Volume 3, Issue 5, May 2025 ISSN (E): 2938-3765

FEATURES OF LOCAL IMMUNITY IN PATIENTS WITH OROPHARYNGEAL CANCER

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Abstract
Cancer of the oral cavity and oropharynx in clinical practice is considered as a single oncopathology, treated as oropharyngeal cancer (OPR). This pathology occupies the 2nd place in the incidence rate among head and neck tumors in the Russian Federation [1]. The incidence of OFR in the Russian Federation is not the same: in the industrial districts, which include the Rostov region, it is high, which put the region in the top ten regions with a high incidence of this pathology.

Introduction

Patients who turn to an oncologist for ORF, as a rule, already have a widespread (grade III—IV) tumor process [2]. The mortality rate of such patients in the 1st year after treatment ranges from 30 to 40% [3]. This necessitates finding out the root causes of this pathology, improving the methods of its diagnosis and treatment using well-established clinical methods [4]. At the same time, modern laboratory methods, which make it possible to predict the patient's condition before the start of treatment and during its implementation, are used in practice in order to successfully correct the treatment. An important role is given to the assessment of the practical experience of related oncological centers dealing with these problems. So, in the Republic of Uzbekistan, the highest incidence of OFR is also detected in areas with industrially developed production: in Tashkent and the Bukhara-Navoi region [5].

The purpose of the study was to conduct a comparative assessment of some factors of local immunity in tissue samples of the tumor and peritumoral zone in patients with ORF with different prevalence of the process.

Tasks: 1) to evaluate the possibilities of using immunological methods in patients with ORF; 2) to determine the levels of cytokines in the tumor tissue and peritumoral zone in patients with widespread OFR without metastases, with metastases and relapses; 3) to evaluate the differences in the content of secretory immunoglobulin A in the tumor tissues and the peritumoral zone of this category of patients.

Materials and Methods

The object of the study were 40 patients with OFR (32 men, 8 women) aged 40 to 74 years who received treatment in the departments of head and neck tumors of the RNIOI of the Ministry of Health of Russia and in the Tashkent regional branch of the RSNPMTSOiR of the Ministry of Health of Uzbekistan in the period from 2007 to 2014 [6, 7]. There were 25 patients with stage III (T1-3N0-1), with stage IV. (T4N0-1) - 7, with widespread recurrence - 8. Prior to admission to the hospital for surgery, all patients received neoadjuvant radiation therapy (40 Gy). Operations

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performed (38 of them at the RNII of the Ministry of Health of Russia, and 12 at the Tashkent regional branch of the RSNPMTSOiR of the Ministry of Health of Uzbekistan) included radical removal of the primary focus, and in the presence of cervical metastases, one-stage cervical lymph node dissection in the volume of IB, IIA-B , III and VA levels. We will not dwell on the details of the operations performed and the results of treatment, as they will be presented in future publications, but we will dwell on the topic of the presented article - some immunological factors in patients with ORF.

During operations, tissue samples of the tumor and peritumoral zone were taken from patients. They were homogenized and the levels of pro- and anti-inflammatory cytokines were determined: interleukins (IL) 1c, IL-6, IL-8, IL-10; interleukin IL-1 receptor antagonist (IL-1RA), interferon (IFN) a and y; tumor necrosis factor a (TNF-a) and secretory immunoglobulin A (SIgA) by enzyme immunoassay (ELISA) with test systems produced by Alfa Med (Bukhara).

From the characteristics of the specific (in terms of 1 g of protein) levels of cytokines in the tissues of the tumor and the peritumoral zone (Table 1), it can be seen that in the tumor tissue, compared to the peritumoral zone, there was a statistically significantly higher content of pro-inflammatory cytokines IL-ie, IL -6 and IL-8 in the group of primary patients without regional metastases, in patients with regional metastases similar differences were observed. With relapses, such a difference was noted only in terms of the level of IL-6, however, it was statistically unreliable due to a small number of observations and high individual variability of indicators. Tissue levels of interferons IL-2 and IL-10 in the tumor and peritumoral zone were low and had no statistically significant differences. It should be noted that differences in IL-ie, IL-6, and IL-8, expressed in 2 other groups, are lost in tissue samples of the peritumoral zone and tumor in relapses. This indicates the approach of visually non-malignant tissue to the tumor in terms of immunological characteristics and may indirectly indicate the loss of its properties that limit the proliferative potential.

