Editorial Commentary

Is there value of tumor stromal infiltrating lymphocytes for response assessment to chemoradiation in esophageal squamous cell carcinoma?

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Although esophagectomy as a single modality remains the cornerstone of treatment for resectable esophageal carcinoma, the incorporation of chemo-radiotherapy (CRT) as neoadjuvant therapy improves overall survival and R0 resection rate compared to surgery alone. Both the CROSS and the NEOCRTEC 5010 trials have demonstrated that neoadjuvant CRT (nCRT) significantly improves overall survival compared to surgery alone, in both adenocarcinoma and squamous cell carcinoma (1-3), without contributing to the morbidity of surgery. Although surgery is still needed after CRT to render the best cure rate, about 13% to 40% of EC patients treated with nCRT will achieve a pathologic complete response (pCR), presenting favorable long-term outcomes compared with patients without pCR (1,2,4). For patients with a complete response after CRT, there is no consensus on the best treatment approach. Meta-analysis showed no significant difference in long-term survival between CRT and surgery and definitive CRT (5,6). It is therefore reasonable to proceed with active surveillance without surgery for these patients, in order to avoid the potential morbidity and mortality of surgery, if there was a way to identify these patients early on. However, being able to accurately identify tumors that will sustain complete response to induction therapy is still an area of unmet need (7). Using clinical parameters, such as magnetic resonance imaging (MRI), computed tomography (CT) and PET/CT, have failed to accurately predict pCR after nCRT (8-10). Diagnostic methods to evaluate clinical CR (cCR) are also not useful since about 19–26% patients with cCR failed to reach pCR after surgery. Recent attempts to use endoscopic ultrasonography with bite-on-bite biopsies to identify residual islands of cancer cells appears to yield early promising results, by missing only 10% residual disease (7), this is still a highly experimental and yet to be fully proven in an ongoing randomized trial. There is still a need to identify biomarkers that could even more accurately identify tumors that will sustain pCR after nCRT.

Given the importance of the immune system in cancer therapy response and in disease surveillance, some studies have revealed that tumor-infiltrating lymphocytes (TILs) correlated with response of neoadjuvant therapy and improved survival (11,12). TILs are located in intra-tumoral and stromal compartments, and composed of various lymphocytes with diverse activities, including $CD4^+$, $CD8^+$, $Foxp3^+$, and $CD57^+$ (13,14). Emerging evidence suggests that the amount of lymphocyte infiltration of primary tumors predicts favorable survival in a number of tumor types (15,16). Qian *et al.* successfully built a model combining tumor regression grade and TILs in locally advanced esophageal squamous cell carcinoma (LA-ESCC)

from post-CRT biopsy to predict the treatment response of neo-CRT and definitive CRT. When response was evaluated by biopsies alone, the sensitive and specificity were only 66.7% and 55.4%. After adding the TIL factor into the evaluation methods, the sensitivity and specificity of predicting pCR greatly increased to 86.7% and 90.0%, respectively (17).

Using TILs as a surrogate biomarker, the Qian *et al*.'s study pointed to the importance of measuring the magnitude of the immune response to the tumor from CRT as a potential to identify pCR. However, there are still some contentious areas related to this area of research. Their study suggested that TILs within the tumor stroma was an important factor, while Jiang *et al*. suggested that TILs associated with tumor cells were associated with better survival (13). Although several studies have already demonstrated that TILs in general were associated with better outcomes, some have shown that TIL subsets, especially $CD8^+$ T cells, were related to survival (18,19). As to the level of TILs that would be prognostic, there is also no consistent cutoff value that exists. Some used a 10% cutoff (13), while others used either 20% or 50% (20,21), and in Qian *et al*.'s study, 60% was adopted. There is substantial heterogeneity between studies that could account such differences. Many used pretreatment tumor biopsies, while others used samples at the completion of CRT (17), or from the surgical specimen (13). The samples will of course vary based on the depth of the biopsies, as well as the operators' experience. Without adequately correcting for sampling heterogeneity or normalizing the proportion of TILs in either tumor or stroma calls into question the use of TILs as a reliable biomarker.

Other limitations including the relatively small sample size and the short follow-up time to reliably score overall survival. It is also quite clear that determining the histomorphologic regression of tumor tissue after nCRT is also subject to pathologic interpretation and has quite a bit of interobserver variability among pathologists. Moreover, there are differences between tumor regression at the primary site and at the metastatic lymph nodes, and both could differentially influence survival (22). However, Qian *et al*. prioritized the response rate and lymphocytes infiltration only within the primary tumor site, without taking into account the remission within metastatic lymph nodes.

In summary, Qian *et al*.'s study provided a potentially promising approach to identify patients whose tumors could be highly sensitive to CRT which confers better survival. Validations using larger datasets from prospective multicenter studies are needed. Accurate and reproducible tools to predict pCR and long-term survival after CRT are still in an urgent need. This is a critical time where these surrogate markers of immunologic activity could be especially useful as a predictive marker in the setting of incorporating immunotherapies with or after CRT.

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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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