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EDITORIAL – TRANSLATIONAL RESEARCH

From NLR to TIN: What Can't Neutrophils Tell Us About Prognosis in Resectable Esophageal Cancer?

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Prognostication of esophageal cancer is complex and relies on multi-dimensional factors, with some factors predictive of the tumor's sensitivity to therapeutic agents. These predictive factors include patient- or tumor-centric features.

Historically, clinical and pathologic characteristics have informed treatment strategies,[1–3] and with an increased armamentarium of available systemic agents, patient selection for trimodal protocols is paramount. Advanced biomarkers are similarly used for this purpose and can provide insight relating to the state of the tumor microenvironment (TME). These have included circulome-based markers such as the neutrophil-to-lymphocyte ratio (NLR),[4] immune-based markers such as PD-L1 expression,[5] and genome-based markers such as the level of microsatellite instability.[6]

Concurrently, evaluation of the TME has proved to be valuable in establishing a better understanding of the pathogenesis in patients with resectable esophageal cancer. Concepts such as chronic inflammation, hypoxia, immunosuppression, acidosis, and angiogenesis occurring in the TME may explain oncogenesis.[7,8]

In this issue of the *Annals of Surgical Oncology*, Cabalag and colleagues report a paired transcriptomic analysis of patients who had esophageal cancer managed with neoadjuvant therapy. The authors evaluated the prognostic value of tumor-infiltrating neutrophils (TIN, defined by CD15 positivity on immunohistochemistry) in patients with residual pathologic disease, synchronously providing insight relating to the immune state of the TME.

Given the established immune-suppressive background present in the TME, Cabalag and colleagues sought to evaluate the effect of neoadjuvant systemic therapy on the immunologic milieu present in the TME using TIN, tumor-infiltrating lymphocyte (TIL), and tumor inflammation signature score (TIS)[9] as markers. Interestingly, the authors report that no changes were appreciated in TIL or TIS surrounding the receipt of neoadjuvant therapy, and that no survival advantage was associated with an increase in TIL or TIS after resection. Upon evaluation of the TIN, stratified around the median value, the authors observed that patients with neutrophil-enriched tumors had inferior rates of progression-free survival (PFS), with a hazard ratio [HR] of 3.00 (95% confidence interval [CI], 1.32–6.83) for probability of mortality.

Further genomic analysis was performed to investigate specific mechanisms, which led to the observation that neutrophil-trafficking genes (IL8, CXCL5, SELE, TREM1) were upregulated in the group of patients with high TIN. Additionally, the authors confirmed the association of elevated NLR with disease recurrence in this cohort. Finally, a subgroup analysis of patients with both high TIN and elevated NLR was performed and showed an association with early disease recurrence (HR, 11.85 for recurrence; 95% CI 4.93–28.47) compared with patients who had low TIN and NLR.

This elegant study by Cabalag and colleagues provides important insights into the TME, specifically, whether improved prognostication can be achieved using these advanced biomarkers. As such, the authors determined that patients with elevated TIN and NLR, may benefit from supplementary perioperative management. Furthermore, the mechanistic depth of this analysis also provides insight

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relating to immunotherapeutic targets and possible resistance patterns. Previous work by Schiffmann et al.[10] showed that TIN counteracts anti-VEGF therapy in metastatic colorectal cancer, possibly secondary to increased vascular mimicry led by TIN[11] in the TME after hypoxia.[12] A study by Zhang et al.[11] also showed that TIN may facilitate invasive phenotypes by inducing an epithelial-mesenchymal transition of tumor cells, which is concordant with the findings in the current study that patients with elevated TIN have decreased PFS.

Before TIN is widely adopted as a biomarker, a few limitations must be discussed, and hurdles passed. First, the sample size may have been too small for a derivation of clean signals from this analysis, as stated by the authors. Additionally, the effect originating from TIN stratified around the median value seemed to be lower (HR: 3.00) than that of the presence of CD15 cells as a continuous variable (HR: 5.55). Although use of a continuous variable is statistically stronger than use of a binary variable, it is possible that a threshold of TIN exists that might be more meaningful than its median. This might warrant further investigation. Furthermore, TIN seems to have a valuable positive predictive value, but its negative predictive value leaves room for improvement. Incorporation of other variables, such as histopathology (squamous vs adenocarcinoma), may improve its clinical use. Finally, and surprisingly, infiltration of CD15+ cells (TIN) did not seem to correlate with nodal invasion, warranting a discussion about its value in prognostication of advanced disease.

Ultimately, the ability to translate TME findings such as the TIN into circulome findings (NLR) is extremely valuable because neoadjuvant multimodal therapy may in time lead to minimal residual disease in most patients. Studies such the one performed by Cabalag and colleagues may further help identify patients who may not benefit from resection due to high disease aggressivity and those who may not require an operation after the benefits harvested from neoadjuvant protocols.

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