



## Neoadjuvant Treatment for Stage IIA Esophageal Adenocarcinoma, No Harm No Foul?

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Despite significant advancements in treatment, esophageal cancer remains the sixth most common cause of cancer death worldwide. Most patients with esophageal adenocarcinoma, the most common subtype in the United States, present with locally advanced disease defined as T3–4 or > N0 tumors. Since the publication of the landmark CROSS trial, neoadjuvant chemoradiation therapy followed by esophagectomy has been established as the “gold standard” treatment for patients with locally advanced esophageal cancer.<sup>1</sup>

Patients with cT2N0M0 disease represent a unique cohort, because there is currently no consensus on the optimal management of these patients. The National Comprehensive Cancer Network (NCCN) Guidelines for clinical stage IIA esophageal adenocarcinoma recommend either upfront esophagectomy or neoadjuvant treatment followed by surgery.<sup>2</sup> Although the presence of high-risk tumor features can help to guide the recommendation for neoadjuvant treatment, the decision is still subject to provider discretion.

In their paper, Stiles and colleagues sought to determine the effect of neoadjuvant treatment on both perioperative and oncologic outcomes for patients with clinical stage IIA disease.<sup>3</sup> Using the National Cancer Database (NCDB), the authors found that among patients with cT2N0M0

esophageal adenocarcinoma, there was no difference in the conversion rate, length of stay, unplanned readmission rate, or 30- or 90-day mortality between patients who underwent upfront surgery compared with those who had neoadjuvant treatment. Although overall survival was comparable between the two groups, neoadjuvant treatment was associated with improved survival among patients who had tumors > 5 cm in size.

In their study, there were some important differences among patients who had neoadjuvant treatment compared with upfront surgery. The neoadjuvant group was younger and had less comorbidities, which suggests that these patients were more likely to be able to complete chemoradiation and make it to surgery compared with older and more frail patients. To further validate this point, only about half of the patients in the surgery alone group who had positive nodal disease on final pathology went on to receive adjuvant treatment. Although the authors attempted to control for differences between the groups with propensity match scoring, this suggests a selection bias that may have affected perioperative outcomes, such as length of stay and readmission rates.

One factor that was not addressed in their paper was the timing of esophagectomy after neoadjuvant treatment. Although controversial, some studies have shown that waiting a prolonged time intervals for esophagectomy can lead to improved pathologic complete response but worse overall survival.<sup>4,5</sup> In particular, it is unclear whether patients who received their esophagectomy > 3 months after completion of neoadjuvant treatment were included in the study. More granular data, including interval time between the completion of chemoradiation and surgery, may demonstrate a survival benefit even among patients with cT2N0M0 disease and tumor sizes < 5 cm.

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Another limitation of the NCDB is the lack of granularity regarding the type and duration of neoadjuvant treatment. The CROSS trial was defined as multiagent chemotherapy plus radiation. It is unclear whether all patients included in the study received multiagent treatment or completed their full course of treatment, which may have affected the outcome of overall survival.

Esophagectomy is a technically challenging operation with high rates of morbidity and mortality even among high-volume thoracic surgeons.<sup>6</sup> Radiation causes significant inflammation, and a fibrotic reaction that can make surgical resection and reconstruction more challenging. Although their paper did not show adverse perioperative outcomes for patients who underwent neoadjuvant treatment compared with upfront surgery, many important complications were not studied. Major morbidity after esophagectomy defined by the Society of Thoracic Surgeons includes return to the operating room, anastomotic leak, pneumonia, reintubation, ventilation beyond 48 h, renal failure, and recurrent nerve paresis.<sup>7</sup> These outcomes will be important to study in the future as they lead to significant morbidity for patients after esophagectomy.

Stiles and colleagues paper provides important insight into the effects of neoadjuvant treatment for patients with early-stage esophageal adenocarcinoma. Similar to current NCCN guidelines, their data suggest that neoadjuvant treatment may be beneficial in a subgroup of patients with cT2N0M0 esophageal adenocarcinoma. Further research is warranted to determine the generalizability of these findings to all patients with esophageal adenocarcinoma and to better define which patients with early-stage disease would benefit most from neoadjuvant treatment.

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