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EDITORIAL – THORACIC ONCOLOGY

Pathologic Complete Response Following Esophagectomy: Lymph Nodes Matter!

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"There is little doubt that the successful outcome of radical curative surgery for esophageal carcinoma remains one of the great challenges of surgical practice."[1] Ask any esophageal surgeon today and you will find that this statement by Ivor Lewis in 1946 still rings true. The fundamental challenge is how to define and predict surgical 'cure' and what, if anything, can be done in the operating room to optimize long-term survival. Schroeder and colleagues[2] have nicely elucidated key factors in assessing the likelihood of cure related to pathologic complete response (pCR) following multimodality treatment of esophageal cancer. The findings in this study are provocative and should be evaluated in the context of modern advancements in medical therapies and surgical techniques.

The CROSS trial, published in 2012, was pivotal in changing contemporary esophageal cancer management. This randomized trial demonstrated that the addition of induction chemoradiotherapy to surgical resection improved survival.[3] Presumably, neoadjuvant treatment decreases occult disease burden, which lay beyond the reach of surgical resection alone. Perhaps not surprisingly, Schroeder et al.[2] found that residual nodal disease following surgical resection is a major driver for recurrence and survival. Patients with complete response in the primary tumor, but residual nodal disease (ypT0N+), experienced survival similar to patients with minimal primary tumor regression or disseminated disease. Residual nodal disease is a harbinger for systemic cancer spread. Unfortunately, modern surveillance techniques (imaging, endoscopic, and/or biomarker assessment) are notoriously poor predictors of true complete response (i.e., ypT0N0). The authors appropriately caution against a 'watch-and-wait' strategy in patients with suspected pCR following induction therapy. While surgical nihilists have argued that esophagectomy in the setting of occult residual disease may not improve survival compared with active surveillance, Checkmate 577 has changed the conversation.

The Checkmate 577 trial[4] randomized patients with residual pathologic disease following trimodality therapy to receive the programmed death-ligand 1 (PD-L1) checkpoint inhibitor nivolumab versus placebo. Patients receiving adjuvant immunotherapy (IO) experienced a doubling in median disease-free survival (DFS) from 11.0 to 22.4 months. Checkmate 577 was published in April 2021, long after the cohort of patients in the present Schroeder et al. study underwent treatment. Today, the 33 patients in the present study with ypT0N+ would be eligible for adjuvant nivolumab, potentially providing significant improvement in DFS. Of course, to be eligible for adjuvant IO, there must be pathologically proven residual disease and this requires esophagectomy—and not just any esophagectomy but rather a high-quality oncologic operation.

Schroeder and colleagues[2] are to be commended for their rigorous surgical approach, which notably included a thorough lymphadenectomy. Sihag et al.[5] from Memorial Sloan Kettering Cancer Center have shown that a more extensive lymphadenectomy during esophagectomy for esophageal cancer is associated with improved survival. In fact, the extent of lymphadenectomy appears to improve survival linearly without a clear maximum effect—the more nodes, the better. What is more, the surgical approach

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may impact the extent of nodal harvest. Several reports have suggested improved nodal harvest with minimally invasive esophagectomy compared with traditional open approaches; the use of robotic-assisted surgery may further improve lymphadenectomy.[6–9] Taken in the context of the present study, one can appreciate the importance of a high-quality oncologic technique during esophagectomy, not only to ensure complete removal of the primary tumor but also to ensure an accurate assessment of post-induction nodal status.

Lastly, it is notable that even in the setting of ypT0N0 (i.e. a true pCR), 22% of patients experienced tumor recurrence within the median 58.9-month follow-up. In other words, we fail to identify residual disease 22% of the time following best-practice trimodality therapy. These data once again highlight our limited ability to accurately prove 'complete response'. It is a loud and clear call for research to identify the holy grail of esophageal cancer management—a non-invasive, accurate biomarker for residual disease.

The study by Schroeder and colleagues[2] provides several key takeaways regarding the management of esophageal carcinoma: (1) a significant proportion (16%) of patients with complete response in the primary tumor will have residual disease in the lymph nodes; (2) residual nodal disease is a major driver of survival following multimodality therapy; and (3) despite our best efforts, some ypT0N0 patients will recur. Now more than ever, with the results of Checkmate 577, the pathologic status of lymph nodes following neoadjuvant therapy is critical. Further study is necessary to determine whether operative approach influences identification of occult residual nodal disease, which may in turn impact survival in the era of adjuvant IO. Nodal status has important implications for prognosis, adjuvant therapy, and ultimately survival. The bottom line is lymph nodes matter and the harder we look for N+ disease, the more likely we are to find it.

DECLARATIONS

CONFLICT OF INTEREST ELS—Consultant, Intuitive Surgical

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