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RENAL CELL CANCER PROGNOSTIC FACTORS

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ABSTRACT

This article analyzes the main clinical, morphological and molecular biological factors that influence the outcome of the disease, and their proportion is determined. Favorable prognosis factors include: lack of lymphovascular invasion, tumor infiltration by lymphocytes, lack of expression of PD-1 / PD-L1, mTOR, VEGF-A and KIT, low proliferation index.

KEYWORDS: Renal cell cancer, immunohistochemistry, prognosis, tumor receptors.

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 2-3% in the structure of all malignant neoplasms in adults, while the incidence is increasing in most developed countries: the annual growth rate is 2.3%.[1] In Russia, in 2017, RCC was first diagnosed in 13556 patients. The standardized incidence rate was 16.87 per 100 thousand population, and the increase in incidence over 10 years was 42.63%.[2] In Uzbekistan, in 2018, RCC was first diagnosed in 717 patients. The standardized incidence rate was 2.2 per 100 thousand population.[3] Despite the fact that in the majority (up to 70%) of patients, RCC is detected at the stage of a localized tumor process, more than half of patients develop metastases after surgical treatment.[4,5] The prognosis of the course of the disease in the development of a metastatic process in patients with RCC is extremely poor: in the absence of specific treatment, the period before progression is 2-4 months, and the average life expectancy after the detection of metastases is no more than 10-13 months.[6,7] To assess the prognosis of RCC development, various factors associated with the characteristics of the tumor and the patient are used: morphological type of neoplasm (clear-cell chromophobic, papillary), Furman's degree of differentiation, stage of the disease, number and localization of metastatic foci, age and status of the patient at the time of detection of the disease.[8, 9,10] The use of immunohistochemical studies in RCC allows not only to determine the management tactics, but also to determine the prognosis. The most common histological form of RCC is the clear cell type.[11,12] It is interesting to note that the prognosis in patients with the same stage of the disease varies widely. With the identification of new biological markers, the classification and approach to the treatment of patients begins to be more differentiated.[13,14]

The outcome and response to RCC treatment are most strongly influenced by the histological, molecular biological characteristics of the tumor, reflecting the pathological mechanisms of the tumor process. With the development of fundamental oncology, many biological markers have been discovered, the influence of which on prognosis remains the subject of research.

OBJECTIVE OF THE STUDY

To improve the results of treatment of patients with renal cell carcinoma by developing a personalized approach to diagnosis and treatment based on the determination of prognostic factors.

MATERIALS AND METHODS

To study the causes and conditions of generalization in patients with RCC, the features of the course, a retrospective analysis of 150 case histories of patients who had previously undergone surgical treatment was carried out.

The study included patients of various age groups from 26 to 78 years old. The distribution of patients by age was even. The average age of the patients was 55 ± 11.3 years.

During the study, such histological indicators as: the degree of differentiation, lymphovascular invasion, the

ratio of parenchyma to tumor stroma, tumor infiltration by lymphocytes were studied.

The tissue matrix was stained with hemotoxylin-eosin, as well as the following reagents: PD-1 / PD-L1, mTOR, VEGF-A, KIT, according to the standard technique based on the diagnostic clinic of PREMIUM DIAGNOSTICS LLC.

Evidence-based statistics were based on: to highlight common factors - factor analysis with the determination of the specific weight of each sign that affects the outcome of the disease; to determine the relationship between indicators ¬nonparametric (rank) correlation analysis using the Kendall method (Rk); to determine the differences - Fisher's angular transformation criterion (Φ *), Pearson's fit (agreement) criterion (x2), relative risk criterion (RR and 1 / RR).

To determine the difference, four main levels of statistical reliability were taken: high - p <0.001, medium p <0.010, low (limiting) p <0.05, insignificant (unreliable) - p> 0.05. The main verifiers of the significance of the difference were the results of multifunctional (universal) methods - Fisher.

RESULTS

It is known that a growing tumor is heterogeneous in its cellular composition, and the population of tumor cells has different biochemical parameters. Taking this fact into account, we carried out a correlation analysis of the dependence of prognosis on tumor differentiation. Analysis of the influence of the degree of tumor differentiation in connection with the probability of generalization of the tumor process is shown in Table 1.

Table 1: Distribution of patients depending on the degree of tumor differentiation and correlation analysis of the connection, with the probability of generalization.

Differentiation degree	N=70	*N=80*	χ^2/ *p*
G1	12	18	3,178
G2	18	37	9,21
G3	40	25	10,606

A general examination of the degree of differentiation with the progression of RCC reveals a statistically significant correlation with poorly differentiated tumors.

Also, from the point of view of individual prognosis, such morphological characteristics of a tumor as lymphovascular invasion, multicentric tumor growth, the ratio of stroma to tumor parenchyma, and lymphocytic tumor infiltration are very interesting.

These characteristics reflect the interactions between the tumor and the biological forces of the organism (Table 2).

Table 2: Distribution of patients depending on the influence of clinical and morphological characteristics and correlation, with the probability of generalization of the tumor process.

