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Case Report

Neoadjuvant Chemotherapy and Adjuvant Chemoradiation Therapy in the Treatment of Resected Gastric Adenocarcinoma: A Case Series

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Abstract
The treatment of gastric cancer requires a multimodal approach to decrease the risk of loco-regional and distant recurrence. The optimal timing of chemotherapy, surgery, and radiation therapy continues to be explored in ongoing trials. In the United States, surgical resection is often followed by adjuvant chemoradiation therapy or by a combination of neoadjuvant and adjuvant chemotherapy. Here we report on 4 patients with resected gastric adenocarcinoma who were treated with a combination of these 2 approaches, receiving neoadjuvant chemotherapy followed by adjuvant chemoradiation therapy.

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Introduction

Gastric cancer remains a major cause of cancer death in the United States with a 5-year overall survival rate of 20–30%, which is likely a reflection of the prevalence of advanced disease at presentation [1, 2]. The high rate of locoregional and distant relapse after gastric resection necessitates a multimodal treatment approach. Therefore, while surgery is the definitive curative therapy, chemotherapy and radiation are often used neoadjuvantly and adjuvantly to decrease the risk of recurrence and improve survival rates. Treatment regimens for patients with locally advanced, resectable gastric carcinoma continue to be evaluated in an attempt to optimize the sequence and timing of chemotherapy, radiotherapy, and surgery.

Currently no global standard of care exists. In Japan and South Korea, D2 lymph node dissection and adjuvant chemotherapy is the model most commonly employed [3]. In the United States, where a more limited lymph node dissection may be performed, resection is often followed by adjuvant chemoradiation as demonstrated by the Intergroup 0116 (INT 0116) trial or by a combination of preoperative and postoperative chemotherapy per the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Gastric Cancer currently recommend that R0 resection be followed by adjuvant chemotherapy alone for patients who received neoadjuvant therapy, and by adjuvant chemotherapy with or without radiation therapy for patients who did not receive neoadjuvant treatment [4]. In the case of R1 or R2 resection, NCCN guidelines recommend adjuvant chemoradiation therapy if it was not received preoperatively.

The aforementioned INT 0116 trial randomized patients with margin-negative resected adenocarcinoma of the stomach or gastroesophageal junction (GEJ) (20%) to either surgery alone or to surgery followed by chemoradiation therapy consisting of 45 Gy in 25 fractions plus 5-fluorouracil (5-FU) and leucovorin. The study demonstrated an improved median survival (36 vs. 27 months), 3-year overall survival (50 vs. 41%), and 3-year relapse-free survival (48 vs. 31%) in the chemoradiation group [5]. Only 10% of patients received a D2 lymph node dissection leading to criticism that inadequate dissection may have led to an overestimation of the benefit of chemoradiation therapy [6]. However, a 10-year update demonstrated continued benefit in the chemoradiation group regardless of the extent of lymphadenectomy with significantly improved overall survival (hazard ratio [HR], 1.32) and progression-free survival (HR, 1.51) compared to surgery alone [7].

The phase III MAGIC trial randomized patients with resectable adenocarcinoma of the stomach, GEJ, or lower esophagus to either perioperative chemotherapy consisting of epirubicin, cisplatin, and 5-FU (ECF) and surgery or to surgery alone. Three cycles of ECF were administered preoperatively and 3 cycles postoperatively. The perioperative chemotherapy group had significantly smaller and less advanced resected tumors in addition to improved overall survival (HR, 0.75), 5-year survival (36.3 vs. 23%), and progression-free survival (HR, 0.66) [8]. Only 42% of patients in the MAGIC trial who were assigned to receive perioperative chemotherapy received all 6 cycles. In addition to toxic effects, reasons for not completing all cycles included a lack of response to preoperative treatment, disease progression or early death, postoperative complications, and patient choice.

