Preoperative Chemoradiation Therapy vs Chemotherapy in Patients Undergoing Modified En Bloc Esophagectomy for Locally Advanced Esophageal Adenocarcinoma: Is Radiotherapy Beneficial?

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Background. **Preoperative chemotherapy (ChT) or chemoradiation (ChRT) are associated with improved outcomes compared with up-front surgical resection in patients with locally advanced esophageal adenocarcinoma (EAC). Two randomized controlled trials comparing these therapies included nonradical resection and failed to reach significance. We hypothesized that additional regional radiotherapy does not benefit patients undergoing en bloc resection.**

Methods. **We performed a multiinstitutional study using three prospectively entered databases from high-volume esophageal centers. Inclusion criteria were patients with EAC treated with preoperative ChT or ChRT, followed by modified en bloc esophagectomy. To minimize issues of stage migration and heterogeneity, we limited the study to patients with cT3 N1 M0 EAC. Survival was assessed by the Kaplan-Meier method, and step-wise multivariable analyses were used to explore variables independently associated with survival outcomes. Radical resections included two- and three-field lymphadenectomies, dependent solely on surgeon/institutional preference.**

Results. **We identified 214 patients with cT3 N1 disease, of which 114 underwent preoperative ChT vs 100 who underwent ChRT. Median survival was 31.2 months (95% confidence interval, 20.7 to 41.7 months) for the ChT group vs 39.2 months (95% confidence interval, 27.3 to 51.0 months) for the ChRT group ($p = 0.665$). Mortality at 90 days was 5.3% for ChT vs 4% for ChRT ($p = 0.754$). No differences were noted between patterns of locoregional and distant recurrence between both groups. There were no significant differences in major postoperative morbidity between both groups.**

Conclusions. **Given a modified en bloc esophagectomy, type of preoperative therapy was not a significant determinant of overall survival or disease-free survival. Although preoperative ChRT did not add perioperative risk, it also did not prolong survival. The role of preoperative radiotherapy in the setting of a planned radical resection should be further evaluated.**

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Esophageal adenocarcinoma (EAC) has become the most common histologic subtype in the Western world, and its incidence is rising faster than any other malignancy in North America [1, 2]. Most patients present with locally advanced disease due to the late occurrence of symptoms and the propensity of this malignancy for early nodal metastasis [3]. The clinical management of esophageal cancer has evolved tremendously during the past 20 years. Staging and treatment paradigms have both shifted greatly with the introduction of endoscopic ultrasound, positron emission tomography scans, and preoperative adjuvant treatment modalities. At present, the ideal therapeutic regimen remains as a source of controversy, and despite our best efforts [4], accurate staging remains elusive in a high proportion of patients [5]. What is clear, however, is that multimodal therapy has become the preferred method of treatment for locally advanced tumors based on the outcomes of recent randomized trials [4].

Two randomized controlled trials have attempted to compare preoperative chemoradiation therapy (ChRT) vs chemotherapy (ChT) alone in esophageal cancer [5, 6]. Neither trial reached its end point due to lack of accrual. Both studies were criticized on a number of aspects. Stahl

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and colleagues [5] found that ChRT trended toward superiority compared with ChT alone (5-year survival: 27.7% vs 47.4%, $p = 0.07$). However, operative mortality was 2.5-fold greater in the ChRT group (10.2% vs 3.8%, $p = 0.26$). An important limitation in this trial was a lack of standardization of surgical resection with respect to resection technique, with 30% of patients undergoing a transhiatal approach in the ChT arm. This raises concern that locoregional control could have been compromised by the choice of resection [5]. Burmeister and colleagues [6] also explored the comparison of ChT vs ChRT in resectable EAC. Their study also closed prematurely due to poor accrual. In this trial; however, median survival was 29 months for ChT vs 32 months for ChRT, which was very similar ($p = 0.83$). Surgical resection was more carefully standardized and favored an en bloc approach, which could account for the similar survival observed between the two groups compared with the findings in the Stahl trial [5].

