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Commentary: After neoadjuvant therapy for esophageal cancer, time is on our side

Taryne Imai, MD,^a and Benny Weksler, MD^b

Neoadjuvant chemoradiation improves overall survival, disease-free survival, and pathological complete response in patients with stage II or III esophageal cancer.¹ Multimodality therapy is currently considered the treatment strategy of choice for esophageal cancer and achieves complete pathological response in 15% to 20% of patients with esophageal adenocarcinoma.² Despite broad agreement on the proven benefits of multimodality therapy, the optimal timing of esophagectomy after neoadjuvant chemotherapy remains controversial.

Most randomized trials have recommended esophagectomy within 3 to 8 weeks after completion of neoadjuvant therapy.^{1,3} The concern regarding delaying surgery after the completion of neoadjuvant chemoradiation centers around the theoretical possibilities of tumor regrowth and dissection difficulties due to radiation-induced fibrosis. In addition, delayed and salvage esophagectomy have been associated with an increased rate of postesophagectomy complications (up to 52.6%), with complications including major cardiovascular events, pneumonia, acute respiratory distress syndrome, a higher than expected leak rate (21%-38%), and conduit necrosis, which is seen in 16% of patients.⁴

Although these reported outcomes are worrisome, several institutions have carefully selected patients to undergo delayed esophagectomy and have demonstrated no differences in perioperative mortality, recurrence, and median and overall survival.^{5,6} These studies raise the possibility that delayed esophagectomy is a feasible therapeutic

Taryne Imai, MD (left), and Benny Weksler, MD (right)

CENTRAL MESSAGE

A new study showed that delaying esophagectomy after neoadjuvant therapy did not affect overall survival, but the higher 90-day mortality seen before delayed resection supports the importance of timely surgery.

option for patients with locoregional failure after chemoradiation. Even though these results are a cause for optimism, recommendations for delayed esophagectomy remain conservative, because of the small sample sizes of supporting studies.

In the current issue of the *Journal*, Levinsky and colleagues⁷ compared the outcomes of timely and delayed esophagectomy in more than 8000 patients with esophageal adenocarcinoma using the National Cancer Database. The authors defined timely esophagectomy as surgery performed less than 90 days from completion of neoadjuvant therapy and delayed esophagectomy as surgery performed more than 90 days after completion of chemoradiation therapy. They also analyzed outcomes for delayed esophagectomies performed 90 to 120 days and more than 120 days from the completion of neoadjuvant therapy. Although there were no differences in 30-day readmissions, the patients with delayed esophagectomy had longer hospital stays and higher 90-day mortality after resection. Intriguingly, the patients who underwent delayed esophagectomy also had a higher rate of complete pathological response (22.2% vs 18.6%), which was defined as pathological T0N0 after neoadjuvant therapy, as well as a higher rate of pathological N0 response (70.5% vs 61%). Despite differences in univariate analysis, multivariate analysis did not show an association of delayed esophagectomy with worse overall survival, even in patients who underwent esophagectomy more than 120 days after neoadjuvant therapy.

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This study clearly shows that the timing of esophagectomy did not influence overall survival, even though it was associated with increased 90-day mortality. The study suggests that waiting until documented recurrence occurs is not a bad option for patients with a clinical complete response on imaging and endoscopy who are reluctant to undergo surgery. Furthermore, surgeons should be less pressed to operate on patients who appear frail from a nutritional or a medical standpoint after chemoradiation. Waiting will not change these patients' overall likelihood of survival, and optimizing their clinical status may improve outcomes.

Another intriguing finding of the study is the observation that a higher rate of complete pathological response, as assessed after esophagectomy, was seen when esophagectomy was delayed. This raises some important questions: are we operating too early on some of these patients, and would waiting a few extra weeks improve their response to neoadjuvant therapy? Regardless, until better trials are available to address the timing of esophageal resection, we believe that the higher 90-day mortality observed in patients with delayed esophagectomy in this study supports operating

within 90 days of completion of chemoradiation therapy whenever possible.

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Commentary: Delayed resection for esophageal adenocarcinoma

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There have now been multiple retrospective studies examining the potential effect of a delayed operation for esophageal adenocarcinoma after chemoradiation therapy. Uniformly, these studies have shown overall survival results comparable to those of immediate, planned resection, but with some differences in short-term outcomes.^{1,2} Results from these single- and multi-institutional studies are now recapitulated in the study by Levinsky and colleagues³

Wayne Hofstetter, MD

CENTRAL MESSAGE

Patients with persistent or recurrent esophageal adenocarcinoma may undergo delayed esophagectomy beyond 90 days after neoadjuvant or definitive chemoradiation with similar prognosis compared with timely, planned esophagectomy.

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