Here we report on a group of 4 patients who received ECF preoperatively without continuing the regimen postoperatively due to 1 or more of these complications. Specifically, they were switched postoperatively to the INT 0116 chemoradiation protocol due to limited

pathologic response to preoperative chemotherapy, chemotherapy toxicity, and/or close surgical margins of the resected tumor.

Presentation of Cases

Patient 1

Patient 1 is a 70-year-old woman who presented with a 2-month history of dysphagia and a 9-pound weight loss. She was found to have uT3N0M0 invasive poorly differentiated adenocarcinoma, diffuse type, in the antrum of the stomach. During her second cycle of ECF, chemotherapy dose reductions were necessary due to mucositis and diarrhea. She underwent a total gastrectomy, Roux-en-Y esophagojejunostomy, and D2 lymphadenectomy. Surgical pathology confirmed a pT3N2 tumor resected to negative margins with a close 1-mm deep margin, and 5/36 lymph nodes positive for metastatic disease. No treatment effect was noted on the resected specimen despite neoadjuvant therapy.

Given chemotherapy toxicities and lack of response to neoadjuvant chemotherapy, postoperative chemoradiation therapy was recommended. She was treated as per the INT 0116 protocol. She developed grade 3 mucositis and diarrhea requiring hospitalization, thus the dose was reduced to 50% for the remainder of treatment. Follow-up EGDs and PET/CT scans showed no evidence of disease until 32 months after surgery when a CT scan demonstrated abdominal ascites as well as mesenteric and peritoneal nodularity suggestive of an early recurrent gastric cancer. Gallbladder pathology from an open cholecystectomy was consistent with metastatic signet ring cell adenocarcinoma. She passed away 34 months after her surgery.

Patient 2

Patient 2 is a 42-year-old woman who presented with a 68-pound weight loss over the last year, epigastric discomfort, and vomiting. She was found to have uT3N1M0 poorly differentiated adenocarcinoma, diffuse signet ring cell type, in the antrum of the stomach extending to the pylorus. During her second cycle of ECF, the patient developed palmar-plantar erythrodysesthesia. 5-FU was stopped and restarted with a 20% dose reduction in the third cycle. Upon completing chemotherapy, the patient underwent a near-total gastrectomy, Roux-en-Y gastrojejunostomy, and D2 lymphadenectomy. Surgical pathology confirmed a pT3N1 tumor resected to negative margins with 1/3 lymph nodes positive for metastatic disease. Given her lack of appreciable pathologic response to ECF, she began chemoradiation therapy as per the INT 0116 protocol. At currently 47 months after gastrectomy, she has no evidence of disease on either CT scans or surveillance EGD. Radiation dose distribution for patient 2 is shown in Figure 1.

Patient 3

Patient 3 is a 55-year-old woman who presented with poorly differentiated adenocarcinoma with signet ring cell features along the lesser curvature of the stomach, extending into the GEJ. She completed 3 cycles of ECF per the MAGIC protocol complicated by neutropenic fever, grade 3 palmar-plantar erythrodysesthesia, grade 3 neuropathy, severe diarrhea, and mucositis. She then underwent a total gastrectomy with antecolic Roux-en-Y esophagojejunostomy for a pT3N1 tumor with negative margins and 3/6 positive lymph nodes. Due to multiple chemotherapy toxicities preoperatively, she was offered adjuvant chemoradiation

with a reduced dose of adjuvant 5-FU/leucovorin and received a total radiation dose of 4,865 cGy.

Two years after surgery, she had a recurrence at the esophagojejunal anastomosis. Although taken to the operating room, resection was not performed as there was evidence of carcinomatosis intraoperatively. Final pathology of omental nodules revealed metastatic adenocarcinoma. Given her prior intolerance of ECF, she was instead started on palliative single-agent irinotecan 250 mg/m^2 given every 21 days. She passed away 3 years after her initial surgery. Radiation fields for patient 3 are shown in Figure 2.

