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Commentary: Are we at a CROSSroads in neoadjuvant therapy for esophageal cancer?

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It has been 12 years since publication of the Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study trial set the standard of care for neoadjuvant chemoradiotherapy followed by esophagectomy for locally advanced esophageal cancer.¹ More recently, the CALGB 80803 trial demonstrated higher rates of pathologic complete response with a fluorouracil-based, positron-emission tomography-directed neoadjuvant strategy.² Long-term outcomes from this trial are pending. Recurrence, particularly distant recurrence, continues to limit survival in locally advanced esophageal cancer. Two analyses of patterns of recurrence after curative resection of esophageal cancer have been performed by Memorial Sloan Kettering Cancer Center. In 2013, Lou and colleagues³ demonstrated that 72% of recurrences included distant metastases. Similarly, in 2019, Nobel and colleagues⁴ showed that even among patients with pathologic T1-2N0 disease recurrence was distant in 56% of patients. These distant failures highlight the need for more effective systemic therapy in esophageal cancer.

Immune checkpoint inhibitors (ICIs) have become important therapeutic agents in many cancers. Evaluation of ICIs in patients with metastatic esophageal cancer have been promising in subsets of patients.⁵ Recently, early data from the ongoing KEYNOTE-590 (NCT03189719) and CheckMate-577 (NCT02743494) trials presented at the European Society for Medical Oncology 2020 Virtual Congress suggest favorable results in both the advanced at adjuvant settings. It is rational to evaluate these promising systemic therapies in the neoadjuvant setting given the frequency of systemic recurrences after esophageal resection.

Systemic recurrence following trimodality therapy for locally advanced esophageal cancer.

CENTRAL MESSAGE

Improved systemic control is needed in esophageal cancer. This study suggests safety and feasibility of esophagectomy following combined neoadjuvant therapy with durvalumab and chemoradiotherapy.

In this retrospective analysis by Sihag and colleagues,⁶ the group from Memorial Sloan Kettering Cancer Center report on the safety and feasibility of esophagectomy following the combination of immunotherapy and chemoradiation. Patients in the study received 2 doses of durvalumab before chemoradiotherapy and esophagectomy. Appropriately, the authors have limited their analysis to short-term perioperative outcomes, delaying discussion of response until trial completion and further analysis. Immune-related toxicities occurred in 28% of patients, but did not result in delays to surgery. There were no episodes of pneumonitis. The crude rates of perioperative morbidities were similar to those seen in most large series and database analyses. The authors selected a comparison group from their institutional database and found only minor differences in outcome between the study and control groups after multivariable analysis. This analysis is statistically limited by the small study group and relatively few adverse events. In addition, the study group has a very low rate of smoking history or comorbid pulmonary disease. Nonetheless, the descriptive statistics regarding completion of therapy, lack of delays to resection, and absence of adverse safety signals are important contributions to the field.

This initial report of perioperative outcomes following neoadjuvant therapy with combined ICI and

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chemoradiotherapy does not suggest significant untoward effects related to the addition of immunotherapy to current trimodality regimens. As we continue to employ novel agents in the neoadjuvant setting, it is incumbent upon surgeon investigators to report clinical results. Hopefully, as this and other esophageal trials reach completion we will see evidence of response to therapy and ultimately in improvement in survival.

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