Preoperative carboplatin and paclitaxel-based chemoradiotherapy for esophageal carcinoma: results of a modified CROSS regimen utilizing radiation doses greater than 41.4 Gy

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Summary. Trimodality therapy for resectable esophageal and gastroesophageal junction cancers utilizing preoperative radiotherapy with concurrent carboplatin and paclitaxel-based chemotherapy is being increasingly utilized secondary to the results of the phase III CROSS trial. However, there is a paucity of reports of this regimen as a component of chemoradiotherapy in North America. We aim to report on our clinical experience using a modified CROSS regimen with higher radiotherapy doses. Patients with advanced (cT2–cT4 or node positive) esophageal or gastroesophageal junction carcinoma who received preoperative carboplatin/paclitaxel-based chemoradiotherapy with radiation doses of greater than 41.4 Gray (Gy) followed by esophagectomy were identified from an institutional database. Patient, imaging, treatment, and tumor response characteristics were analyzed. Twenty-four patients were analyzed. All but one tumor had adenocarcinoma histology. The median radiation dose was 50.4 Gy. Pathologic complete response was achieved in 29% of patients, with all receiving 50.4 Gy. Three early postoperative deaths were seen, due in part to acute respiratory distress syndrome and all three patients received 50–50.4 Gy. With a median follow-up of 9.4 months (23 days–2 years), median survival was 24 months. Trimodality therapy utilizing concurrent carboplatin/paclitaxel with North American radiotherapy doses appeared to have similar pathologic complete response rates compared with the CROSS trial, but may be associated with higher toxicity. Although the sample size is small and further follow-up is necessary, radiation doses greater than 41.4 Gy may not be warranted secondary to a potentially increased risk of severe radiation-induced acute lung injury.

KEY WORDS: acute lung injury, chemoradiotherapy, esophageal neoplasms, neoadjuvant therapy.

INTRODUCTION

Worldwide, esophageal cancer is the sixth leading cause of cancer-related mortality.1 In the USA, adenocarcinoma histological subtype is most common because of higher rates of obesity and gastroesophageal reflux disease.2 The 5-year overall survival (OS) rates for locally advanced esophageal cancer remain poor. Treatment typically consists of multi-modality therapy including preoperative radiation and chemotherapy followed by surgery. Since Walsh and colleagues first published their results showing a survival benefit to preoperative chemoradiotherapy (CRT) over surgery alone,3 our institution has been utilizing preoperative CRT followed by minimally invasive esophagectomy for most patients with regionally advanced, surgically resectable, esophageal cancer.4

Extrapolating from the success of concurrent carboplatin and paclitaxel for non-small cell lung cancer,5,6 van Meeteren and colleagues showed the safety and efficacy of this concurrent chemotherapy
regimen for esophageal cancer. In a follow-up phase III randomized study of surgery with or without preoperative CRT with concurrent carboplatin and paclitaxel, the CROSS group reported an overall increase in median survival from 24 months after surgery alone to 49.4 months in patients receiving trimodality therapy. In the CROSS trial, preoperative radiation (RT) dose was 41.4 Gray (Gy) as compared with the North American standard of 50.4 Gy per the CALGB 9781 trial, which utilized concurrent cisplatin/5-FU.

At our institution, we have been treating patients with resectable regionally advanced esophageal or gastroesophageal junction (GEJ) cancers in a manner similar to the CROSS regimen as the tolerability of concurrent carboplatin and paclitaxel appeared to be superior to other concurrent chemotherapy regimens. However, we routinely utilize a more standard radiation dose of 50 or 50.4 Gy, as has been the clinical experience prior to the CROSS publication. Therefore, our specific aim was to analyze the outcomes of a modified CROSS regimen utilizing carboplatin and paclitaxel with a dose of 50 to 50.4 Gy, instead of 41.4 Gy as used in CROSS.

