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Clinical Investigation: Gastrointestinal Cancer

Intensity-Modulated Radiation Therapy With Concurrent Chemotherapy as Preoperative Treatment for Localized Gastric Adenocarcinoma

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Summary

This single-institution retrospective study evaluated preoperative IMRT with concurrent chemotherapy for gastric cancer, in patients treated with induction chemotherapy, chemoradiation and surgery. Preoperative IMRT was well tolerated, with grade 3 acute toxicity in 56% but grade 4 in none. There was, however, no significant difference when compared to patients treated with preoperative 3-D conformal RT and concurrent chemotherapy. Preoperative IMRT led to appropriate pathologic outcomes with R0 resection in 80% and

Purpose: The goal of this study was to evaluate dosimetric parameters, acute toxicity, pathologic response, and local control in patients treated with preoperative intensity-modulated radiation therapy (IMRT) and concurrent chemotherapy for localized gastric adenocarcinoma.

Methods: Between November 2007 and April 2010, 25 patients with localized gastric adenocarcinoma were treated with induction chemotherapy, followed by preoperative IMRT and concurrent chemotherapy and, finally, surgical resection. The median radiation therapy dose was 45 Gy. Concurrent chemotherapy was 5-fluorouracil and oxaliplatin in 18 patients, capecitabine in 3, and other regimens in 4. Subsequently, resection was performed with total gastrectomy in 13 patients, subtotal gastrectomy in 7, and other surgeries in 5.

Results: Target coverage, expressed as the ratio of the minimum dose received by 99% of the planning target volume to the prescribed dose, was a median of 0.97 (range, 0.92−1.01). The median V_{30} (percentage of volume receiving at least 30 Gy) for the liver was 26%; the median V_{20} (percentage of volume receiving at least 20 Gy) for the right and left kidneys was 14% and 24%, respectively; and the median V_{40} (percentage of volume receiving at least 40 Gy) for the heart was 18%. Grade 3 acute toxicity developed in 14 patients (56%), including dehydration in 10, nausea in 8, and anorexia in 5. Grade 4 acute toxicity did not develop in any patient. There were no significant differences in the rates of acute toxicity, hospitalization, or feeding tube use in comparison to those in a group of 50 patients treated with preoperative three-dimensional conformal radiation therapy with concurrent chemotherapy. R0 resection was obtained in 20 patients (80%), and pathologic complete response occurred in 5 (20%).

Conclusions: Preoperative IMRT for gastric adenocarcinoma was well tolerated, accomplished excellent target coverage and normal structure sparing, and led to appropriate pathologic outcomes.

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Introduction

According to the American Cancer Society, the incidence of gastric adenocarcinoma in the United States was an estimated 20,000 cases in 2010 (1). For localized gastric adenocarcinoma, the mainstay of management is surgical resection. However, even with curative resections, there is a relatively high rate of local recurrence (2–4). The addition of adjuvant chemoradiation has been shown to improve survival; the Intergroup 0116 trial showed an increase in median overall survival from 27 months to 36 months with the addition of postoperative chemoradiation over surgery alone (5). Compared with surgery alone, perioperative chemotherapy has also been shown to improve the 5-year survival rate from 23% to 36% (6).

A number of studies have also evaluated the role of preoperative chemoradiation for gastric cancer (7–9). Investigators at the MD Anderson Cancer Center conducted a trial on 41 patients who were treated with induction fluorouracil, paclitaxel, and cisplatin followed by radiation therapy with concurrent fluorouracil and paclitaxel (7). Patients had a pathologic complete response (pCR) rate of 20% and R0 resection rate of 78%. A multi-institution trial on 34 patients treated with induction fluorouracil, leucovorin, and cisplatin followed by radiation therapy with concurrent fluorouracil, showed a pCR rate of 30% and R0 resection rate of 70% (8). In the Radiation Therapy Oncology Group 9904 Phase II trial, 49 patients received induction fluorouracil, leucovorin, and cisplatin followed by radiation therapy with concurrent fluorouracil and paclitaxel; patients had a 26% pCR rate and 77% R0 resection rate (9). These trials have shown that preoperative chemoradiation is a potential treatment option for gastric cancer.

