Evaluating the significance of density, localization, and PD-1/PD-L1 immunopositivity of mononuclear cells in the clinical course of lung adenocarcinoma patients with brain metastasis

**Background.**
Management of lung cancer patients who suffer from brain metastases represents a major challenge. Considering the promising results with immune checkpoint inhibitor treatment, evaluating the status of immune cell (IC) infiltrates in the prognosis of brain metastasis may lead to better therapeutic strategies with these agents. The aim of this study was to characterize the distribution of ICs and determine the expression of the checkpoint molecules programmed death protein 1 (PD-1) and its ligand, PD-L1, in brain metastasis of lung adenocarcinoma (LUAD) patients and to analyze their clinicopathological correlations.

**Methods.**
We determined the presence of peritumoral mononuclear cells (mononuclear ring) and the density of intratumoral stromal mononuclear cells on brain metastasis tissue sections of 208 LUAD patients. PD-L1/PD-1 expressions were analyzed by immunohistochemistry.

**Results.**
Mononuclear rings were significantly associated with better survival after brain metastasis surgery. Cases with massive stromal IC infiltration also showed a tendency for better overall survival. Lower expression of PD-1 and PD-L1 was associated with better survival in patients who underwent surgery for the primary tumor and had multiple brain metastases. Steroid administration and chemotherapy appear not to influence the density of IC in brain metastasis.

**Conclusion.**
This is the first study demonstrating the independent prognostic value of mononuclear rings in LUAD cases with brain metastasis. Our results also suggest that the density of tumor-associated ICs in addition to PD-L1 expression of tumor cells and ICs as well as PD-1 expression of ICs may hold relevant information for the appropriate selection of patients who might benefit from anti–PD-L1 or anti–PD-1 therapy.