Prognostic value of the study of inflammatory lymphoid infiltrate of the peritumorous zone of malignant neoplasms (literature review)

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Abstract. *The review presents the state of the problem of studying the prognostic value of lymphoid infiltrate in the peritumorous zone of malignant neoplasms of various localizations.*
Keywords: *malignant neoplasms, peritumorous zone, lymphoid infiltrate.*

Currently, the dominant approach in pathological anatomy is the approach to the study of the predominantly parenchymal component of malignant neoplasias, which was formed, first of all, for diagnostic purposes, but it can be significantly expanded due to the study of tissue reactions occurring in structures located near the tumor [1]. In addition, the prognostic value of inflammatory infiltration of the peritumorous zone [PZ] carcinomas has been studied much less than that of the intratumorous zone. Several studies have shown that an increase in the number of lymphocytes in PZ tumors was associated with a better prognosis for patients [2]. In other studies, it was shown that the density of PZ infiltration by immune cells is interrelated with the progression of the neoplasm. According to these authors, tumor-associated cytokines have an effect on lymphocytes, inhibiting their antitumor properties. The ability of immune cells to acquire new properties promoting tumor progression is allowed [3,4].

This review presents data on the study of the prognostic value of lymphoid infiltration in PZ tumors of some localizations.

Research by Vieira F.L. et al. (2008) found that the most extensive population of lymphoid cells in PZ squamous cell carcinoma of the oral cavity were T-lymphocytes, among which CD8+

cells (cytotoxic T-lymphocytes) predominated, relative to CD4+ T-lymphocytes, B-lymphocytes were the second type of infiltration cells -the one in number [5].

In PZ ovarian cancer, a high expression of CD3+ cells was found in unfavorable carcinomas, and a higher number of CD4+ cells was noted in tumors with a favorable prognosis. The absence of CD20+ B-lymphocytes was associated with the absence of metastases to the lymph nodes [6].

In colorectal cancer, postoperative survival of patients was significantly more associated with a low level of infiltration with PZ CD8+ T-lymphocytes than with a high level of these cells ($p = 0.01$). The authors conclude that the content of CD8+ T cells in PZ indicates their antitumor effect in patients with colorectal cancer [7]. Song E. et al. (2000) found that the expression of the Fas ligand on the membrane of peritumorous lymphocytes is interrelated with the apoptotic index of tumor cells [8]. Data from Nakagawa K. et al. (2015) showed that the 5-year postoperative survival in colorectal carcinoma in patients with high infiltration of PZ by regulatory T cells (Tregs) was 74.8%, while in patients with low infiltration Tregs PZ was 40.3% ($p <0.01$) [9]. According to Xu F.Y. et al. (2003) PZ lymphoid infiltration in colorectal cancer was an independent prognosis factor [10].

An increase in the number of CD20+ peritumoral lymphocytes in soft tissue sarcomas was associated with a short survival of patients after surgery ($p = 0.03$). In multivariate analysis, the high content of CD20+ lymphocytes in the PZ ($P = 0.03$) was an independent factor of poor prognosis. Similar relationships were not found for CD3+, CD4+ and CD8+ lymphocytes [11].

In skin melanoma, a high number of peritumoral lymphocytes was associated with low levels of Clark carcinoma grading ($p = 0.001$) and lower mitotic tumor activity ($p = 0.01$). A trend was found for longer survival in cases with a high lymphocyte count in the PZ ($p = 0.07$) [12].

Liu L et al. (2016) showed that peritumoral CD8+ T cells were predictive factors of postoperative survival in patients with pancreatic carcinoma, but no correlations with clinical and morphological prognostic factors were found [13].

The density of peritumorous lymphocytic infiltrate in squamous cell skin cancer was correlated with the age of patients and the degree of malignancy and tumor differentiation, but it was not correlated with the survival of patients [14].

In hepatocellular carcinoma, the density of distribution of peritumoral Tregs (T-regulatory lymphocytes) positively correlated with the density of distribution of mast cells ($r = 0.35$; $p <0.001$). Tregs, especially in combination with mast cells, had better predictive value than mast cells alone [15].

The density of lymphoid infiltrate in the PZ in kidney cancer was associated with such important prognostic factors as stage ($r = 0.31$); Fuhrman degree of anaplasia ($r = 0.57$); tumor size ($r = 0.34$) and the presence of metastases ($r = 0.42$) [16,17]. The number of peritumoral Tregs in

PZ in kidney cancer positively correlated with intratumoral COX-2 expression (r = 0.34; p <0.001). The number of peritumoral Tregs was associated with TNM stage (P = 0.001) and tumor size (p = 0.002). Multivariate analysis showed that a high number of peritumoral Tregs was an independent predictor for shorter patient survival [18].

Squamous cell lung cancer with metastases to regional lymph nodes in the PZ tumor was characterized by a predominance of CD4+, CD8+ and CD20+ lymphocytes [19].

According to M.A. Senchukova. et al. (2015) in gastric cancer, focal low density of distribution of CD20+ B-lymphocytes in the PZ was significantly associated with the early stages of the disease and was not associated with long-term results of treatment, and the presence in PZ of pronounced infiltrates with multiple lymphoid follicles from CD20+ cells was associated with a diffuse type of gastric cancer and a poor prognosis [20]. Tomchuk O.N. (2016) showed that pronounced CD20+ B-lymphocytic infiltrates were present in the PZ of large tumors (> 5 cm) and in multiple metastases of gastric cancer [21].

In breast cancer, depending on the increase in the degree of tumor malignancy in the PZ, the number of CD4+ cells and CD20+ B-lymphocytes increased, with the formation of follicle-like structures without germinal centers, while the number of NK cells, CD8 cells and CD56 cells (natural killers) decreased [22]. Menegaz RA et al. (2008) found that the phenotype of PZ inflammatory infiltrate lymphocytes is associated with tumor size. A significant decrease in peritumous CD3+ T lymphocytes was found in tumors larger than 2 cm, compared with carcinomas smaller than 2 cm [23].

The density of the inflammatory infiltrate in the PZ of laryngeal cancer was the highest in high-grade carcinomas, the infiltrate was characterized by a large number of CD20+ B-lymphocytes, sometimes with a tendency to the formation of follicle-like formations without germinal centers. The number of CD4+, CD7+, CD8+ and CD56+ cells increased with an increase in the clinical stage of the disease. An interrelation was also revealed between the density of the inflammatory infiltrate in the PZ and the size of the neoplasm [24].

Thus, the data obtained in the study of the prognostic value of peritumous lymphoid infiltrate of malignant carcinomas are few and contradictory, and therefore this issue needs further study.

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