compared to chemotherapy alone in HER2 positive gastric cancer.
- Immune checkpoint inhibition appears to have activity in metastatic gastric cancer.

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Figure 1. Overall survival. XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin, on the ARTIST Trial (4).

Time-to-treatment failure (TTF) according to treatment arm (Kaplan-Meier estimation).

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Figure 2. Time-to-treatment failure (TTF) according to treatment with ECX or FOLFIRI (10). ECX arm: epirubicin, cisplatin, and capecitabine as the first-line treatment; FOLFIRI arm: irinotecan, leucovorin, fluorouracil bolus, and continuous infusion as the first-line treatment. HR, hazard ratio.