Table 1. Relative levels of cytokines in the tumor tissue and peritumoral tissue in patients with oropharyngeal cancer, pg/g of protein

Cytokine	tumor	Peritumoral zone	tumor	Peritumoral zone	tumor	Peritumoral zone
	no regional metastases		*with regional metastases*		*with relapse*	
TNF-a	2,32 ± 2,16	1,47 ± 0,24***	2,83 ± 0,91	3,10 ± 0,96	2,82 ± 0,78	2,320 ± 0,357*,**
IL-8	16,3 ± 3,5*	5,50 ± 2,33	26,7 ± 7,2*	7,30 ± 2,78	17,0 ± 7,4	12,7 ± 7,2
IL-6	7,1 ± 3,2*	0,71 ± 0,158	5,90 ± 22,03*	1,23 ± 0,49	13,0 ± 7,33	1,40 ± 0,56
IL-10	2,50 ± 0,33	2,42 ± 0,33	2,92 ± 1,10	3,64 ± 1,69	1,23 ± 0,40	1,84 ± 0,50
IL-1B	14,4 ± 3,8*	4,70 ± 0,71***	19,0 ± 4,2*	6,7 ± 2,1	17,5 ± 8,2	26,5 ± 10,7**
IFN-a	0,576 ± 0,100	0,548 ± 0,090	0,442 ± 0,110	0,47 ± 0,08	-	-
IFN-Y	1,3 ± 0,2	1,576 ± 0,190	1,26 ± 0,17	2,35 ± 0,76	-	-

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Differences in two parameters were found in the peritumoral zone: the levels of TNF-a and IL-ie in relapses were higher than in primary tumors without regional metastases.

According to the content of SIgA in the studied tissues (Table 2), it can be seen that in patients without metastases and with them there were no differences in the tissue specific content of SIgA between the tumor and the peritumoral area, while in patients with relapses higher levels were observed in the tumor tissue compared with the peritumoral zone. In tissue tumor samples of patients of the same group, the amount of SIgA was statistically significantly higher than in the group with metastases, in which its level was minimal among all the studied groups, which indicates the inhibition of its local synthesis. In the peritumoral zones, this indicator was statistically the same in all groups.

Table 2. Relative levels of the secretory immunoglobulin in the tumor tissue and peritumoral tissue in patients studied, mg/mL/g of protein

Tissue samples	**Groups of patients**		
	no regional metastases	*with regional metastases*	*with relapse*
Tumor tissue	0,274 ± 0,09	0,05 ± 0 01**,***	0,47 ± 0,08*,**
Peritumoral tissue	0,293 ± 0,15	0,142 ± 0,08	0,08 ± 0,02

Discussion

The study of local immunity factors in patients with widespread OFR revealed ambiguous indicators depending on the presence or absence of regional metastases or relapse. In the tumor tissue, hyperproduction of cytokines, mainly pro-inflammatory: IL-ie, IL-6 and IL-8, was established. At the same time, the dependence of their level on the formation of regional metastases was not revealed. The observed high level of TNF-α and IL-β in the peritumoral zones of recurrent tumors, compared with the peritumoral zones in patients without metastases and with them, indicates their cytokine characteristics approaching the tumor tissue of a recurrent tumor. Both cytokines, according to the literature, can exhibit both anti- and pro-oncogenic properties due to angiogenic activity and, in all likelihood, at a high content can stimulate the development of relapse [8, 9].

A decrease in the content of SIgA in the tumor tissue during its metastatic spread, compared with the peritumoral zone, recurrent and non-metastatic tumors, indicates the suppression of the B-cell link of local immunity and possible functional disorders in the preceding links of the immune system (macrophage and T-cell).

Conclusions

1. Clinical data in combination with immunological parameters should be used to supplement an objective assessment of the status of patients with oropharyngeal cancer.

2. The emerging high level of pro-inflammatory cytokines in the tumor tissue promotes progression and dissemination, which may be a consequence of both their production by tumor cells and a local inflammatory process; the levels of cytokines in the tumor tissue exceed their content in the peritumoral zone.

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3. The level of SIgA is minimal in the tissue of a metastasizing tumor and maximal in the tissue of a recurrent tumor. However, no statistically significant differences were noted.

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