Influence of Preoperative Radiation Field on Postoperative Leak Rates in Esophageal Cancer Patients after Trimodality Therapy

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Introduction: Postoperative morbidities, such as anastomotic leaks, are common after trimodality therapy (chemoradiation followed by surgery) for esophageal cancer. We investigated for factors associated with an increased incidence of anastomotic leaks.

Methods: Data from 285 esophageal cancer patients treated from 2000 to 2011 with trimodality therapy were analyzed. Anastomotic location relative to preoperative radiation field was assessed using postoperative computed tomographic imaging. Logistic regression was used to evaluate for factors associated with any or clinically relevant (CR) (≥ grade 2) leaks.

Results: Overall anastomotic leak rate was 11% (31 of 285), and CR leak rate was 6% (17 of 285). Multivariable analysis identified body mass index (odds ratio [OR], 1.09; 95% confidence interval [CI], 1.00–1.17; OR, 1.11, 95% CI, 1.01–1.22), three-field surgery (OR, 10.01; 95% CI, 3.83–26.21; OR, 4.83; 95% CI, 1.39–16.71), and within radiation field ("in-field") anastomosis (OR, 5.37; 95% CI, 2.21–13.04; OR, 8.63; 95% CI, 2.90–25.65) as independent predictors of both all grade and CR leaks, respectively. While patients with distal esophageal tumors and Ivor-Lewis surgery had the lowest incidence of all grade (6.5%) and CR leaks (4.2%), most of the leaks were associated with the anastomosis constructed within the field of radiation (in-field: 39% and 30% versus out-of-field: 2.6% and 1.0%, respectively, for total and CR leaks, p less than 0.0001, Fisher's exact test).

Conclusions: Esophagogastric anastomosis placed within the preoperative radiation field was a very strong predictor for anastomotic leaks in esophageal cancer patients treated with trimodality therapy, among other factors. Surgical planning should include a critical evaluation of the preoperative radiation fields to ensure proper anastomotic placement after chemoradiation therapy.

Key Words: Anastomotic leaks, Esophagectomy, Radiation, Esophageal cancer, Trimodality therapy.

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Surgical resection alone remains a worldwide standard for the management of esophageal cancer, but the 5-year survival usually does not exceed 20%.[1] Neoadjuvant chemoradiation before surgical resection (trimodality therapy) allows for disease downstaging and increases tumor resectability, with increased cure rates. Older randomized trials demonstrated probable survival benefit of preoperative chemoradiation although a number of negative studies made the indication controversial. A meta-analysis of the trials showed a 2-year overall survival benefit of 13% for patients treated with neoadjuvant chemoradiation followed by surgery compared with patients treated with surgery alone.[2] Recently, a large randomized trial demonstrated significant improvement in overall survival and disease-free survival with the use of neoadjuvant chemoradiation compared with surgery alone.[3] Chemoradiation before surgery improved median overall survival to 49.4 months compared with 24.0 months in patients treated with surgery alone.

However, preoperative chemoradiation increases the chance for toxicity and postoperative morbidity compared with surgery alone. There are several nonrandomized studies in the literature that showed an increase in surgical morbidity in patients undergoing neoadjuvant chemoradiation.[4–7] Postoperative pulmonary complications have been well studied and have been shown to be related to radiation dose to the lungs.[8]

The effects of neoadjuvant radiation on postoperative anastomotic leaks have been less extensively studied. In an older study, anastomotic leaks were found in 17% of patients who underwent esophagectomy with cervical anastomosis; however, the use of preoperative radiotherapy was not associated with the incidence of leaks.[9] A systematic review showed that reports in the literature for anastomotic leak rates vary between 0% and 26% and that the leak rate is not influenced by method of anastomosis, either stapled or hand-sewn.[10] A recent Belgian study with 54 patients treated with neoadjuvant

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radiation followed by Ivor-Lewis esophagectomy showed that the dose to the gastric fundus was a significant predictor for anastomotic complications (leakage, ischemia, and stenosis).[11]

The aim of the present study was to determine the clinical and dosimetric factors that can influence the risk of developing any grade leaks or the more clinically relevant leaks of ≥ grade 2 (or what we will term as "CR leaks" throughout the article) in patients undergoing trimodality therapy. Dose to the whole stomach and associated gastric substructures were studied as well as the impact of the positioning of radiation field and the location of the anastomotic site.