Patient 4

Patient 4 is a 38-year-old woman who presented with a 4-year history of gastroesophageal reflux, epigastric pain, and a 20-pound weight loss over the last year. She was found to have uT3N0M0 poorly differentiated adenocarcinoma in the pyloric channel and began a modified MAGIC regimen substituting capecitabine for continuous infusion 5-FU. During the third cycle, capecitabine was reduced by 30% due to significant weakness and nausea. She then underwent a subtotal gastrectomy and enucleation of a proximal gastric wall mass. Final pathology revealed a pT3N1 tumor with negative margins and 2/7 lymph nodes positive for metastatic disease. The enucleated proximal posterior wall nodule showed a low-risk gastrointestinal stromal tumor.

The patient began her fourth cycle of the dose-reduced epirubicin, cisplatin, and capecitabine (Xeloda) (ECX) but was hospitalized for intractable nausea and vomiting. Her case was discussed at the multidisciplinary tumor board where it was recommended that she receive radiation therapy with capecitabine monotherapy. She was treated to 4,500 cGy in 25 fractions during which she received 1,600 mg of capecitabine daily. At 25 months after subtotal gastrectomy, she has no evidence of disease on PET/CT or endoscopy. Radiation dose distribution for patient 4 is shown in Figure 3.

Discussion

Although postoperative chemoradiation is not the standard of care for patients being treated preoperatively with ECF, it may be a reasonable alternative for patients who cannot tolerate chemotherapy, do not demonstrate pathologic response to the initial 3 cycles, or do not have adequate margins on surgical resection. Several ongoing studies continue to examine the role of chemotherapy and chemoradiation therapy in the treatment of gastric cancer. The Dutch phase III CRITICS trial is currently comparing adjuvant chemoradiation therapy to adjuvant chemotherapy. Patients are randomized to postoperative chemoradiation therapy (45 Gy with cisplatin and capecitabine) or to 3 cycles of chemotherapy with epirubicin, cisplatin, and capecitabine (ECC) [9]. Both groups receive 3 cycles of induction ECC and an adequate (D1+) surgery. This addresses concerns raised by the high percentage of D0 lymph node dissections in the INT 0116 trial possibly leading to an overestimation of the benefit of chemoradiation therapy. The CRITICS sequence of neoadjuvant chemotherapy and adjuvant chemoradiation therapy is the order of treatment employed in the 4 cases presented. Conversely, the Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma (TOPGEAR) compares preoperative chemoradiation therapy with concurrent 5-FU or capecitabine to preoperative ECF alone. Both groups will receive 3 cycles of ECF postoperatively [10].

All 4 patients presented were staged as node positive on surgical pathology. The role of chemoradiation therapy in node-positive disease is an area of ongoing research stemming from the Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial. In this trial, patients with resected gastric cancer and D2 lymphadenectomy received either adjuvant chemoradiation therapy (2 cycles of capecitabine and cisplatin followed by chemoradiotherapy and then 2 additional cycles of cisplatin) or adjuvant chemotherapy (6 cycles of cisplatin). No difference in disease-free survival or overall survival was seen between the 2 groups [11]. However, a subgroup analysis demonstrated that patients with lymph node-positive disease had improved outcomes in the chemoradiation group compared to the chemotherapy group. The hypothesis-generating finding that patients with D2 lymphadenectomy and node-positive disease may benefit from adjuvant chemoradiation therapy over chemotherapy alone will further be explored in the phase III randomized ARTIST-II trial.

