Commentary

# Tumor infiltrating lymphocytes in lung cancer: a new prognostic parameter

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There has been a long-lasting interest in the role of the immune system in the development, progression and prognosis of cancer. A seemingly straightforward way to investigate the role of the immune system in cancer is to look at the immune infiltration in the tumor. It is indeed known for many years that the microenvironment in the tumor contains natural killer cells, different types of lymphocytes and antigen presenting cells, all of which play a role in the tumor immune response. As early as 2002, the complex role of lymphocytes in cancer growth was becoming clear (1). Tumor lymphocytic infiltration (TLI) and macrophages may both promote or suppress tumor progression. Consequentially, it should not come as a surprise that studies that looked at tumor-infiltrating lymphocytes as a single entity found contradicting results for survival (2-10). Therefore, more biology-driven TIL subsets were studied (11-17). The infiltration in the tumor stroma of CD4+/CD8+ T-cells was the most consistently correlated with survival, with a higher ratio being related to a better survival in surgical patients.

However, larger studies with external validation were lacking and besides the prognostic, also the predictive influence of the TIL infiltration is of great interest. The study of Brambilla *et al.* (18) should therefore be welcomed. This large international effort in patients with localized non-small cell lung cancer (NSCLC) investigated the effect of intense versus non-intense TLI on overall survival (OS), disease-free survival (DFS) and specific disease-free survival (SDFS). A discovery set (one trial, 824 patients) and a validation set (three trials, 984 patients) of patients treated with surgery with or without adjuvant chemotherapy, was studied. Intense TLI referred to a strong heavy lymphocytic infiltrate (intralobular and/or perilobular) of a density equivalent to that seen in a lymph node with metastasis.

The median follow-up was in both groups long enough (4.8 and 6 years, respectively) to draw reliable conclusions. TLI was intense in 11% of the patients in the discovery set compared with 6% in the validation set (P<0.001). TLI was prognostic for OS, DFS and SDFS in both the discovery set (OS: HR, 0.56; P=0.002; DFS: HR, 0.59; P=0.002; SDFS: HR, 0.56; P=0.003) and in the validation set (OS: HR, 0.45; P=0.01; DFS: HR, 0.44; P=0.005; SDFS: HR, 0.42; P=0.008). There was no heterogeneity across trials. Interestingly, no significant predictive effect for the use of adjuvant chemotherapy was observed for TLI (P≥0.78 for all end points).

Besides TLI, in the multivariate Cox model, also gender, WHO performance status, tumor stage and histology were significant prognostic factors for OS and PFS in the discovery and the validation set.

Although the proportion of patients with an intense TLI is small, it is surprising and unusual to observe such a strong influence on strong endpoints such as the OS. Moreover, TLI intense patients form a very heterogeneous population and the current study did not look at the specific lymphocytic subsets that may be related to the prognosis. It is conceivable that focusing on a specific cell subset within TLI could amplify its prognostic value.

Although a multivariate analysis was done, we do not have a prognostic model that incorporates all co-variates in a quantitative prognostic model. Clinicians do need this information, displayed as e.g., nomograms, in order

to make decisions or to counsel patients. Although at the moment no therapeutic consequences should be considered in relation to the intensity of TLI, these models may give us information how much of the variability in survival is due to TLI *vs.* other prognostic parameters.

The findings of this study indicate that a strong tumor immune response has significant prognostic potential. Although Brambilla *et al.* could not show any predictive impact of TLI's for chemotherapy, we should not dismiss the predictive potential of tumor immune infiltration too soon. Immune therapy has been searching for predictive parameters for several years, mainly focusing on expression of a specific therapy target like PD-L1. Testing TLI intensity in an immune therapy setting might still showcase it as instrument to select patients who gain the most therapy benefit. For example, it has already been suggested that parameters like CD8+ infiltration determine efficacy of immune therapy and radiotherapy combinations (19). Findings like these stress the importance of the immune environment in predictive and prognostic settings and thus, open up options for TLI to find additional clinical meaning. However, the broad nature of TLI obscures the specific immune cell subsets that play a role in an antitumor response, both positively like effector T cells and negatively like regulatory T cells. It might be beneficial to focus on a certain immune cell subset rather than pooling them into a general parameter like TLI if you want to find a therapy response predictor.

When testing TLI as a predictive parameter for (immune) therapy, another interesting question that must be asked is the impact of therapy on TLI itself. Immune therapy is currently not a first line treatment for NSCLC. Often, those patients have been exposed to radiation therapy of chemotherapy, which both have an impact on the tumor immune environment. Does this change prognostic and/or predictive impact of preoperatively determined TLI? The influence of different therapies on TLI itself is a big question mark that needs to be addressed if TLI is to be used in a clinical setting.

For the immediate future, it is key to dig into the details of the TLI and to characterize them in relation to genetic and microenvironment characteristics. In large databases such as used in the study of Brambilla *et al.* it may be possible to explore many fundamental questions regarding the immune biology of tumors. This will aid dramatically the improvement of immune therapy for lung cancer, which already now has led to long-lasting responses in patients with metastatic disease.

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## Footnote

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