Ann Surg Oncol (2019) 26:2313–2315
https://doi.org/10.1245/s10434-019-07491-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – THORACIC ONCOLOGY

Does a Lymph Node-Based Model Predict Clinical Value for Adjuvant Therapy in Squamous Cell Carcinoma of the Esophagus Treated With Upfront Surgery?

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The management of esophageal cancers is different outside the Western world, where the majority of esophageal cancer histology is squamous cell carcinoma (SCC) and many high-volume centers still use an esophagectomy-first approach. This differs from Western methodology, which is rooted in the landmark 2012 randomized CheMoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) trial, which demonstrated a clear difference in median overall survival of 49.4 versus 24.0 months between neoadjuvant chemoradiotherapy plus surgery and surgery only, respectively.[1] The safety and efficacy of the CROSS regimen led to its wide adoption in North America, with neoadjuvant chemoradiotherapy for all esophageal carcinomas and consideration of surgery as trimodality therapy for appropriate candidates.

The response to neoadjuvant treatment appears to matter regardless of histology. Unlike the epidemiologic pattern in the remainder of the world, SCC comprised only 23% of all histology in the CROSS trial, but it was more responsive to upfront treatment than adenocarcinoma (AC), with a complete response rate of 49%. The complete response with neoadjuvant therapy certainly has prognostic merit.[2, 3] Nevertheless, despite promising data for complete pathologic responders, 33% of these patients will experience recurrence, often with metastatic disease and a poor prognosis. To identify these patients early and treat them aggressively seems logical, but to date, no clear randomized data exist to support adjuvant therapy. Based on National Comprehensive Cancer Network (NCCN) guidelines, no clear treatment recommendations are made for ypT + or ypN + resected squamous cell carcinomas, and only limited data support delivery of adjuvant therapy in the adenocarcinoma group.[4–9]

Because the majority of histology and tumor biology differs outside the Western world, it is understandable that neoadjuvant therapy has not been widely adopted for treatment of squamous cell esophageal carcinoma. Supporting the findings of the CROSS trial, Yang et al.[10] randomized a non-Western group of squamous cell carcinoma patients to neoadjuvant chemoradiotherapy followed by surgery compared with surgery alone for locally advanced esophageal cancers and demonstrated a significant prolonged disease survival of 100.1 versus 41.7 months, respectively. Despite an accruing body of data from these and other international trials, a surgery-first approach to esophageal squamous cell carcinoma still is most popular currently. Without a downstaging opportunity using chemoradiotherapy, the adjuvant management of pathologically positive lymph nodes, even after radical three-field lymphadenectomy, becomes extremely important for survival optimization.

In the context of a surgery-first approach, we applaud Li et al.[11] in their attempt to establish prognostic criteria to define patients most suitable for adjuvant therapy. The authors evaluated the utility of pN stage, lymph node ratio (LNR, calculated as the number of positive nodes/total number of nodes), and total number of resected lymph

Editorial on "Predicting the Value of Adjuvant Therapy in Esophageal Squamous Cell Carcinoma by Combining the Total Number of Examined Lymph Nodes With the Positive Lymph Node Ratio" by Li, Yida et al. (ASO-2019-02-0317.R1).

First Received: 28 May 2019;
Published Online: 11 June 2019

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nodes (TLN) for predicting the value of adjuvant therapy after esophagectomy for patients with esophageal squamous cell carcinoma.

This retrospective study from China included 298 patients who underwent esophagectomy with R0 resection and three-field lymph node dissection without neoadjuvant therapy during a period of 8 years. The median TLN was 28, and the median LNR was 4.17%. Among the study population, 62.4% had metastatic nodal disease with a 5-year survival rate of 48.1%. Despite administration of adjuvant therapy to 57% of the patients, no significant impact on overall survival was observed ($p = 0.629$). In a subgroup analysis of survival after adjuvant therapy, the authors identified a significant advantage for patients, with an LNR higher than 4.17% and TLNs of 28 or more ($p < 0.001$), with a longer median overall survival than experienced by those without adjuvant therapy (28 vs. 15 months; $p = 0.030$). The authors concluded that the combination of TLNs and LNR may be useful in determining which patients may benefit from adjuvant therapy.[11]

One major limitation of the study was the heterogeneity of actual adjuvant therapy delivery because this was performed in multiple centers, unlike the esophagectomies standardized to a single institution. Without standardization of treatment, comparison of different adjuvant therapies (chemotherapy, radiation therapy, chemoradiation) and variations in doses makes abstraction of clinical outcomes difficult.

Additionally, timing of therapy after surgery is paramount because major treatment delays occur due to complexity of postoperative recovery after esophagectomy, which helps to justify an upfront treatment approach in North America. The authors report that more than 50% of their esophagectomies were able to receive adjuvant treatment, which speaks highly for the technical quality of the group's practice and ability to recover patients well enough to initiate additional toxic therapies.

With a growing international body of evidence supporting neoadjuvant treatment for most esophageal cancers, the data presented by Li et al.[11] become even more important as controversy grows regarding adjuvant therapy after trimodality therapy. Persistent nodal disease still is one of the most critical factors portending a worse overall prognosis because it reflects a potentially medically recalcitrant tumor biology. Predictive classification systems are needed to identify suitable candidates for adjuvant therapy, especially in the context of persistent nodal disease. The LNR and TLNs model proposed by Li et al.[11] is a creative way of collating quality and quantity of lymphadenectomy to predict outcome for this challenging group.

The results of this study, as well as other results available in the literature, highlight the ongoing need to establish criteria for administration of adjuvant therapy in esophageal cancer. Although the ideal timing and therapeutic strategy for adjuvant therapy remain an area of ongoing investigation, current evidence demonstrates some survival advantage for a select cohort of patients who have locally advanced cancers with persistently positive lymph node disease. Beyond the tumor-node-metastasis (TNM) 8 classification, clinical and pathologic predictive models as described by Li et al.[11] will be necessary to help tailor delivery of adjuvant therapies. Although differences in histology and tumor biology clearly exist internationally, we encourage external validation of the proposed model described in this report with a broader cohort of esophageal cancer patients treated with neoadjuvant chemoradiotherapy.

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