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Timing of esophagectomy after neoadjuvant chemoradiation treatment in squamous cell carcinoma ☆

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ABSTRACT

Background: Time interval between neoadjuvant (combined) chemotherapy and radiation (nCRT) and surgery has been linked to pathologic response rates and outcomes in patients with various solid cancers. The optimal timing between nCRT and esophagectomy in patients with esophageal squamous cell carcinoma (SCC), however, is not known. Our aim was to analyze the relation between elapsed time from completion of nCRT to esophagectomy and postsurgical mortality and overall survival.

Methods: We reviewed the National Cancer Database for patients with SCC ($n = 1,244$) of the esophagus diagnosed between 2003 and 2011 who were treated with nCRT followed by esophagectomy within 26 weeks after completion of nCRT.

Results: Thirty-day mortality was 5.6% and 90-day mortality was 11.1%. The duration of post-nCRT interval was not a predictor of 30-day and 90-day postoperative mortality in multivariate models, but 30-day postoperative mortality was predictable based on increasing Charlson-Deyo comorbidities (adjusted odds ratio [aOR] 1.77, $P = .054$) and improved in academic institutions (aOR 0.66, $P = .005$). Similar findings were found for 90-day mortality (comorbidity index aOR 1.58, $P = .046$) and for treatment at an academic facility (0.82, $P = .062$). In a multivariate survival analysis, the duration of the post-nCRT interval was not found to be a predictor of overall survival ($P = .769$), whereas increasing age (hazard ratio [HR] 1.02, $P = .005$), increasing comorbidity score (HR 1.38, $P = .005$), treatment at an academic hospital (HR 0.84, $P = .001$), and post-treatment nodal status (HR 1.73, $P < .001$) were predictors.

Conclusion: Perioperative mortality and overall survival are not affected by the time interval between completion of nCRT and esophagectomy among patients with SCC histology.

Introduction

Trimodality therapy with neoadjuvant chemoradiation (nCRT) followed by esophagectomy has emerged as the standard of care for management of locally advanced esophageal carcinoma.[1–4] The timing of esophageal resection after nCRT may influence pathologic complete response rates, circumferential margin status, and possibly overall survival.[5,6] Our group and others have found previously that earlier rather than later esophagectomy is associated with better perioperative mortality and overall survival, yet causality versus a simple correlation of this relationship remains unknown.[6]

There is a paucity of studies focusing on the dominant individual histologic classifications of esophageal cancer (squamous cell carcinoma [SCC] and adenocarcinoma), and the preponderance of literature examines the disease in aggregate. Contrary to the case in adenocarcinoma, the role of esophagectomy after nCRT for SCC has been questioned by 2 remarkable randomized trials, where similar survival was reported for those treated with definitive CRT as opposed to trimodality treatment of esophageal SCC.[7,8] Avoidance of esophagectomy, although not a subject of the present manuscript and not yet proven to be an accepted treatment modality, remains an attractive research topic because it avoids the considerable morbidity (17%–48%) of an esophagectomy.[9]

The CROSS (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery) study resulted in a paradigm shift in the management of esophageal cancer by showing a dramatic survival benefit of preoperative nCRT followed by esophagectomy 4 to 6 weeks later with a median overall survival 49.4 months vs 24 months, respectively.[1] Notably, only a quarter of enrolled patients on CROSS had SCC.[1] Also, whereas prior randomized trials generally required that esophagectomy be performed within 2 to 8 weeks of completing CRT, existing guidelines of the National Comprehensive Cancer

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Network and Society of Thoracic Surgeons do not address optimal timing of esophagectomy after nCRT. Wang et al[10] reported that 30- and 90-day operative mortality and the rate of a pathologic complete response (pCR) were best in the group of patients who waited 60 to 90 days after completion of nCRT, with those treated within 30 days after neoadjuvant therapy suffering disproportionately greater perioperative mortality. Shaikh et al[11] also found that patients waiting longer than 64 days had a 40% pCR, where the response in SCC tended to be better versus adenocarcinoma.

No influence of the post-nCRT interval before esophagectomy on perioperative mortality and overall survival was found in some high-quality, retrospective institutional studies.[12,13] Yet some studies reported improved survival with a greater post-nCRT interval,[14] whereas others suggested the contrary conclusion, especially in patients who have a good response to nCRT.[10,15]

Given the mixed data in the literature and our own prior report of the timing of esophagectomy in adenocarcinoma, we sought to determine if delaying esophagectomy after nCRT in patients with SCC of the esophagus resulted in improved pCR, 30-day and 90-day mortality, and overall survival.

Methods

A retrospective review of the cases of invasive squamous cell carcinoma of middle and distal esophagus in the National Cancer Database (NCDB) was performed as provided by the NCDB Participant User File—December 2014 release. The NCDB is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. The NCDB is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that captures about 70% of all newly diagnosed malignancies in the United States annually. Patients diagnosed in 2003–2011 and with a single lifetime incidence of cancer who underwent nCRT and then underwent esophagectomy less than 26 weeks after completion of nCRT were identified.

