See Article page 135.

Commentary: Systemic adjuvant therapy for esophageal adenocarcinoma

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CENTRAL MESSAGE

Residual nodal disease after neoadjuvant therapy and surgery for esophageal cancer is a poor prognostic sign. Adjuvant systemic therapy may improve survival, and immunotherapy is a promising choice.

Esophageal cancer remains a challenging disease to treat, with poor prognosis. Most patients are diagnosed with either distant metastases or locoregional disease, and therapeutic interventions have limited effects. In patients without metastatic disease, neoadjuvant chemoradiation therapy is beneficial and improves survival as compared with surgery alone. However, despite advances, only 18% to 22% of patients with esophageal adenocarcinoma who receive neoadjuvant therapy have a pathologic complete response. Because clinical staging of esophageal cancer is unreliable, the true rate of downstaging as a result of neoadjuvant chemoradiation is unknown, but ~80% of patients will have residual disease at the time of surgery with residual nodal disease in a significant portion.[1] Positive nodal disease is a harbinger of systemic disease and poor survival, and the best management strategy for patients with residual nodal disease after neoadjuvant therapy is still debated. However, one promising development is the use of immunotherapy in the adjuvant setting.

In the current issue of *JTCVS Open*, Kandilis and colleagues[2] report on survival after neoadjuvant therapy and esophagectomy in patients with adenocarcinoma of the distal esophagus. For this study, the patients were divided into 3 groups based on pathologic staging after neoadjuvant therapy and resection: patients with a complete response (ypT0N0, 22%), patients with residual tumor (ypT + N0, 46.2%), and patients at least 1 positive lymph node (ypTanyN1-3, 31.8%). This study by Kandilis and colleagues confirmed a complete response rate of less than 25% in patients with esophageal adenocarcinoma undergoing preoperative therapy. It also confirmed that approximately one third of patients will have residual nodal disease after therapy. The main findings of the study were poor overall survival for patients with residual nodal disease, lack of a difference in survival between patients who had ypN1 versus ypN2-3 disease, and improved survival in patients who underwent adjuvant chemotherapy.

Previous retrospective studies, including several National Cancer Database studies and one retrospective multi-institutional study, have similarly shown that adjuvant chemotherapy may improve survival in patients with residual disease.[1,3,4] However, until recently, level 1 evidence showing improved survival in this group of patients was lacking. The similar overall survival observed between patients with ypN1 disease and patients with ypN2-3 disease is more difficult to explain and may be due to the effects of neoadjuvant therapy on tumor biology (tumors with biological behavior that trumps stage) or due to a relatively small sample size. The possibility that the study lacks power in this regard is suggested by the difference observed in disease-free survival between patients with ypTanyN1 and patients with ypTanyN2-3.

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Disclosures: B.W. is a proctor for Intuitive Surgery and speaker for AstraZeneca.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication Jan 3, 2021; revisions received Jan 3, 2021; accepted for publication Jan 4, 2021; available ahead of print Feb 13, 2021.

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JTCVS Open 2021;5:148-9
2666-2736

https://doi.org/10.1016/j.xjon.2021.01.002

A very exciting recent development is the finding that adjuvant nivolumab significantly prolonged disease-free survival in patients with residual disease after neoadjuvant therapy and resection of esophageal or gastroesophageal junction cancer. This was presented during the European Society of Medical Oncology meeting in September 2020[5] and has already been adopted in treatment guidelines from the National Comprehensive Cancer Network. The potential for anti-programmed cell death protein 1/programmed cell death ligand 1 agents, which are immune checkpoint inhibitors, to improve the treatment of patients with esophageal cancer is a very welcome development and may be as practice-changing as the randomized studies on neoadjuvant therapies were in the early 2000s.[6] In addition, a few studies investigating the use of immunotherapeutic agents in the neoadjuvant setting are currently accruing patients.

Surgery for esophageal cancer is changing, and more surgeries are being performed using minimally invasive techniques. Multiple studies have shown improvement in perioperative outcomes and quality of life using minimally invasive approaches. The study by Kandilis and colleagues reminds surgeons that our work is not limited to surgery. We should also be the drivers behind better neoadjuvant and adjuvant therapies to improve survival for patients with an otherwise-poor prognosis.

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