T2N0 esophageal cancer—We can't know where to go unless we know where we've been

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An old English proverb of unknown origin states “You don’t know where you’re going unless you know where you’ve been.” Unfortunately, the controversy regarding the treatment of T2N0 esophageal carcinoma stems from such a predicament. It has been well documented that despite advances in staging with endoscopic ultrasound and positron emission tomography/computed tomography (CT), the majority of patients with T2N0 esophageal carcinoma are either overstaged, approximately 20% to 30%, or understaged, approximately 40% to 55%, with 40% to 50% of patients having positive lymph nodes at esophagectomy.^{1,2} This carries major implications for treatment, as neoadjuvant therapy is associated with morbidity, and evidence exists showing patients with surprise T3 or nodal disease do poorly after upfront esophagectomy.³

Some groups have postulated that given the propensity for understaging, T2N0 patients should receive neoadjuvant treatment,^{4,5} and in a recent paper Semenkovich and colleagues⁶ used formal decision analysis to suggest a benefit to neoadjuvant therapy in T2N0 patients with risks factors (length >3 cm, lymphovascular invasion, high grade). Unfortunately, no randomized trial exists that verifies this hypothesis. The ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) trial contained few patients with T2N0 and the FFCD 9901 trial’s perioperative mortality of 11.1%⁷ in the neoadjuvant group render its results suspect when contemporary centers of excellence claim mortality rates of 1% to 2% in large series. Retrospective studies both with large databases and local data have shown both survival advantages and no difference with neoadjuvant therapy.⁸⁻¹⁰

The authors present a relatively large series of 767 patients from 15 high-volume institutions that show no survival advantage with neoadjuvant chemotherapy or chemoradiotherapy in an unselected T2N0 cohort. Although the authors should be commended for a well-written and thoughtful paper, the study does fall prey to some of the traps of registry studies. Notably, staging methods were not standardized,

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Central Message

Until staging accuracy for T2N0 esophageal cancer is improved, controversy regarding optimal treatment strategies will remain.

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and only 42.8% and 49.1% of patients definitively had a positron emission tomography/CT and endoscopic ultrasound, respectively. Given the relatively poor ability of CT to distinguish T stage, these results should be viewed skeptically, as an unknown proportion of stage I cancers may have biased the study toward the null. The authors also show that tumor length and lymphovascular invasion are risk factors for nodal disease, but no survival benefit was seen with neoadjuvant therapy even in these high-risk patients. Given the proven benefit of neoadjuvant therapy in the T3 or greater and node positive esophageal cancer cohort, this suggests that the cited indirect risk factors for this pathology, namely tumor length and lymphovascular invasion, are still inadequate to guide therapy.

The ongoing controversy over the best treatment for T2N0 patients suggests that new technology is needed to improve staging accuracy. Whether this comes from improved endoscopic ultrasound techniques such as high-frequency probes or elastography or improved molecular methods of staging, it will be impossible to settle the argument on what the best treatment algorithm is for patients with T2N0 disease until we confidently say which patients actually have it.

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