MATERIALS AND METHODS

Patient selection

Institutional Review Board approval was obtained prior to data collection (IRB# 1759). Patients with cT2–T4 or node-positive histologically confirmed adenocarcinoma or squamous cell carcinoma of the esophagus or GEJ (defined as no greater than 2 cm of gastric cardia involvement) who had their surgical portion of their trimodality treatment at our institution were included for retrospective analysis. Only patients without distant metastatic disease and who received preoperative CRT with concurrent carboplatin/paclitaxel and radiation doses greater than 41.4 Gy (either at our institution or closer to home) followed by esophagectomy at our institution were included for analysis. Patients were staged with preoperative imaging (positron emission tomography/computed tomography [PET/CT] and endoscopic ultrasound [EUS]). Following initial clinical staging, all patients were discussed at a multidisciplinary esophageal tumor board with treatment recommendations for preoperative CRT followed by esophagectomy approved by physicians within the specialties of surgical oncology, thoracic surgery, gastroenterology, radiation oncology, medical oncology, radiology, and pathology.

Treatment

All patients received preoperative CRT with weekly concurrent carboplatin/paclitaxel with adherence to the doses used in the CROSS trial. Radiotherapy consisted of conventional fractionation (1.8–2 Gy/day) intensity-modulated radiotherapy (IMRT) or three-dimensional conformal radiotherapy (3D-CRT) designed to include gross tumor and nodal disease as noted on staging imaging and EUS, subclinical paraesophageal and celiac axis lymph node involvement, all with a therapeutic margin. The majority of CRT was conducted at our institution; however, few patients elected to have preoperative treatment closer to home. Radiation fractionation and dosage schema were physician-dependent.

Following CRT, a repeat staging PET/CT was routinely obtained at 4–5 weeks to assess for treatment response and to ensure no metastatic disease was identifiable prior to esophagectomy. Surgery was ideally performed 6–8 weeks following the completion of CRT.

All esophagectomies were performed at our institution. An open esophagectomy was performed on one patient as originally described by Lewis with minor modifications while three-field minimally invasive esophagectomies were performed as previously described on the majority of patients. Briefly, thoracoscopic esophageal mobilization with en bloc lymphadenectomy of paraesophageal, subcarinal, and pulmonary ligament nodes was performed through the right side of the chest. The abdominal portion of the operation consisted of laparoscopic conduit preparation with en bloc upper abdominal central lymphadenectomy starting at the origin of the left gastric vessels. A left neck approach was performed and the conduit was brought up into the neck where an end-to-side stapled cervical esophagogastric anastomosis was created using a modification of the technique originally described by Orringer.

Data collection

All patient charts were reviewed retrospectively. Information obtained included: pertinent patient characteristics (performance status, demographic information, comorbidities), pretreatment tumor characteristics (histology, clinical staging, location of tumor, PET/CT maximum serial uptake values [maxSUWs]), treatment characteristics (CRT parameters, surgery performed, postoperative pathology), and post-treatment characteristics (length of hospital stay, postoperative complications, early postoperative deaths [<30 days]). Radiation treatment plans were reviewed retrospectively and normal tissue dose volume histogram (DVH) parameters recorded. Additionally, clinical follow-up with medical, radiation, or surgical oncology was reviewed and serial imaging reports examined for evidence of local or distant tumor recurrence, with date of death from all causes were recorded.
Statistical analysis

Simple descriptive analyses (mean, median, range, frequency, and relative frequency) were calculated for all patients. Kaplan–Meier survival analysis was performed utilizing SPSS Version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient and tumor characteristics

A total of 24 patients with histologically confirmed esophageal cancers diagnosed between December 2010 and September 2012 were included for analysis. Median follow-up in our cohort was 9.4 months (23 days–2 years). Demographics and pretreatment tumor characteristics are summarized in Table 1. The majority of the patients were male (83%) with a median age of 65 years. ECOG performance status ranged from 0 to 1. Tobacco use was common in our patient cohort, with 79% of patients reporting either current or former use. The majority of tumor histologies were adenocarcinoma, with only one patient having biopsy-proven squamous cell carcinoma. The majority of patients presented with cT3 tumors (80%) and/or cN1 disease (54%). Only one patient presented with cN2 disease.