The role of adjuvant chemotherapy after D2 resection was explored in 2 large randomized Asian trials, both of which demonstrated survival benefit in the chemotherapy group. The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) was a Japanese trial that randomly assigned patients following gastrectomy with D2 lymphadenectomy to adjuvant chemotherapy with S-1 or to surgery alone. The 3-year overall survival rate was significantly higher (80.1 vs. 70.1%) in the S-1 group than in the surgery-only group [12]. The trial was stopped after 1 year due to a clear overall survival benefit in the S-1 group. The Adjuvant Capecitabine and Oxaliplatin for Gastric Cancer after D2 Gastrectomy (CLASSIC) trial took place in 37 centers in South Korea, China, and Taiwan. Patients who had curative D2 gastrectomy were randomized to adjuvant chemotherapy with capecitabine and oxaliplatin or to surgery alone. The 3-year disease-free survival was significantly improved in the chemotherapy group (74 vs. 59%) compared to the surgery group [13]. Both studies supported D2 lymphadenectomy followed by postoperative chemotherapy as the standard of care in many Asian centers. It is unclear, however, whether this modality is as effective in Western populations where D2 lymphadenectomy is less commonly performed.

Conclusion

Our 4 cases demonstrate a potential utilization of preoperative chemotherapy with postoperative chemoradiation therapy in patients with gastric cancer. While we cannot draw any conclusion regarding the efficacy of this sequence of therapy, we note that chemoradiation therapy was generally well tolerated by the patients presented, and that 2 patients continue to show no evidence of disease more than 2 and 4 years after surgery. The other two patients in this series both survived for approximately 3 years. The ideal timing and sequence of neoadjuvant and adjuvant therapy continue to be explored in multiple ongoing trials. Additionally, the idea of stratifying patients by node-positive disease may be an important component in choosing the type of adjuvant treatment. While the need for a multimodal approach to the treatment of gastric cancer has been well established, the optimal approach continues to be refined as new data become available.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare that they have no conflicts of interest concerning this article.

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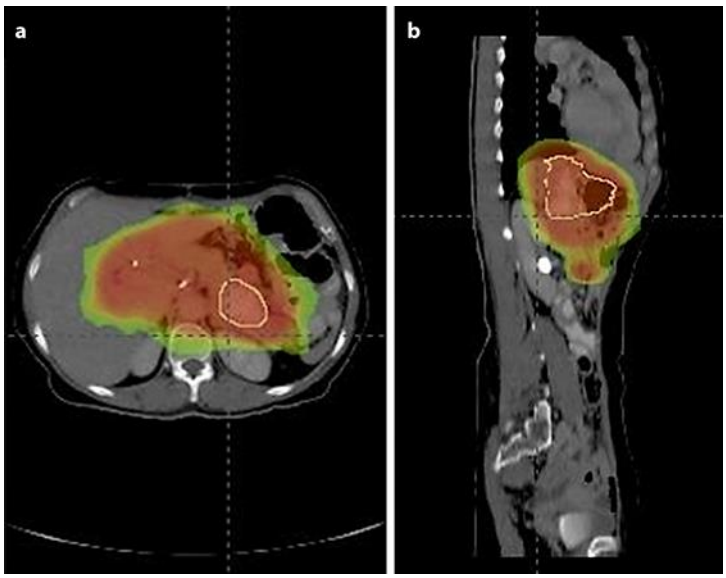

Fig. 1. Radiation dose distribution for patient 2 with stomach remnant outlined in yellow: axial view (**a**) and sagittal view (**b**). A total dose of 45 Gy was prescribed, shown in color wash to the 70% isodose surface (green), 90% isodose (red).

