МЕДИЦИНСКИЕ НАУКИ

KIDNEY TUMORS: MORFOLOGICAL DIAGNOSTICS AND SURVIVAL PROGNOSIS

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ABSTRACT.
Background. The article aims to present a comparative analysis of literature materials and research data on the epidemiology, morphology and prognosis of disease in patients with renal tumors in Saratov region, Russia. *Methods.* Analysis was performed on clinical and morphological parameters of 469 patients with kidney tumors who were examined and treated at the Clinical Hospital №3 of "Saratov State Medical University" within a 5-year period (from 2006 to 2010). *Results*. Age- and gender-related characteristics of benign and malignant tumors of the kidneys, their morphological, immunohistochemical characteristics and relationships with disease prognosis have been established. *Conclusions*. Early diagnosis, precise morphological characterization and timely, adequate treatment of kidney tumors will improve the quality of life and reduce morbidity and mortality rates.
Key words: kidney tumors, epidemiology, morphology diagnostics, immunohistochemistry, prognosis.

Introduction. Recent years have seen an increase in the number of kidney oncological diseases located in different geographic regions There is an increasing number of cases of kidney tumors in the Saratov Region. It may be determined by unfavourable ecological situation in the region due to the presence of atomic power station and the development of chemical industries and fertilizers production in Balakovo. Significant growth in the incidence of malignant kidney tumors from 6 to 9% is marked annually in Russia. According to the reported rates of morbidity and mortality, kidney cancer has become a more common malignant process than lung cancer (Charlesworth et al [2]). Research regarding early detection, identification of risk factors, early diagnosis, appropriate treatment and prognosis of survival and quality of life is needed to resolve this urgent problem, taking into account the unfavourable oncological conditions.

It is known that the tactics of treatment and prognosis of malignant disease are determined mostly by the morphological characteristics of the tumor process (Eble et al [3]). Therefore, the aim of our study is to compare the clinical and morphological manifestations of the tumor process to determine the risk factors and prognosis of the disease. Moreover according to the information on cancer registry of the Saratov Region the survival analysis and the analysis of average life expectancy were conducted after the diagnosis had been confirmed in the group of patients who had died. The survival analysis has been evaluated by the Kaplan–Meier estimator using log-rank test.

Methods. We analyzed clinical and morphological parameters of 469 patients with kidney tumors examined and treated at the Clinical Hospital №3 n.a. R.V. Mirotvortsev of Saratov State Medical University n.a. V.I. Razumovsky during a 5-year period (from 2006 to 2010).

Detailed medical records and cancer registries in the Saratov region were analysed. Macroscopic, histological, histochemical and immunohistochemical studies of kidney tumor tissues were performed.

Results. Analysis of the material showed that the annual increase of renal tumor morbidity in the Saratov region was confirmed: in 2006, 65 cases were registered, in 2007, 85 cases, in 2008, 102 cases, in 2009, 104 cases and in 2010, 113 cases.

According to our data, the average age at which renal tumors were first detected was 57 years (according to the literature review (Jemal [7]), 62 years). The number of typical "adult" renal cell carcinomas diagnosed in young adults (30-35 years old) and in adolescents and children also increased (Helmy et al [6]). We noted nearly the same incidence of renal tumors in men and women (52% and 48%, respectively).

According to research, the incidence of malignant renal tumors increased by 94,24% according to literature review (Smith et al [9]). The most common malignant kidney tumor is renal cell carcinoma (RCC), which can have various presentations of histological structure. In the present study, clear cell carcinoma is the most common, constituting 80,54% of cases (358 cases: 198 men and 158 women). Other forms of RCC are much less common: papillary – 0,07% (31 cases); chromophobe – 0,05% (22 cases); multilocular – 0,03% (14 cases). Rarer forms of RCC, including carcinoma of the collecting ducts of Bellini, renal medullary carcinoma, Xp.11 translocation carcinoma, mucinous tubular, spindle cell carcinoma and unclassified forms have been identified in 0,002-0,01% according to the data received (Brunelli et al [1]).

Benign tumors of mesenchymal origin, such as angiomyolipoma – 51,85% (14 cases), haemangioma and leiomyoma most commonly develop in the kidney. Renal fibromas also occur in isolated cases.

To establish a plan for treatment and prognosis of the disease, it is necessary to obtain information on the germination of the tumor within the kidney structure and surrounding tissue and information on histology of the tumor and the degree of tumor differentiation - grade G (Han et al [5]).

We conducted a morphological study that showed that with an increased tumor grade G (higher G meaning lower cell differentiation), the aggressiveness of the tumor also increased, which manifested by increased proliferative activity of tumor cells and reduced apoptosis indices, resulting in increased germination of the tumor in the kidney and in different structures beyond its limits (metastasis). 320 of 442 tumors had evidence of invasion, of which 46 showed signs of metastasis. However, according to a literature review, the typical renal cell cancer is relatively "quiet" for a long time - it has a fibrous capsule, grows slowly and metastasizes late (Patard et al [8]).

