Short Communication

Stop hedging your bets: reasons for non-adherence to a tri-modality regimen in the treatment of esophageal cancer in a multidisciplinary setting

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Background: In locally-advanced esophageal cancer (LAEC), providers' concerns regarding eventual surgical candidacy can persuade physicians to defer to definitive doses of 50 Gy or higher preoperatively. We report the successful completion rate of tri-modality therapy (TMT) (documented at the outset) and reasons for TMT non-adherence at a large multi-disciplinary esophageal program.

Methods: LAEC patients diagnosed 2007–2016 from a prospective institutional database were subdivided into CRT/S+ [completed chemoradiation (CRT) and surgery] and CRT/S- (CRT and no subsequent surgery) groups. Chart review provided surgery non-adherence reasons.

Results: A total of 283 patients met planned TMT criteria: 164 (58.0%) patients received 50 or 50.4 Gy CRT, 27 patients (9.5%) received greater than 50.4 Gy, and 92 patients received less than 50 Gy (32.5%, only 8 patients received CRT to 41.4 Gy); 221 (78.1%) completed surgery (CRT/S+), while 62 (21.9%) failed to advance to surgery (CRT/S-): 25 of 62 CRT/S- patients (40.3%) evidenced metastatic progression before surgery, 4 (6.5%) were deemed unresectable intraoperatively, 4 (6.5%) expired prior to planned surgery (3 from unknown causes, 1 suicide), 8 (12.9%) experienced significant CRT-related medical decompensation and were withdrawn from surgical consideration, 16 (25.8%) voluntarily declined surgery post-CRT (largely due to long-term quality of life concerns), and 5 (8.1%) failed to advance for unknown reasons. Four of the 16 patients who voluntarily declined surgery after CRT received less than 50 Gy. The 22.2% of CRT/S+ patients achieved pathologic complete response (21.6% for adenocarcinoma and 29.0% for squamous cell carcinoma).

Conclusions: Our institution's 78% surgery completion rate among TMT-indicated patients highlights the benefits of upfront multidisciplinary care. Metastatic disease development most commonly truncated TMT with a low rate failing due to medical decompensation. Given the number of patients who voluntarily declined surgery following CRT, TMT counseling and involvement of a patient advocate are paramount prior to treatment planning.

Keywords: Esophagectomy; neoadjuvant chemoradiation; esophageal cancer

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Introduction

Outcomes for patients treated for esophageal cancer have improved in the current era of multi-modality therapy. However, nearly 17,000 Americans will be diagnosed with esophageal cancer in 2018, and a nearly equivalent number will succumb to the disease (1). For locally-advanced esophageal cancer (LAEC), tri-modality therapy (TMT) consisting of chemoradiation (CRT) and esophagectomy remains the standard-of-care in North America (2,3). However, many radiation oncologists have concerns regarding eventual surgical candidacy following neoadjuvant therapy, potentially influencing radiation dose decision making. Consequently, some recommend a modified CROSS regimen (4) consisting of 50 Gy or higher definitive radiation doses with concurrent carboplatin/paclitaxel rather than risking the possibility of no surgery taking place for a patient who had received only a "neoadjuvant" radiation dose (41.4 Gy) per the published CROSS regimen (3,5).

Outside of prospective randomized trials, the course of post-neoadjuvant therapy for patients with LAEC has not been reported. Such information would be of considerable benefit to better aide radiation oncologist behavior in determining an appropriate dose prescription. To this end, we aimed to examine the rate of TMT and reasons for non-adherence to TMT in patients treated at a large multidisciplinary esophageal program.

Methods

From 2007 to 2016, we identified LAEC patients diagnosed from a prospective institutional database. Patients indicated for TMT (documentation of planned TMT at the outset in either tumor board or consultation notes) were divided into CRT/S+ (documentation of completed surgery) and CRT/S- (no subsequent surgery) groups. Detailed chart review provided TMT non-adherence reasons.

