Editorial

Tumor lymphocytic infiltration in non-small cell lung cancer: the ultimate prognostic marker?

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Lung cancer is still the leading cause of death worldwide despite recent improvements in early diagnosis and treatment. Only about 20–25% of patients are resectable at the time of diagnosis (stage I–IIIA), but clinical outcomes vary among the same TNM stage. The high recurrence rate has prompted many authors to look for new biomarkers to identify patients who can benefit from adjuvant therapies.

Malignant tumors constitute a microenvironment themselves, containing tumor, endothelial, stromal and immune cells. The study of tumor-infiltrating lymphocytes (TILs) has advanced in the last years, as it has been shown that immune cells have impact on the clinical course of several solid tumors (1). TILs can be seen in approximately 25% of patients with lung tumors, more frequently in poorly differentiated carcinomas and in tumors with microscopic vascular invasion (2).

The immune infiltrate in solid tumors comprise adaptive and innate immune cells. All cell types may be present in a tumor, (macrophages, neutrophil granulocytes, dendritic cells, natural killer cells, mast cells, B cells and effector T cells), but T lymphocytes constitute 80% of TILs, and among them, $CD8^+$ cytotoxic lymphocytes are the effector arm of adaptive immunity (1,3-5).

Several published studies show a positive prognostic effect of $CD8^+$ cytotoxic T cells in different tumors, especially in colorectal cancer, but also in breast tumors, ovarian, esophageal and pancreatic cancer (6,7).

The studies published analyzing the prognostic influence of TILs in non-small cell lung cancer (NSCLC) had some contradictory results. The series published by Ruffini *et al.* in 2009 (2) showed that $CD8^+$ T cells were related to a prolonged survival in squamous cell carcinoma. Similar results were observed in patients with high infiltration of CD3 or a high ratio CD4/CD8 and CD20 in tumor stroma (8,9). Longer survival was also found in two series of stage I patients with increased total TILs (10,11).

In a recently published series of 552 tissue microarrays, $CD3^+$ and $CD8^+$ T cells were associated with better outcome, but only CD8 provided independent prognostic value in NSCLC. In the same series of patients, the degree of lymphocytic infiltration failed to have prognostic value (12).

The study recently published by Brambilla *et al.* (13) in the *Journal of Clinical Oncology* analyzes the prognostic value of tumor lymphocytic infiltration (TLI) in a group of completely resected NSCLC patients. The authors validated the predictive value of TLI in patients included in two adjuvant chemotherapy randomized trials. The intensity of TLI was divided in two categories, intense TLI and nonintense.

The analysis showed a longer overall survival (OS) in the group of patients with an intense TLI, 59% 5-year OS compared to 40% in the non-intense group (P=0.001). The analysis of disease-free survival (DFS) showed similar results with 54% 5-year DFS for the intense group compared to 35% (P=0.001) (13).

The results of validating the prognostic value of TLI in the adjuvant chemotherapy trials were also similar. OS and DFS were longer in the intense TLI group, 85% 5-year OS compared to 58%, and 79% 5-year DFS compared to 50% respectively (13).

Recently, a review of the role of TILs in development, progression and prognosis of NSCLC has been published (14). Seventeen studies were included in the review. Half of them found that $CD8^+$ T cells were and independent positive prognostic factor for NSCLC patients (14).

The location of lymphocytic infiltration has also been

analyzed. Different publications show that immune cell populations are distributed strategically within different tissue compartments: the tumor core, surrounding the tumor stroma, or at the invasive margin. All these characteristics, cell type, density and location, constitute the immune contexture (14). Schalper *et al*. suggest that the spatial location of the immune cell subtypes in relation to cancer cells may have biological relevance (12).

The Brambilla *et al*. study did not differentiate the immune cell subtypes among the TLI, therefore the authors could not assess whether the effect of intense lymphocytic infiltration could be related to one subtype of immune cells: $CD4^+$, $CD8^+$, CD20 or regulatory T cells (13).

Donnem *et al*. found that the density of stromal $CD8^+$ T cells was a strong independent positive prognostic factor on DFS, OS and disease-specific survival (15). The evidence that analyses the prognostic value of TILs in the different compartments is increasing, and stromal TILs appear to have a superior prognostic impact than the epithelial ones (14,16,17).

The Brambilla *et al*. study did not include the stromal and epithelial discrimination of the lymphocytic infiltration, because the authors believe that it could add confusion and impair inter-observer reproducibility (13).

The concept of immune-editing refers to the capacity of the immune system to shape the emerging tumors. This process describes the interactions between immune and tumor cells. It involves three phases. In the first phase innate and adaptive cells destroy early tumors. The second one is the equilibrium phase, in which those cells that have not been eliminated are held latent. The last phase is the escape phase, in which tumor cells produce cytokines and growth factors that induce an immunosuppressive state so that the tumor cells may avoid immune recognition leading to tumor growth (14,18).

The role of the immune system is dual; it can suppress tumor growth but also promote it by selecting cancer cells that can evade surveillance. As suggested in the series published by Chiba (19) and Ruffini (2), TILs may have an immune-surveillance effect against the growth of micro-metastasis. That effect could explain why some early stage patients develop distant metastasis shortly after a lung resection (2,19).

The study of Brambilla *et al*. (13) failed to identify any interaction between TLI and chemotherapy treatment, with an OS HR of 0.88 for patients treated with chemotherapy *vs*. 0.90 for the non-chemotherapy group (P=0.96). The analysis of DFS and SDFS respectively showed similar results (13). In other malignancies like breast cancer, a high amount of infiltrating $CD4^+$ T cells after palliative chemotherapy were related with improved clinical response (20,21). In light of these results, Brambilla *et al*. raise the question about the suitability to use TLI as a stratification factor in trials testing immunotherapy.

The literature published, show TLI as an independent prognostic factor suggest that intense lymphocytic infiltration could be a good marker to establish a TNM immune-score, as it has been proposed for colorectal cancer (6,7).

Bremnes *et al*. (14) developed a Immuno-score classifying the density of $CD8^+$ T cells in the tumor stroma of lung cancer patients in three categories (low, intermediate or high). They managed to demonstrate a prognostic impact of the Immuno-score within IA to IIIA pStages similar to TNM pStage. These results should be validated in large prospective studies before they are implemented, but in the future could be a tool for predicting patient's response to immune therapies.

The results published by Brambilla *et al*. (13) are of clinical importance. The presence of a high TLI suggests that the immune system plays a key role in the tumor evolution and the patient's outcome. Evaluation of the immune cell infiltration should be a standard practice in the management of cancer patients. The development of a TNM immune-score could be a good tool to identify patients who would benefit from new immune therapies.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Comment on: Brambilla E, Le Teuff G, Marguet S, *et al*. Prognostic Effect of Tumor Lymphocytic Infiltration in Resectable Non-Small-Cell Lung Cancer. J Clin Oncol 2016;34:1223-30.

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