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IMPACT OF CD4+ LYMPHOCYTE DISTRIBUTION ON THE IMMUNE MICROENVIRONMENT, MORPHOLOGICAL CHANGES, AND THERAPEUTIC OUTCOMES IN SOFT TISSUE SARCOMAS

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Abstract

This study examines the significance of CD4 lymphocyte localization in the tumor microenvironment of soft tissue sarcomas and their impact on the efficacy of therapy. The analysis showed that intratumoral (intra-umoral) infiltration of these cells is significantly associated with pronounced morphological regression and a high level of therapeutic pathomorphosis, indicating the important role of immune mechanisms in the formation of an antitumor response. Localization of CD4+ T lymphocytes inside the tumor enhances the immune response, stimulates cytotoxic cells and helps to reduce tumor volume, which confirms the theoretical concept of strengthening local immune activation to improve treatment efficacy. At the same time, the effect of CD4 lymphocyte localization on short-term clinical indicators of responses to therapy (complete, partial, stabilization, progression) was statistically insignificant, which indicates the need for further research for a deeper understanding of the mechanisms of interaction between immune cells and the therapeutic effect. The data obtained emphasize the prospects of using CD4 lymphocyte localization as a prognostic marker for assessing the morphological and long-term response, as well as for the development of new methods for optimizing immunotherapy for soft tissue sarcomas.

Keywords: *soft tissue sarcoma, tumor microenvironment, chemotherapy, radiation therapy*

Introduction

The rapid development of areas in oncology, especially the active study of the role of the tumor's immune microenvironment as a key factor influencing the progression, response to treatment, and prognosis of patients, necessitates the relevance of the study. According to modern international data, soft tissue sarcomas are a heterogeneous group of malignant tumors, comprising more than 50 histological subtypes united by a common term. These tumors constitute approximately 1% of all malignant neoplasms and are characterized by high morphological and molecular diversity,

which makes diagnosis, selection of effective therapy, and prediction of clinical outcomes difficult (Huang H., Fan Y., Zhang S., Bai X., Wang X., Shan F., 2025).

Numerous studies show that in soft tissue sarcomas, the immune microenvironment plays a significant role, and the specific status of active immune cells within the tumor is a predictor of therapeutic outcomes and long-term prognosis. A particularly significant factor is the localization and activity of CD4+ T-lymphocytes, which perform regulatory and supporting functions in anti-tumor immunity, activating cytotoxic T-lymphocytes and enhancing the body's immune response. These cells participate in the regulation of immune mechanisms and the creation of an immunoactive microenvironment, which contributes to more pronounced morphological regression of the tumor (Van der Graaf WTA., Orbach D., Judson I. R., Ferrari A., 2017.

In the context of the introduction and widespread use of immune methods of cancer treatment, such as control point inhibitors, the study of the role and localization of CD4+ T-lymphocytes within tumor structures is becoming particularly relevant. International studies confirm that active $CD4^+$ lymphocytes within the tumor tissue are associated with more favorable outcomes, less recurrence, and increased survival. However, the role of their localization – within the tumor (intra-umoral infiltration) or around it (peritumoral infiltration) – has not been fully studied and requires additional evidence (Lee A. Q., Hao C., Pan M., Ganjoo K. N., Bui N., 2024).

Thus, the relevance of the study is especially high in light of the need to improve the accuracy of diagnosis and prognosis of treatment for soft tissue sarcomas, the prospects of implementing immunological markers for personalized treatment, as well as the development of new combined therapeutic strategies that increase the effectiveness and resistance of treatment. These tasks correspond to global standards and trends in the field of oncology and require further research to optimize the diagnosis, treatment, and prevention of relapses, which determines the scientific and practical relevance of this work (Wood G. E., Meyer C., Petitprez F., D'Angelo S. P., 2024; Recine F., Vanni S., Bongiovanni A., Fausti V., Mercatali L., Miserocchi G., et al., 2024).

Materials and methods

The study was conducted at the Children's Oncology, Hematology and Immunology Scientific and Practical Medical Center, as well as the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology and its Tashkent City Branch, in the period from 2014 to 2024. 174 patients diagnosed with rhabdomyosarcoma of various localizations participated in the study.

Inclusion criteria: diagnosis of soft tissue sarcoma, availability of data on chemotherapy and material for immunohistochemical analysis. Patients with preliminary immunotherapy or insufficient volume of biopsy material were excluded.

Tumor tissue samples obtained by biopsy were used to assess the immune microenvironment. The samples were fixed in 10% formalin and enclosed in paraffin. 4 μm thick sectional cuts were stained using antibodies to determine the status of CD4, CD8, CD20, and CD68. The results of the pathohistological examination were evaluated by two independent pathologists.

Assessment of the localization of immune cell infiltration was carried out by dividing the samples into intratumoral and peritumoral zones. Cell counting was performed in 5 independent fields of view using microscopy. The results were recorded as the percentage of positive cells from the total number of cells in the visual field.

To analyze the differences in the level of infiltration and response to chemotherapy, Pearson's chi square and Fisher's precision criteria were used. The significance level was established at $p<0.05$. All calculations were carried out using statistical software.

This approach provided a detailed assessment of the immune microenvironment and its impact on clinical outcomes in patients with soft tissue sarcomas.

Results

We analyzed the effectiveness of therapy depending on the location of CD4 lymphocytes in the tumor stroma or parenchyma.