Results

We identified 283 patients with documentation of planned TMT prior to CRT. Of the TMT-indicated patients, 221 (78.1%) completed surgery after CRT (CRT/S+), while 62 (21.9%) failed to advance to surgery (CRT/S-) (*Figure 1*). A total of 164 (58.0%) patients received 50 or 50.4 Gy CRT, greater than 50.4 Gy for 27 (9.5%), and less than 50 Gy for 92 (32.5%, only 8 patients received RT to 41.4 Gy). Concurrent chemotherapy largely consisted of cisplatin/5FU (predominating pre-CROSS trial therapy) or carboplatin/paclitaxel (post-CROSS trial therapy).

Twenty-five of 62 CRT/S- patients (40.3%) had evidence of metastatic progression following CRT (20 identified on imaging, 5 identified intraoperatively), 4 (6.5%) were unresectable intraoperatively, 4 (6.5%) expired prior to planned surgery (3 from unknown causes, 1 committed suicide), 8 (12.9%) experienced significant medical decompensation from CRT and were no longer surgical candidates, 16 (25.8%) voluntarily declined surgery following CRT (largely due to the concerns of long-term quality of life) and 5 (8.1%) failed to advance to surgery for unknown reasons (*Figure 1*). Four of the 16 patients who voluntarily declined surgery after CRT received RT doses of less than 50 Gy.

CRT/S+ patients demonstrated a 21.8% pathologic complete response rate (20.3% for adenocarcinoma and 29.0% for squamous cell carcinoma). In total, 157 (90.8%) of 173 patients without pathologic complete responses had no tumor at the resection margins (R0).

Discussion

Our institution's 78% surgery completion rate among TMT patients highlights the benefits of upfront multi-disciplinary care (6). In addition, we are increasingly utilizing the published CROSS regimen RT doses for surgical candidates. We present every esophageal cancer patient seen by our providers, regardless of stage, at our bi-weekly multidisciplinary Esophageal Care Conference in a prospective manner. Our upper foregut surgical team uses a consistent methodology regarding surgical candidacy. Creating clarity between oncologists, our group is almost always aware of a patient's eventual surgical candidacy prior to initiating neoadjuvant therapy. This essential multidisciplinary approach allows for the prescription of shorter and more tolerable neoadjuvant regimens.

Our rate of completion of TMT was lower than that of the randomized CROSS trial, where 161 of 171 (94.2%) patients who completed CRT eventually underwent resection. However, the CROSS protocol did not require re-staging imaging, whereas our practice does so routinely per National Comprehensive Cancer Network guidelines. We identified 25 patients in our cohort with metastatic disease immediately prior to surgery. This supports the use of lower pre-operative radiation doses as higher definitive doses will have no bearing on disease outcome for this unfortunate subset of patients.