As a result of the various patient inclusions, benefits, and drawbacks of the trials reaching significance in favor of preoperative therapy, there is a propensity for "gastric" esophagogastric junction tumors to be treated with ChT, followed by resection, whereas tumors at the esophagogastric junction and above may also undergo ChRT, followed by resection. Accepting a far lower potential pathologic complete response, groups that favor planned radical surgical resection may prefer ChT rather than ChRT compared with groups who would consider selective resection in patients who have had a complete clinical response. A recent meta-analysis published in *Lancet Oncology* demonstrates that clinical equipoise exists with regards to preoperative treatment regimens [4, 7].

Our study draws from three prospectively entered institutional databases at 3 North American centers with extensive expertise with ChT and ChRT as well as with the intricacies of radical esophageal operations. We focused on patients with locally advanced disease with a goal to clarify the benefit of radiotherapy in patients who uniformly received en bloc esophagectomy.

Patients and Methods

Patients

We analyzed all patients with thoracic and esophagogastric junction EAC and cT3 N1 M0, based on the Sixth edition of the TNM system, who underwent preoperative ChT or ChRT, followed by a modified en bloc esophagectomy, were obtained from 3 prospectively entered institutional databases between 2002 and 2012. The 3 sites were MD Anderson Cancer Center, the McGill University Health Center, and Weil Cornell-New York Presbyterian Hospital. Although differences existed among the 3 sites with respect to staging protocols, the clinical stage for all patients was based on the pretreatment ChT scan that was most commonly supplemented but with variable use of positron emission tomography/computed tomography (PET/CT) and endoscopic ultrasound (EUS) imaging. We chose stage III disease for our study because (1) it is the most common stage of presentation for potentially resectable patients in the 3 respective sites of the study, (2) this stage is most likely to be considered for preoperative therapy because it was the predominant stage in all of the recent randomized trials, and (3) in our experience this is a stage which is less likely to suffer from stage migration issues.

After therapy patients, were monitored according to local surveillance protocols, which included interval imaging with CT or PET/CT and in some cases routine endoscopy. Exclusion criteria were patients with clinically positive nonregional lymph nodes or other signs of metastasis, cT4 lesions, patients with Siewert 3 esophagogastric junction lesions, and patients who underwent non-en bloc or standard esophagectomy [8]. This study protocol was approved across all sites by each Institutional Review Board, and data-sharing agreements were signed across the 3 sites.

Preoperative Treatment Regimens

Patients undergoing preoperative ChRT were given concurrent ChT and radiotherapy with a target dose of 50.4 Gy in the planned target volume (PTV). ChT usually consisted of a fluoropyrimidine and a platinum-based compound or a taxane, as previously described. Surgical resection for these patients was generally planned for 6 or more weeks after the completion of ChRT. Those who underwent preoperative ChT only received platinum or taxane-based doublet, or both (Cornell), or 3 cycles of docetaxel/cisplatin/5-fluorouracil (McGill) based on the promising results of a local phase II trial with this regimen [9]. Similarly, surgical resection was performed 4 to 6 weeks after completion of preoperative therapy.

Esophagectomy

All patients underwent a modified en bloc esophagectomy. In brief, this consisted of an abdominal D2 lymphadenectomy, followed by a complete mediastinal lymphadenectomy. The margins of resection were the pericardium (noninclusive) anteriorly, spine posteriorly, and accompanied by a 180 to 270 degree periaortic dissection. Lateral margins extended from pleura to pleura. Length of this resection is from diaphragm to above the azygous arch or higher, determined by tumor location or surgeon preference. The thoracic duct was included in the specimen and ligated at the base of the chest. Location of the anastomosis was generally dictated by the location and extent of the lesion. For those patients who underwent a three-field lymphadenectomy, surgeon preference was the primary reason and consisted of a full cervical node dissection in the most cases. Three surgeons (L.E.F., N.K.A., and W.B.H.) performed all of the cases presented here.

Statistical Analyses

Patients who received preoperative ChT or ChRT were compared for overall survival (OS) and disease-free survival (DFS) calculated using Kaplan-Meier estimators. Statistical significance was set at $p < 0.05$. Univariate analyses were performed to identify predictors of OS and DFS, and those with p values of less than 0.25 were