Primary endpoints were 30- and 90-day mortality and overall survival (available for cases diagnosed until 2011). The follow-up was complete as of 2013. Secondary objectives included rates of ypT0, ypN0, and margin-negative resections.

Regression models were built using a backward elimination method with inclusion probability of $P = .2$ with each initial full model, including all independent variables: median income, weeks delay after nCRT, presence of insurance, race, distance to facility, sex, analytic stage, radiation dose, pathologic nodal status, rural versus urban, age, facility type, and Charlson-Deyo Comorbidity Score.

Clinical stage was provided by the NCDB coded with respective staging edition. We have converted this variable to a collapsed American Joint Committee on Cancer seventh edition staging (eg, stages IA and IB are designated as stage I). *Clinical nodal status* was analyzed as a dichotomized variable (cN0 versus cN+).

Time elapsed between completion of nCRT and esophagectomy was designated as *post-nCRT interval* as described previously.[5] This interval is not directly provided by the NCDB in compliance with the US federal privacy regulations. For patients of interest in this study (nCRT cases only), one can calculate post-nCRT interval $= E_{days} - (RT_{days} + RT_{duration})$, where E_{days} represents number of elapsed days until definitive esophagectomy from case reference day, RT_{days} represents radiation therapy commencement since reference date, and $RT_{duration}$ represents duration of radiation therapy. The post-nCRT *interval* variable was calculated with a precision to a single day, converted to weeks for the purpose of this study, and evaluated as a categorical variable in quartiles divided at several clinically meaningful cutoff levels: 5 weeks (approximately 25th percentile), 7 weeks (50th percentile), and 9 weeks (75th percentile). We limited the scope of this study to those who received esophagectomy within 26 weeks (approximately 6 months) of completion of the nCRT to help filter out patients whose initial treatment intention might have been definitive chemoradiation but who were directed later to salvage esophagectomy.

Continuous variables were tested using analysis of variance with Bonferroni correction when applicable. Proportions were compared using Pearson χ^2 test, and their trends were evaluated by Cuzick nonparametric trend test. Logistic regression models were used to analyze binary outcomes, and goodness of fit was assessed by Pearson test, Fisher exact test, and Hosmer-Lemeshow χ^2 test. Survival was assessed by Kaplan-Meier estimates. We used Stata statistical software Version 10 (Stata Corporation, College Station, TX) for statistical analysis.

Results

There were 1,244 patients available for analysis. The majority were men ($n = 810$; 65%), with a male-to-female ratio of 1.9:1. The average post-nCRT interval until esophagectomy was 8.0 ± 3.8 weeks (median 7.3 weeks; interquartile range 5.7–9.5 weeks). In all, 472 (38%) patients had an esophagectomy after 8 weeks (but before 26 weeks) after completion of the nCRT. Demographics and characteristics of staging and treatment characteristics are outlined in Tables I and II.

All patients received concurrent nCRT. Average time from diagnosis to initiation of chemotherapy was 37 ± 27 days (median 33), and average time to initiation of radiotherapy was 39 ± 25 days (median 34). Radiation dosing reports were available for 1,121 patients (90% of all cases; median dose was 4500 cGy; interquartile range 4,400–5,040 cGy). A dose of 4140 cGy was reported for 47 patients (3.7%), a dose of 4,500 cGy was reported for 356 patients (28.6%), and 345 patients (27.7%) received 5,040 cGy; the remainder received other doses.

Effect on ypT0, ypN0, and resection margin status

We analyzed ypT status variable dichotomized to ypT0 versus ypT+. The proportion of primary pCR increased with a greater waiting time period (Table II). In total, there were 315 ypT0 patients (36.2%) among those with known ypT status.

We analyzed ypN status also dichotomized to ypN0 versus ypN+. In all, ypN0 status was found in 667 cases (72.8%, excluding missing cases; Table II). Resection margin was originally reported by the NCDB as R0, R1, and R2. We collapsed R1 and R2 categories to an R+ category. A negative resection margin was reported in 93% of cases. No trend was observed based on duration of post-CRT delay for ypN and resection status (Table II).

Effect on perioperative mortality

Thirty-day mortality was 5.6% ($n = 61$), and 90-day mortality was 11.1% ($n = 119$, Table I). Odds of both 30-day and 90-day mortality were unaffected with increasing the post-nCRT interval (Tables III and IV).

Effect on overall survival

We analyzed the effects of post-nCRT interval on overall survival (Table IV and Fig. 1). Median follow-up for survivors was 44.4 months after diagnosis (interquartile range 27–75 months). Overall median survival was 35.2 months since diagnosis (95% confidence interval 32–34.7 months), and 5-year survival rate was 37.1%. Median survival was 35.6, 30.7, 46.0, and 30.8 months for those with post-nCRT intervals <5 weeks, ≥5 and <7 weeks, ≥7 and <9 weeks, and ≥9 weeks, respectively. Corresponding 5-year overall survival rates were 32.3% (95% confidence interval 25.2–39.6), 37.6% (31.4–43.7), 43.6% (37.0–50.1), 34.1% (27.9–40.3), respectively.

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