Radiation therapy to the abdomen can result in significant toxicities related to gastrointestinal mucosal exposure. For instance, in the Intergroup 0116 trial, 17% of the patients assigned to chemoradiotherapy stopped treatment because of toxicity from therapy (5). In addition, radiation therapy for gastric cancer may also affect normal structures such as the liver, kidneys, lungs, and heart, resulting in long-term toxicity. Therefore it is key to minimize dose to the surrounding structures to prevent acute and long-term sequelae of radiation therapy and compounded toxicity from chemoradiotherapy, all the while maintaining adequate coverage of the target. Target volumes and dose to normal tissue can potentially be reduced with preoperative radiation vs. postoperative radiation (10). Likewise, intensity-modulated radiation therapy (IMRT) can potentially reduce toxicity by reducing radiation exposure to adjacent normal structures. Previous studies have shown that for postoperative treatment of gastric cancer, IMRT reduces dose to adjacent organs such as the kidneys, spinal cord, and liver compared with three-dimensional (3D) conformal radiation therapy (CRT) (11–13). Although these studies have evaluated the role of IMRT for postoperative treatment, to our knowledge, the role of IMRT for preoperative treatment of gastric cancer has not been investigated previously.

The objective of this single-institution retrospective study was to evaluate preoperative IMRT with concurrent chemotherapy for gastric adenocarcinoma. Specifically, we evaluated dosimetric parameters, acute toxicity, pathologic response, local control, and survival in patients with localized disease undergoing preoperative chemoradiation.

Methods

Between November 2007 and April 2010, 27 patients with newly diagnosed localized gastric adenocarcinoma were treated with preoperative IMRT and concurrent chemotherapy, followed by surgical resection, at The University of Texas MD Anderson Cancer Center. Of these 27 patients, 2 were excluded: 1 patient who was also treated with radiation therapy for a synchronous primary malignancy and 1 patient who had a prior esophagectomy.

Patient and tumor characteristics

Patient and tumor characteristics are shown in Table 1. The median age at the time of diagnosis was 62 years. Pretreatment evaluation included esophagogastroduodenoscopy, endoscopic ultrasound, and computed tomography (CT) scans in all patients, as well as staging laparoscopy (with feeding jejunostomy tube placement) in 24 patients (96%). Tumor staging was established according to the 6th edition of the American Joint Committee on Cancer's staging handbook (14). The clinical T classification was T2 in 2 patients (8%), T3 in 21 (84%), and T4 in 2 (8%). The clinical N classification was N0 in 8 patients (32%), N1 in 13 (52%), N2 in 3 (12%), and NX in 1 (4%). The tumor location was at the gastroesophageal junction in 11 patients (44%), body in 5 (20%), antrum in 2 (8%), and both body and antrum in 7 (28%).

Treatment

Treatment characteristics are show in Table 1. All patients received induction chemotherapy; induction chemotherapy regimens comprised 5-fluorouracil (5-FU), oxaliplatin, and leucovorin in 17 patients (68%); docetaxel, 5-FU, and oxaliplatin in 4 (16%); and other regimens in 4 (16%). Concurrent chemotherapy was administered with 5-FU and oxaliplatin in 18 patients (72%), capecitabine in 3 (12%), docetaxel and 5-FU in 2 (8%), docetaxel and capecitabine in 1 (4%), and 5-FU and carboplatin in 1 (4%). Of the patients, 17 (68%) were treated as part of an institutional Phase II trial of preoperative 5-FU, oxaliplatin, and leucovorin, followed by radiation therapy with concurrent 5-FU and oxaliplatin. The remaining 8 patients were treated preoperatively based on institutional preference, with the induction and concurrent regimens selected by the treating medical oncologist.

All patients underwent CT simulation. The prescribed dose was 45 Gy in 23 patients (92%) and 50.4 Gy in 2 (8%), all given in 1.8-Gy fractions. The actual delivered dose was 43.2 Gy in 1 patient (4%), 45 Gy in 22 (88%), and 50.4 Gy in 2 (8%). All patients fasted for 3 hours before CT simulation and each treatment to account for variability in distention of the stomach with gastric filling. The gross tumor volume was delineated based on endoscopic and CT findings (Fig.). The clinical treatment volume included the gross tumor volume with a 3-cm mucosal expansion, involved nodes, and