Editorial Commentary

Percentage of tumor-infiltrating lymphocytes after chemoradiation therapy for locally advanced esophageal squamous cell carcinoma: a biomarker for pathological response rates and cancer-specific survival?

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Both the innate and adaptive immune systems play a central role in the surveillance and control of neoplasia. A source of much recent attention, tumor infiltrating lymphocytes (TILs) are a population of T-cells, which have a greater degree of immunological reactivity against neoplastic cells, as compared with circulating (non-tumor infiltrating) lymphocytes. Given the key role that they play, TILs have been explored as prognostic biomarkers for a number of solid organ malignancies, including breast cancer (1), head and neck cancers (2), melanoma (3), colorectal cancer (4), non-small cell lung cancer (5), malignant pleural mesothelioma (6), and esophageal cancer (7).

Qian and colleagues assessed the association between the percentage of TILs after neoadjuvant chemo- (docetaxel/cisplatin) radiation (40 Gy) therapy (n=48) or definitive chemo- (docetaxel/cisplatin) radiation (60 Gy) therapy (n=116) for T2-4aNanyM0 esophageal squamous cell carcinoma (8). At the completion of radiation therapy, biopsies were obtained by endoscopic ultrasound (EUS). The authors found a significant association between the percentage of TILs and degree of pathologic response and cancer-specific survival. On multivariable analysis, TIL expression was associated with improve survival rates, but it did not reach statistical significance. The lack of statistical significance could be due to type II error or due to multicollinearity from including highly correlated variables in one model, which would decrease the precision of their estimates

Two important factors have been identified that positively impact the outcome of esophageal cancer patients: (I) use of multimodal therapy and (II) disease response to neoadjuvant therapy. Numerous previous studies have demonstrated that a complete pathologic response (pCR) to neoadjuvant therapy is independently associated with improved survival (9-11). Using a CROSS Trial regimen, the degree of pathologic complete response to neoadjuvant chemoradiation therapy approaches 50% for esophageal squamous cell carcinoma (12). However, short of performing an esophagectomy, commonly used clinical parameters, including EUS (13) and positron emission tomography/computed tomography scans (14), lack sufficient sensitivity for predicting pCR. As such, novel biomarkers are needed to guide treatment decisions.

Qian and colleagues found that >60% stromal TILs were associated with a 66.7% sensitivity and accuracy of 58.3% for predicting pCR (8). While TILs alone are insufficient in predicting pCR, perhaps they could be combined with PET/CT, endoscopic parameters, or other biomarkers to improve its sensitivity and accuracy. We know that neoadjuvant chemoradiation therapy increases TILs in

esophageal squamous cell carcinoma (15). Unfortunately, we don't know from the available data in the literature whether the change in the percentage of TILs over the course of treatment or simply the post-treatment percentage of TILs are more important. It is also unknown whether TILs play such a role in esophageal adenocarcinoma. Further studies are needed.

Finally, these studies beg the question of whether immunotherapy could improve the pCR rate to neoadjuvant therapy and improve survival. Several phase III clinical trials exploring perioperative chemotherapy for esophageal cancer many patients (up to 50%) cannot tolerate any adjuvant chemotherapy (16,17). Consequently, efforts should be made in the neoadjuvant setting to optimize pathologic response rates. Clinical trials examining the use of immunotherapy in esophageal cancer are underway.

The study by Qian and colleagues is thoughtful and timely. It provides additional insight into the prognostic importance of the tumor microenvironment. Further studies are needed to determine whether the tumor microenvironment can be manipulated through immunotherapy to improve survival.

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Footnote

Conflicts of Interest: 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.

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