Editorial Commentary

Neoadjuvant chemo-immunotherapy still not as nice as neoadjuvant chemoradiation therapy for locally advanced esophageal carcinoma

Matthew M. Rochefort^, Jon O. Wee

Division of Thoracic Surgery, Department of Surgery, Brigham and Women's Hospital, Boston, MA, USA

Correspondence to: Matthew M. Rochefort, MD. Division of Thoracic Surgery, Department of Surgery, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA. Email: mrochefort@bwh.harvard.edu.

Comment on: Yang Y, Liu J, Liu Z, *et al.* Two-year outcomes of clinical N2-3 esophageal squamous cell carcinoma after neoadjuvant chemotherapy and immunotherapy from the phase 2 NICE study. J Thorac Cardiovasc Surg 2024;167:838-847.e1.

Keywords: Chemotherapy; immunotherapy; esophageal caner

Submitted Feb 07, 2024. Accepted for publication Jun 07, 2024. Published online Jul 26, 2024.
doi: 10.21037/jtd-24-222
View this article at: https://dx.doi.org/10.21037/jtd-24-222

We would like to commend Drs. Yang *et al.*, on their well-designed and completed study in *The Journal of Thoracic and Cardiovascular Surgery*. The main objective of this study was to compare the efficacy of neoadjuvant chemo-immunotherapy on the rate of pathologic complete response in the resected esophagus and regional lymph nodes, in patients with previously untreated esophageal squamous cell carcinoma (1). Secondary endpoints that were studied included recurrence-free survival (RFS) and overall survival (OS). The paper evaluated 60 patients, enrolled across four institutions, between November 2019 and December 2020. They concluded that neoadjuvant chemo-immunotherapy had a favorable impact with respect to oncologic outcomes, including a 2-year OS of 78.1% and a 2-year RFS of 67.9%, and achieved a pathologic complete response in 39.2% of patients. These latter results are mostly in line with prior published results on combination chemotherapy and immunotherapy demonstrating pathologic complete response rates of 17% to 50% (2). The study also brings to light the impressive difference in OS conveyed by a major pathologic response (MPR), with a 91.4% 2-year survival in those who had an MPR, versus an only 47.7% in those who did not.

Esophageal cancer incidence continues to increase worldwide, with over 600,000 estimated cases in 2020 (3). Neoadjuvant chemotherapy and radiation therapy, what has come to be referred to as the CROSS regimen, followed by esophagectomy with radical lymphadenectomy has become the standard of care for patients with potentially surgically curable disease (4). This treatment paradigm increased the OS for patients with operable esophageal cancer from 50% with surgery alone to 67% with neoadjuvant chemoradiotherapy followed by surgery (4). In the intervening decade, since the publication of the CROSS trial, there has been increased focus on the utilization of immune checkpoint inhibitors in the treatment of a myriad of malignancies, including esophageal cancer (5). A great deal of this focus has been on the programmed cell death 1 (PD-1) and programmed cell death 1 ligand 1 (PD-L1) pathway, and development of antibody inhibitors targeting this pathway as a mechanism to treat advanced esophageal cancer (5).

The role of additional adjuvant therapy following radical surgical resection after definitive neoadjuvant therapy in esophageal cancer has been somewhat controversial in the post-CROSS era. However, more recent studies have indicated the benefit of adjuvant immunotherapy in this patient population (6), significantly increasing post-

^ ORCID: 0009-0001-1046-4701.

resection disease-free survival. The current study could also be considered a combination neoadjuvant and adjuvant study, as while it was not explicitly stated in the methods, almost half of the patients received some sort of adjuvant therapy following definitive surgical resection, including 25% that proceeded to receive chemoradiation therapy.

The study brings up the possibility of a high rate of non-tumor related deaths following neoadjuvant chemoradiation therapy as a prospective benefit of neoadjuvant immunotherapy over the standard of care. These non-tumor deaths are theorized to be related to the detrimental effects of the radiation therapy, leading to late mortalities not attributable to the cancer but attributable to the treatment itself. However, the 10-year follow-up of the CROSS trial specifically found that neoadjuvant chemoradiation therapy did not lead to an increased risk of death from other causes and that the survival benefit of the long-term survivors in the neoadjuvant chemoradiotherapy cohort was similar when compared to the long-term survivors in the surgery alone group (7).