Histological characteristics	Main group	Control group	χ^2/ *p*
Lymphovascular invasion There is Not	 34 36	 15 65	15.094/<0,001
Ratio of stroma to tumor parenchyma Pronounced stroma	 29 41	 18 62	6.217/<0,01
Infiltration of the tumor with lymphocytes There is Not	 15 55	 29 51	3,956/<0,05
R = 0,001			

From the table. 2 shows that the presence of tumor invasion into the lymphatic and venous vessels of the organ with a high probability was a sign contributing to the early progression of the tumor (RR = -19.771, p <0.001). Another unfavorable sign found with an experienced pathologist is the ratio of stroma to tumor parenchyma (RR = -17.693, p <0.001). Tumor infiltration with lymphocytes, on the contrary, is a highly reliable favorable sign and was more common in patients with long-term remission of RCC (RR = 16.454, p <0.001).

We studied the patterns of RCC progression. It was assumed that the nature of correlations between clinical and morphological, immunohistochemical and molecular biological characteristics may have a prognostic value in the development of early progression of the disease (r = 0.001).

In retrospective analysis, there was a correlation between such data as multifocal tumor growth, invasion by tumor tissue of the lymph vascular system, with a scanty stroma and the absence of tumor infiltration by lymphocytes. All these signs were highly reliable adverse histological symptoms.

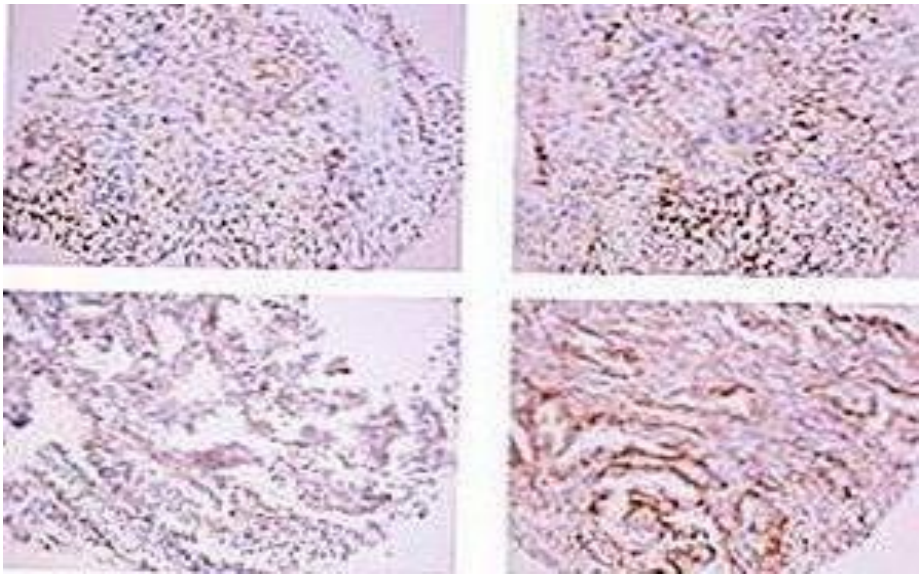
At the same time, in tumors with the above histological features, there was a statistically significant increase in the number of cells with one ($p = 0.001$) and two ($p = 0.008$) MA, as well as the total number of cells with MA $p = 0.005$ compared with tumors without data. Signs.

Infiltration of the tumor with lymphocytes was a sign of a high immunological defense of the body, creating a kind of barrier for tumor expansion.

More valuable, in prognostic terms, are the data of the immunohistochemical analysis of the tumor.

THE DISCUSSION OF THE RESULTS

Studying the literature and archival material of patients, using immunohistochemical and molecular studies, it turned out that the most sensitive tumors with PD-1 / PD-L1 status were the most sensitive to immunotherapy, the use of immunotherapy in which significantly increased disease-free and overall survival, in contrast to PD- 1 / PD-L1 negative patients.



IHC positive status: expression of PD-1 / PD-L1, mTOR, VEGF-A and KIT is a very unfavorable sign that increases the risk of tumor progression after surgery.

PD-1 / PD-L1 is an adaptive immune resistance mechanism that is elicited by tumor cells in response to endogenous immune antitumor activity. PD-L1 is usually overexpressed on tumor cells or on nontransformed cells in the tumor microenvironment. PD-L1, expressed on tumor cells, binds to PD-1 receptors on activated T cells, resulting in inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. Expression of PD-1 / PD-L1 is associated with poor prognosis. Along with the above data, positive mTOR and VEGF-A receptor status play an important role in the prognosis of the disease. The lack of expression in IHC studies, as well as a low proliferation index are signs indicating a favorable outcome of the disease (Table 3).

Table 3: Distribution of RCC patients depending on the receptor status.

IHC status:	**N=70**	***N=80***	χ^2/ ***p***
PD-1 (positive)	28	12	11,932/<0,001
PD-L1 (positive)	14	6	5,048/<0.025
VEGF-A (availability)	45	39	3.657/<0,05
KIT(availability)	54	30	23,811/<0,001
mTOR	9	1	8,08/<0,005

With a high index of tumor cell proliferation, a statistically significant increase in the expression of VEGF-A and KIT was revealed.

CONCLUSION

Favorable histological signs: absence of lymph vascular invasion, tumor infiltration with lymphocytes, pronounced stroma.

The following were attributed to favorable IHC and molecular biological characteristics: the absence of PD-1 / PD-L1, mTOR, VEGF-A and KIT expression, a low proliferation index.

Histological findings such as multifocal growth, non-clear cell variant, lymph vascular invasion, scant tumor stroma and absence of tumor infiltration by lymphocytes adversely affected the outcome of the disease.

Thus, our work has shown that the nature of the correlation between molecular biological, clinical, and morphological characteristics of a tumor reflects its biological potential and indicates the ability to early progression.

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