Preoperative treatment characteristics and tumor response to therapy

Trimodality treatment characteristics are summarized in Table 2. Patients received a median number of 6 weeks of concurrent chemotherapy. The median RT dose was 50.4 Gy (2 patients received 54 Gy, 19 received 50.4 Gy, 2 received 50 Gy, and 1 received 45 Gy). RT fraction size was 1.8 Gy for all but two patients, each of who received 2 Gy fractions to 50 Gy total. CRT was well tolerated with a median weight loss of 7 lb (range: 0–39 lbs) and no patients required enterostomy tube placement while on treatment, although three patients had prophylactic enterostomy tubes placed prior to CRT. No Radiation Therapy Oncology Group (RTOG) grade 4 esophageal toxicities were observed. Two patients (8%) exhibited RTOG grade 3 esophageal toxicity, with severe dysphagia and odynophagia resulting in a greater than 15% weight reduction from baseline.

Surgical pathology and tumor response characteristics are summarized in Table 3. Average pre- and post-CRT maxSUVs were 11.4 (3.4–35) and 4.97 (2.7–7.9), respectively. An R0 resection was achieved in 88% of patients. Pathologic complete response (pCR) was achieved in 29% of patients, with all of these receiving a total dose of 50.4 Gy. Of the seven patients who received a total dose of 50.4 Gy, 8% had Grade 3 esophageal toxicity (RTOG), with severe dysphagia and odynophagia resulting in a greater than 15% weight reduction from baseline.

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<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics and tumor characteristics</th>
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<tbody>
<tr>
<td>n = 24</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>20 (83%) male</td>
</tr>
<tr>
<td>Median age</td>
<td>65 (44–76) years old</td>
</tr>
<tr>
<td>Pretreatment median weight</td>
<td>173 (117–242) lb</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>0 3 (13%), 1 21 (87%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Former</td>
<td>12 (50%), Current 7 (29%)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Coronary artery disease 8 (33%), Hypertension 12 (50%), Chronic kidney disease 2 (8%), COPD/OSA 3 (13%), Diabetes mellitus 3 (13%), History of Barrett’s esophagus 7 (29%), Clinical stage</td>
</tr>
<tr>
<td>cT Stage</td>
<td>T2 3 (13%), T3 19 (80%), T4 2 (7%)</td>
</tr>
<tr>
<td>cN stage</td>
<td>N0 10 (42%), N1 13 (54%), N2 1 (4%)</td>
</tr>
<tr>
<td>Tumor histology</td>
<td>Adenocarcinoma 23 (96%), Squamous cell carcinoma 1 (4%)</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>Well differentiated 0 (0%), Moderately-differentiated 24 (100%)</td>
</tr>
<tr>
<td>Histology subtype</td>
<td>Signet-ring 7 (29%), Gastroesophageal junction 17 (71%)</td>
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COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; OSA, obstructive sleep apnea.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Treatment and clinical parameters</th>
</tr>
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<tbody>
<tr>
<td>Carboplatin/paclitaxel</td>
<td>24 (100%)</td>
</tr>
<tr>
<td>Median number of weeks of chemotherapy</td>
<td>6</td>
</tr>
<tr>
<td>Radiation dose</td>
<td>5400 cGy 2 (8%), 5040 cGy 19 (80%), 5000 cGy 2 (8%), 4500 cGy 1 (4%)</td>
</tr>
<tr>
<td>Radiation dose per fraction</td>
<td>180 cGy 22 (92%), 200 cGy 2 (8%)</td>
</tr>
<tr>
<td>Radiation modality</td>
<td>IMRT 14 (58%), 3D conformal 10 (42%)</td>
</tr>
<tr>
<td>Esophagectomy procedure</td>
<td>Open Ivor-Lewis 1 (4%), Minimally invasive transthoracic 1 (4%), Minimally invasive three field 22 (92%)</td>
</tr>
<tr>
<td>Elapsed time (median days)</td>
<td>Diagnosis to end CRT 62.5 (46–91), Diagnosis to surgery 121 (100–272), CRT to surgery 59.5 (47–211)</td>
</tr>
</tbody>
</table>

†Received a total of 50 Gy. ‡Synchronous colon cancer resected same day per open laparotomy. §Diagnosis was defined by the date of endoscopic ultrasound. CRT, chemoradiotherapy; IMRT, intensity-modulated radiotherapy.
patients in our cohort that achieved a pCR, four had improvement of post-CRT PET maxSUVs as compared with pre-CRT, with maxSUV reductions ranging from 14.3 to 1.0. Additionally, one of seven patients had equivalent maxSUVs between pre- and post-CRT PET, and the remaining two patients exhibited increased maxSUVs on post-CRT PET.