Esophageal cancer also represents a unique cancer manifestation, along with other hollow organ pathologies, whereby local control of recurrence is important not only from an OS perspective, but also a functional perspective for the patient. Minimizing local recurrence and recurrence associated strictures, which can lead to the inability to tolerate an oral diet, has a great deal of effect on overall patient satisfaction and willingness to pursue additional therapies in the face of recurrent cancer (8). Therefore, the ability to control for and minimize local recurrences is more clinically relevant in esophageal cancers than it might otherwise be in a different malignancy. The article itself comments on the apparent weaker effect that chemo-immunotherapy has on local control of disease in comparison to neoadjuvant chemoradiation therapy (1), and this could lead to an unacceptably high rate of local recurrences.

The limitations mentioned in the paper and some that are not explicitly mentioned also impede the ability to translate the results of this study to a more general population of patient with esophageal cancer. The very high-performance status, with 95% of the patients having a Eastern Cooperative Oncology Group (ECOG) performance score of 0, in and of itself may explain some of the survival benefit, simply due to the healthier status of these patients compared to standard patients with advanced esophageal cancer. The specific evaluation of squamous cell carcinoma also limits the generalizability of these outcomes to the more commonly encountered distal esophageal adenocarcinoma in Europe and North America. A specific study on the role of neoadjuvant chemo-immunotherapy for adenocarcinoma would likely need to be performed, as these represent distinct patient populations with distinct histological and oncological outcomes.

Comparison of the outcomes of this study and contemporary studies is also somewhat challenging by the current study's utilization of the Efficacy population in the determination of the overall and recurrence free survival. Treatment studies and especially randomized controlled studies are usually designed with intention to treat analysis and as such, except for the one patient who withdrew consent, the remainder of the patients, whether or not they progressed to surgical resection, would have been considered in the evaluation of outcomes. While not mentioned again in the article, the results indicate that by an intention to treat analysis, the 2-year survival in this cohort was 70%, which is very similar to the 67% reported in the CROSS trial.

Neoadjuvant chemo-immunotherapy appears to be a safe alternative treatment for locally advanced esophageal cancer, mostly in the investigative phase, with chemoradiation therapy remaining as the first line treatment. However, the incorporation of a variety of immune checkpoint inhibitors in the adjuvant setting (6) has contributed to further reduction in distant metastatic recurrence as these treatments provide superior systemic disease management. This is especially true for patients without a complete or MPR at the time of surgical resection, who we consider at the highest risk for recurrence, and who's care remains an active area of ongoing study.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease*. The article has undergone external peer review.

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-222/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.

com/article/view/10.21037/jtd-24-222/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Yang Y, Liu J, Liu Z, et al. Two-year outcomes of clinical N2-3 esophageal squamous cell carcinoma after neoadjuvant chemotherapy and immunotherapy from the phase 2 NICE study. J Thorac Cardiovasc Surg 2024;167:838-847.e1.
2. Li Q, Liu T, Ding Z. Neoadjuvant immunotherapy for resectable esophageal cancer: A review. Front Immunol 2022;13:1051841.
3. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
4. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
5. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet 2021;398:759-71.
6. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. N Engl J Med 2021;384:1191-203.
7. Eyck BM, van Lanschot JJB, Hulshof MCCM, et al. Ten-Year Outcome of Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal Cancer: The Randomized Controlled CROSS Trial. J Clin Oncol 2021;39:1995-2004.
8. Conroy T, Marchal F, Blazeby JM. Quality of life in patients with oesophageal and gastric cancer: an overview. Oncology 2006;70:391-402.

Cite this article as: Rochefort MM, Wee JO. Neoadjuvant chemo-immunotherapy still not as nice as neoadjuvant chemoradiation therapy for locally advanced esophageal carcinoma. J Thorac Dis 2024;16(7):4829-4831. doi: 10.21037/jtd-24-222