PATIENTS AND METHODS

Patient Data

This investigation was approved by the institutional review board and was conducted in compliance with the Health Insurance Portability and Accountability Act. This was a retrospective analysis of esophageal cancer patients treated at M. D. Anderson Cancer Center with neoadjuvant chemoradiation followed by surgery between 2000 and 2011. Because we wanted to evaluate the radiation dosimetry to the stomach, only patients with full dose-volume histogram data were included. Patients who had gastrectomy were excluded. We also included only patients treated with photon-based therapy (three-dimensional conformal radiation therapy [3D-CRT] or intensity-modulated radiation therapy [IMRT]).

A thorough chart review was done to document the clinical and treatment-related factors for this cohort of patients. Following surgery, follow-up monitoring included interval history and physical examination at the discretion of the treating physicians. Incidence of perioperative anastomotic leaks was recorded by grade for each patient, defined as radiographic leak only (grade 1), minimal intervention/stent placement (grade 2), major intervention/reoperation (grade 3), and conduit loss (grade 4). CR leaks were defined as leaks ≥ grade 2. Postsurgical computed tomography (CT) scans were examined to determine if surgical anastomosis was in or out of the radiation field. Contouring of the whole stomach, fundus, antrum, and lateral body was done by one person using the Pinnacle planning software. Associated 3D and IMRT treatment plans were used to generate dose-volume histograms for each of the contoured gastric regions of interest.

Treatment Approach

Patients in this study cohort were treated with neoadjuvant chemoradiation of 50.4 Gy at 1.8 Gy per fraction. Combinations of 5-fluorouracil and taxane, or with platinum-based compounds were administered concurrently with radiotherapy. Several weeks after completion of chemoradiation, most patients were restaged using CT, positron emission tomography/CT, or esophagoduodenoscopy (EGD) with biopsy of the primary disease site and evaluated for surgical management. The most common esophagectomy procedure was Ivor-Lewis, whereas a few patients also received transhiatal, left thoracotomy, radical (en block) resection, or minimally invasive esophagectomy.

The technique of 3D-CRT or IMRT was used for this patient cohort. The internal gross tumor volume was delineated based on the four-dimensional CT simulation images to account for tumor motion relative to diaphragmatic motion, fluorodeoxyglucose (FDG)-positron emission tomography/CT, and endoscopy results. The clinical target volume (CTV) included the internal gross tumor volume with a radial margin of 0.5 to 1 cm and a proximal and distal margin of 3 to 4 cm. Elective nodal regions were not covered, unless in the proximal locations where the supraclavicular fossa bilaterally were included in the target volume, and in the distal esophagus where the celiac axis was covered if it was involved. The nodal CTV was defined by 0.5 to 1 cm expansion from the nodal gross tumor volume. The planning target volume was the CTV plus a uniform 0.5-cm expansion margin.

Statistical Methods

Logistic modeling was used to assess associations between leak incidence and various continuous and categorical variables. The continuous variables studied were age, body mass index (BMI), tumor length, planning target volume, prescribed dose, and mean dose to whole stomach, lateral body, antrum, and fundus. Categorical variables studied were Karnofsky Performance Status, coronary artery disease history, diabetes history, smoking history, tumor location, presence of in-field anastomosis, radiation modality, use of induction chemotherapy, salvage surgery (defined as ≥90 days after chemoradiation), surgical margin status (R0 versus R1–2), and type of surgery (Ivor-Lewis, transhiatal, three-field, or hybrid). Logistic regression analysis was then used to perform multivariable analysis of factors that were significant ($p \leq 0.05$) on univariable analysis. The two-tailed Fisher's exact test was used to test the significance of proportions.

RESULTS

Patient Cohort

A total of 285 patients diagnosed with esophageal cancer and treated with neoadjuvant chemoradiation followed by esophagectomy were included in our analysis; 158 patients were treated with 3D-CRT and 127 were treated with IMRT. Concurrent chemotherapy was given to all patients during chemoradiation, and 151 patients were treated with induction chemotherapy before chemoradiation. Following radiation, the most common surgical procedure was Ivor-Lewis surgery ($n = 222$) followed by three-field and transhiatal surgery ($n = 31$ and 29, respectively). Three patients had hybrid open thoracotomy/laparoscopy resections. Nearly all of the patients had creation of a gastric conduit (97.9%, 279 of 285) with only five cases of jejunal interposition (for one case the origin of the conduit is not known). There was no association between leaks and jejunal interposition (3 of 5 had no leaks).

Factors Associated with Anastomotic Leaks

Overall, there were 14 grade 1, 8 grade 2, 8 grade 3, and 1 grade 4 leaks. Anastomotic leaks of any grade occurred in 31 patients for an overall incidence rate of 11%, and 17 patients (6%) had grade 2 or higher leaks. Table 1 shows patient and treatment-related characteristics that were associated with the