**Morbidity, postoperative complications, and patient follow-up**

Median postoperative hospital stay was 10 days (8–28 days). Three patients died prior to hospital discharge following minimally invasive esophagectomy. All three acquired acute respiratory distress syndrome (ARDS) and all received 50–50.4 Gy of preoperative RT. Mean total lung radiation doses, and volume of the total lung receiving 20 Gy (V20), 10 Gy (V10), and 5 Gy (V5) of radiation in addition to the volume of lung spared doses of 5 Gy or more (VS5) for the entire cohort are listed in Table 4. None of the three early postoperative deaths had comorbid lung disease (chronic obstructive pulmonary disease or obstructive sleep apnea); however, two of the three patients were either current or former smokers. Additionally, two of the three patients were treated with an IMRT plan, while the third was treated with a 3D-CRT plan. Median survival for the entire cohort was 24 months with a median follow-up of 9.4 months. At the time of analysis, 15 patients were still alive, with seven of these patients free of disease on surveillance imaging.

**DISCUSSION**

Trimodality therapy has rapidly become the standard of care for resectable esophageal
A 2007 meta-analysis of randomized studies published prior to the CROSS results has shown a 2-year OS benefit of 13% for combined preoperative therapy compared with surgery alone. However, the traditional North American chemoradiation regimen of cisplatin and 5-FU is poorly tolerated secondary to moderate to severe gastrointestinal and hematologic toxicities. More recently, the CROSS investigators have introduced concurrent weekly carboplatin/paclitaxel as an alternative concurrent chemoradiation regimen with favorable toxicity and patient outcomes.

We have been treating locally advanced esophageal cancer patients in a manner similar to the CROSS regimen. However, in our study, patients received a median radiation dose of 50.4 Gy as compared with the 41.4 Gy used in the CROSS regimen. In addition, our standard radiation fields encompassed the celiac lymph node regions, while these were excluded in the CROSS trial. Our overall pCR rate of 29% was very comparable with that of the CROSS regimen, which was 29% for all histological types and 23% for adenocarcinoma subtype only. Of the seven patients in our cohort that achieved a pCR, four had improvement of post-CRT PET maxSUVs as compared with pre-CRT, one patient had equivalent maxSUVs between pre- and post-CRT PET, and the remaining two patients exhibited increased maxSUVs on post-CRT PET. In a retrospective analysis of over 200 patients undergoing trimodality therapy for gastroesophageal cancers who received PET/CT and endoscopy before and after CRT, the specificity of a clinical complete response for pCR was very low at 28%. Our findings are consistent with this study and suggest that a radiographic/metabolic response has a poor association with pCR.

Worldwide, different CRT regimens are currently in use based on multiple experiences and no clear consensus. A marked difference between our study and the CROSS regimen is seen in the utilization of higher RT doses, with the majority of patients receiving 50.4 Gy as compared with 41.4 Gy per the CROSS regimen. In North America, traditional preoperative CRT regimens consist of concurrent cisplatin and 5-FU with RT to 50.4 Gy as per CALGB 9781. In CALGB 9781, occurrences of grade 3 or higher toxicities (neutropenia, esophagitis, pain) were quite high with one postoperative death. In comparison, the CROSS regimen appeared to be much better tolerated with comparatively lower grade 3 or higher toxicities, albeit with slightly higher postoperative mortality (4% in the CRT arm). Multiple retrospective analyses comparing the CALGB approach and the CROSS approach have concluded that the CROSS regimen appears to have less toxicity with nonsignificant differences in response rates and long-term survival.