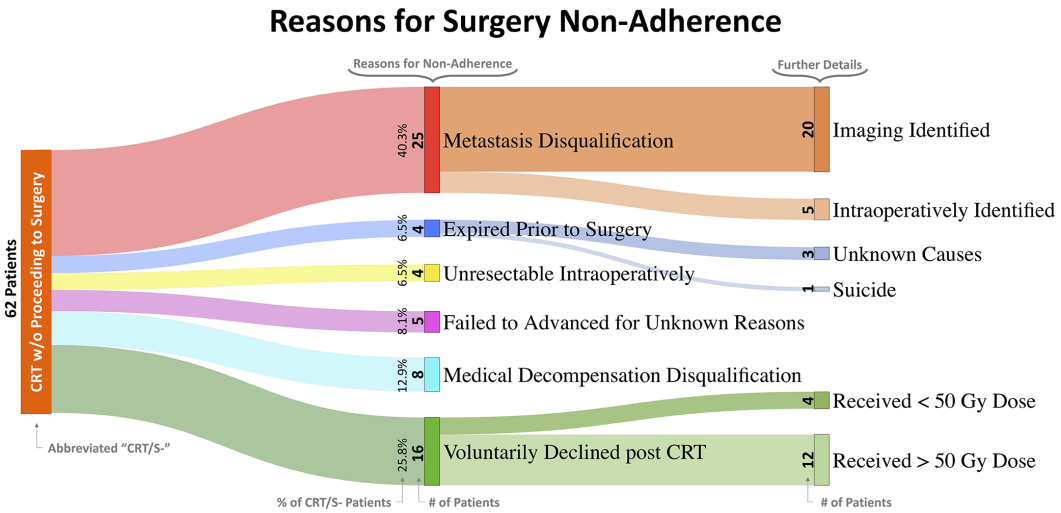

Figure 1 Reasons for surgery non-adherence following CRT. CRT, chemoradiation.

Possibly, the only patients who may have benefited from definitive doses of radiation in our cohort were those who medically decompensated following CRT thereby negating any further surgical interventions or those who voluntarily declined surgery after CRT, representing 24 out of 283 patients (8.5%). Additionally, only 2.8% (8 of 283) failed to advance to surgery due to documented medical decompensation. Of these 8 patients, four received RT doses of 50 Gy or higher. It remains unknown whether non-definitive doses (<50 Gy) would've mitigated the medical decompensation to further allow surgical resection.

Furthermore, despite early engagement of the surgery team, 16 (6%) patients declined esophagectomy voluntarily following CRT. Most cited quality of life concerns. Four of these patients potentially received under-treatment due to delivery of neoadjuvant doses of radiation. These patients possibly felt overwhelmed shortly after diagnosis and only fully processed the ramification of TMT during the course of neoadjuvant therapy. We have not formally assessed whether patients harbor decision regret. To further provide early assistance, patient support groups can provide social and cultural support, assisting patients in surgical decision making prior to neoadjuvant therapy initiation. At our institution, CP, a retired general surgeon, patient advocate, and longtime survivor of TMT for LAEC attends all multidisciplinary tumor conferences. This person makes himself available both in-person and by-phone to patients and caregivers alike who embark on TMT. Frequently, patients appreciate the presence of someone who underwent their journey and now lives a fruitful and normal life.

Minimizing overall radiation dose delivered to the thorax during neoadjuvant CRT undoubtedly reduces toxicity, as mean lung radiation doses have been strongly associated with pulmonary complications post-operatively (7) and increased cardiac radiation doses may portend to ischemia (8), pericardial effusions (9) and resultant detriment to overall survival (10). Surveying 274 radiation oncologists, the majority of respondents believed that 50.4 Gy would yield a higher pathologic complete response (pCR) rate (236, 86%) and increased R0 resection rates (185, 68%) despite greater toxicity (147, 54%) than 41.4 Gy (5). In our study, CRT/S+ patients who received doses of 50 Gy or greater did not see quantitative improvements of pCR and R0 rates compared to the published CROSS trial. This finding is in line with a negative esophageal RT dose-escalation study (11) and a large National Cancer Database analysis which found no survival benefit to neoadjuvant RT above the CROSS regimen (12). Strengths of this present analysis include the large sample size and comprehensive assessment of reasons of failing to advance to surgery. This study is limited by the relatively small number of patients receiving the published CROSS regimen, interfering with statistical comparisons of dose prescriptions.

In summary, a 78% surgery completion rate among TMT patients highlights the benefits of upfront multidisciplinary care. As nearly 25% of our CRT/S- patients declined esophagectomy voluntarily, thorough surgical counseling, patient advocacy, and patient education prior to CRT is essential to avoid under-treatment. For our CRT/S+ patients, pCR and R0 resection rates did not quantitatively

improve over the published CROSS trial. In the absence of a demonstration of superiority of radiation doses greater than 41.4 Gy, the robust CROSS regimen should be the standard of care in managing esophageal TMT patients, especially if evaluated upfront in a multidisciplinary setting.

Acknowledgements

None.

Footnote

Conflicts of Interest: Previous presentation: digital poster presentation at ASTRO Annual Meeting 2018 in San Antonio, TX, USA.

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