A statistically significant difference ($p = 0.020$) was revealed when analyzing the relationship between the degree of pathomorphism and the localization of CD4 lymphocytes. In particular, in intratumoral

infiltration, cases of low-grade pathomorphosis are more pronounced, while in peritumoral infiltration, more pronounced changes (grade II and higher) are more frequently recorded. This suggests that the activity of CD4 lymphocytes, localized within tumor structures, can play a more significant role in tumor regression, contributing to a more pronounced morphological response, higher pathomorphism.

Table 1. *Analysis of therapy effectiveness depending on location*

Indicators	Category	localization (intratumor-1, peritumor-2)			p
		intratumoral infiltration	peritumoral infiltration	Indicator 3.	
Chemotherapy effect (complete-1, partial-2, stabilization-3, progression-4)	Full effect	3 (6.8)	12 (18.8)	4 (12.5)	
	Partial effect	17 (38.6)	23 (35.9)	17 (53.1)	
	Stabilization	22 (50.0)	27 (42.2)	7 (21.9)	
	Progression	2 (4.5)	2 (3.1)	4 (12.5)	0.071
Degree of therapeutic pathomorphosis	therapeutic pathomorphosis I	14 (31.8)	7 (10.9)	6 (18.8)	0.020* intratumoral infiltration – peritumoral infiltration = 0.019
	therapeutic pathomorphosis II	20 (45.5)	23 (35.9)	9 (28.1)	
	therapeutic pathomorphosis III	6 (13.6)	21 (32.8)	8 (25.0)	
	therapeutic pathomorphosis IV	4 (9.1)	13 (20.3)	9 (28.1)	
Radiation therapy response	Full effect	6 (15.8)	10 (18.9)	2 (11.1)	
	Partial effect	20 (52.6)	19 (35.8)	6 (33.3)	
	Stabilization	6 (15.8)	15 (28.3)	7 (38.9)	
	Progression	6 (15.8)	9 (17.0)	3 (16.7)	0.521

** – differences in indicators are statistically significant ($p < 0.05$)*

When comparing the response to chemotherapy and radiation therapy by localization types, no significant statistical differences were found ($p > 0.05$). This suggests that, despite the effect of CD4 lymphocyte localization on tumor morphological regression, they are less dependent on the short-term clinical effectiveness of therapy.

The localization of $CD4^+$ T-lymphocytes within the tumor tissue (intratumoral infiltration) may indicate an active immune response to tumor development, contributing to its regression, as these cells perform regulatory and auxiliary functions, activate cytotoxic T-lymphocytes, and contribute to the synthesis of antibodies, enhancing the anti-tumor immune response. In peritumor infiltrates (peritumoral infiltration), the role of these cells may be less stable or less active in the context of the morphological response, which is associated with less permeability or less intensive activation of immune mechanisms within the tumor.

It has been proven that the localization of CD4 lymphocytes plays a significant role in the morphological regression of the tumor and the degree of pathomorphism, which is important for prognostic assessment and the development of immunotherapeutic strategies. It should be noted that the activity of circulating or peritumor CD4-lymphocytes may have less value for predicting short-term clinical effects, while localization within the tumor is a critical factor for assessing the potential of the immune response.

The localization of CD4 lymphocytes within the tumor (intratumoral infiltration) is significantly related to the severity of mor-

phological regression and a higher level of therapeutic pathomorphosis. The activity of immune cells within the tumor stroma component contributes to a more effective morphological response to treatment and can serve as a prognostic marker for assessing the potential of immune-responsible regression in soft tissue sarcomas. At the same time, the effect of CD4 localization in the peri-tumor zones is less pronounced and does not significantly affect the response to reconstructive therapy.

Conclusion

As a result of the conducted research, it was established that the localization of CD4-lymphocytes within the tumor tissue – in particular, their infiltration into the tumor parenchyma (intratumoral infiltration) – is significantly related to the pronounced morphological regression of the tumor process and the high level of therapeutic pathomorphosis, which indicates the important role of these cells in the formation of an effective antitumor immune response. The activity of CD4+ T-lymphocytes within tumor structures contributes to the strengthening of the immune mechanism, stimulates cytotoxic T-lymphocytes and other components of the immune system, which conditionally leads to a decrease in tumor volume and more pronounced morphological tissue. These data confirm the theoretical concept that local immune activity within the tumor is the most important driver of therapy, capable of improving morphological indicators and, possibly, long-term clinical outcomes.

At the same time, the absence of statistically significant differences in clinical response, expressed in the form of complete, partial, stabilizing effects and progression, indicates the complexity of the relationship between immune activity and short-term therapeutic outcomes. This may be due to the fact that immune status, especially the localization and activity of CD4-lymphocytes, primarily affects morphological regression and long-term defense mechanisms rather than acute clinical indicators such as symptomatic dynamics or shortened response time.

These results emphasize the need to consider immune factors when planning complex therapy for soft tissue sarcomas. In particular, assessing the localization of CD4-lymphocytes in tumor tissue can serve as an additional predictor of the effectiveness of the morphological response and long-term prognosis. In the future, the use of this marker in clinical practice can contribute to individualizing treatment strategies, increasing the effectiveness of immunotherapy, and developing new methods for activating immune mechanisms within the tumor microenvironment. Overall, the obtained conclusions confirm the prospects for further research aimed at a deeper understanding of the role of the immune system in the regression of sarcomas and the optimization of immunotherapy.

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Kahharov A. J. – assistance in text correction

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