In our cohort of patients who all received esophagectomy, preoperative CRT consisted of a combination of the CALGB and CROSS regimens utilizing the better tolerated chemotherapy of carboplatin/paclitaxel and a higher dose RT. Esophageal radiation dose escalation has been studied previously in a phase III study, albeit to a much higher dose (high-dose arm: 64.8 Gy, standard-dose arm: 50.4 Gy) with more toxic concurrent chemotherapy (cisplatin and 5-FU). Minsky and colleagues showed no difference in OS or locoregional failure with increased treatment-related deaths in the high-dose arm. Interestingly, 7 of the 11 treatment-related deaths in the high-dose arm occurred at radiation doses of less than 50.4 Gy.

A smaller retrospective analysis by Platz and colleagues of 16 patients receiving concurrent carboplatin/paclitaxel and 50.4 Gy of radiation has shown similar rates of pCR as compared with the CROSS regimen including a 100% R0 resection rate and no postoperative deaths. Our results are comparable with Platz and colleagues with similar pCR and R0 resection rates. However, one gross difference is our early postoperative mortality rate of 12.5% (three patients), which is greater than the CRT arm of the CROSS study.

In our cohort, all in-hospital deaths suffered from a complicated postoperative course that prompted further investigation. All three patients had ARDS requiring mechanical ventilation among many other medical and surgical ailments including sepsis, enterostomy tube complications, ischemic colitis, and cardiac arrhythmias. Preoperative radiation dose was 50–50.4 Gy for all of these patients, with two of three receiving IMRT. It is well known that thoracic irradiation can cause acute lung injury. The absolute volume of total lung spared from radiation doses of greater than 5 Gy (V5) has been shown previously to be strongly associated with postoperative complications in esophageal cancer patients receiving preoperative CRT. Collectively, patients with small lung volumes may be at greater risk for developing pulmonary complications even with a relatively low V5. No specific cutoff has been established, but Wang and colleagues have fitted a logistic model to their data estimating the incidence of pulmonary complications versus total lung V5. Using this model, in the three postoperative deaths from ARDS in our cohort, their preoperative risk of pulmonary complications following esophagectomy ranged from 10% to 50%. Additionally, the CROSS study utilized only 3D-CRT techniques including a simple anterior-posterior/posterior-anterior treatment field, which in turn greatly reduces total lung V5 in exchange for greater heart dose. The relatively greater pulmonary toxicities exhibited in our study may be related to the increased use of IMRT with inadvertently higher total lung V5s and smaller V5s.
There are a number of limitations to our study. First, a small sample size and short interval follow-up limits the interpretation of results. However, given that all patients received surgical resection at a tertiary academic center under the direction of a multidisciplinary upper foregut malignancy program, the 12.5% postoperative mortality rate is concerning. Given that we have shown comparable pCR and R0 resection rates as the CROSS study, dose escalation above 41.4 Gy to 50.4 Gy with concurrent CRT may be deleterious in patients with unfavorable DVH parameters. Two of our patients had cT4 tumors, which were excluded in the CROSS trial; however, neither one of these patients experienced an early postoperative death, although increased subacute postoperative toxicity in these two patients may have negatively affected our reported OS. Finally, two of the three patients who underwent an early postoperative death received preoperative CRT closer to home, outside of the discretion of our multidisciplinary program. One wonders if their complicated postoperative course could have been prevented if they had received all aspects of their trimodality therapy at one institution. Nevertheless, longer term follow-up will be warranted to elucidate locoregional control patterns, late-term toxicities, and OS.

Finally, a randomized trial of 41.4 Gy versus 50.4 Gy with carboplatin and paclitaxel is needed to determine the benefits/detriments of a 20% dose increase. Only a randomized trial meticulously executed with excellent radiotherapy quality assurance may answer this question. Our data supports a lower dose of radiation; however, until further studies are published, physicians need to use their judgment to determine the dose based on patient’s comorbidities, tumor characteristics, and detailed knowledge of DVH parameters, and how they are associated with pulmonary toxicity with the understanding that doses above 41.4 Gy may be deleterious.

References

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