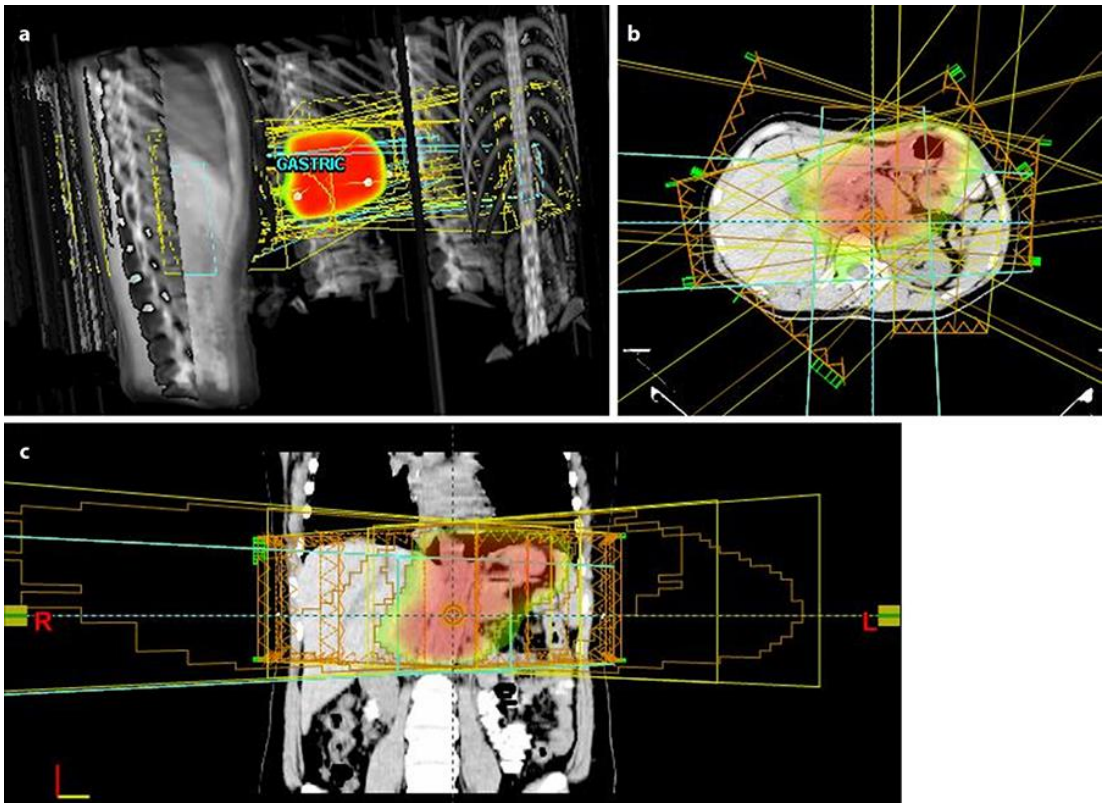

Fig. 2. Patient 3 radiation fields shown in three-dimensional view (**a**), axial view (**b**), and coronal view (**c**) color washed to the 70% isodose surface (green), 90% isodose (red).

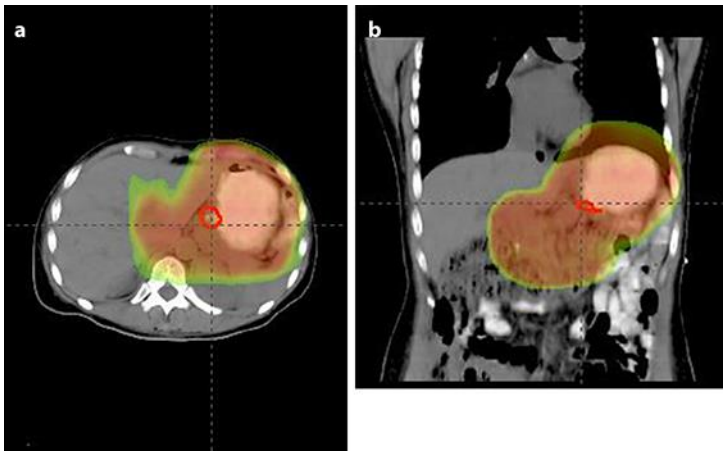

Fig. 3. Radiation dose distribution for patient 4 with gastrojejunal anastomosis outlined in red: axial view (**a**) and coronal view (**b**). A total dose of 45 Gy was prescribed, shown in color wash to the 70% isodose surface (green), 90% isodose (red).