The most unfavourable malignant renal tumors in terms of aggressiveness, invasiveness and metastatic potential are: papillary (31 cases - 29 with signs of invasion and 6 metastases) and chromophobe (22 cases - 13 with signs of invasion and 4 metastases). Single cases of medullary, mucinous, unclassified tumors, tumors of the ducts of Bellini, and anomalies of the eleventh chromosome also had signs of infestation.

Among the 356 cases of the most common variant of RCC, clear cell renal carcinoma, 245 cases (68,82%) had signs of invasion, and 35 cases (9,83%) had metastases, all of which were regarded as unfavorable prognostic signs.

Multilocular polycystic variants of RCC are the most favorable in terms of likelihood of survival. In these variants, only 3 cases out of 14 had signs of early invasion, and no cases of metastasis were observed. These results are supported by extensive data from published scientific works, such as Gong et al [4].

However the histological method of determination of the variant and the differentiation degree of tumor in the kidney is considered as subjective. In this case the immunohistochemistry is known to be the most reliable study. Using this method it is possible to determine both the tumor histogenesis and the tumor grade maximally. Its usefulness is proved by the fact that in low degree of RCC differentiation epithelial cells lose their own characteristic features and obtain the characteristic features of mesenchimal cells. The reactions of different antibodies in various variants and in various grades of RCC have been studied and the specificity of immunohistochemical reaction has been revealed (Tab.1,2). Consequently by means of a definite set of immunohistochemical markers with relevance to tumor histological variants and differentiation degrees correct pathological diagnosis may be formed.

Table1 ***Comparison of antibodies reactivity for select different variants of RCC by immunohistochemistry***

Antibodies / ***Material***	***CK7***	***CK18***	***AMACR***	***Ki67***	***P53***	***PCNA***	***E-cadhe-Rin***	***Bcl-2***	***VEGF***	***EGFR***
N tissue (epithelium of tubules)	***3+***	***3+***	***3+***	***1+***	***1+***	***2+***	***3+***	***2+***	***1+***	***0***
Multilocular cystic RCC	***3+***	***3+***	***1+***	***1+***	***1+***	***2+***	***2+***	***2+***	***1+***	***0***
Clear cell RCC	***0***	***3+***	***3+***	***2+***	***0***	***3+***	***1+***	***3+***	***3+***	***1+***
Chromo-phobe RCC	***2+***	***3+***	***0***	***2+***	***1+***	***2+***	***2+***	***1+***	***1+***	***1+***
Papillary RCC	***2+***	***3+***	***2+***	***2+***	***1+***	***3+***	***1+***	***0***	***2+***	***1+***
Mucinous tubular and spindle cell RCC	***3+***	***1+***	***3+***	***3+***	***2+***	***3+***	***0***	***0***	***2+***	***2+***

Note: 0 – no reaction, 1+ weak positive reaction, 2+ moderate positive reaction, 3+ strong positive reaction.

Table 2

Antibodies / **Material**	**СК 5\6**	**СК 7**	**СК 8**	**СК 10\13**	**СК 17**	**СК 18**	**СК 19**	**СК 20**
N tissue (epithelium of tubules)	**2+**	**3+**	**1+**	**2+**	**2+**	**3+**	**3+**	**0**
G1	**2+**	**0**	**2+**	**2+**	**2+**	**3+**	**2+**	**2+**
G2	**1+**	**0**	**2+**	**2+**	**2+**	**3+**	**2+**	**2+**
G3	**0**	**0**	**2+**	**0**	**0**	**3+**	**2+**	**0**
G4	**0**	**0**	**2+**	**2+**	**3+**	**0**	**3+**	**3+**

Comparative characteristics of cytokeratin reaction due to different degrees of differentiation of clear cell renal cell carcinoma

Note: 0 – no reaction, 1+ weak positive reaction, 2+ moderate positive reaction, 3+ strong positive reaction.

An analysis of medical records showed that between 2008 and 2010, 16 people died as a result of kidney cancer and its complications at this hospital. Stage III cancer by TNM classification was established in 11 patients, Stage IV was established in 4 patients, and only one case of Stage II was established. This indicates late overall diagnosis of the disease. Histological analysis showed that all patients who died had signs of tumor sprouting into the renal capsule, pelvis, or fat, as well as elements of metastasis (cancerous emboli or blood clots in the renal vessels), or the presence of metastases in the lymph nodes and distant metastases. In 2008 1 patient out of 16 died, in 2009 – 4, in 2010 – 7, and in 2011 – 4. The Kaplan–Meier estimator and log-rank test helped estimate the proportion of the survived patients with the described pathology. That represented 0,933. The survival analysis revealed 12 months in RCC Stage II (probably the tumor was aggressive even at early stage), 17,4 months in RCC Stage III and 2,24 months in RCC Stage IV. The survival time after diagnosis in all this group of patients ranged from several days to 2 years, 4 months.

Discussion. Our research has mentioned the increased incidence of kidney tumors annually from 2006 until 2010 in the Saratov Region. In comparison to literature reviews, the study has discussed the early development of the initially diagnosed kidney cancer. In practice, RCC is the most common type of kidney cancer. A considerable number of clear cell renal cell carcinomas were also revealed. Other forms of cancer were discovered rarely, in less than 1% of all cases overall. Mesenchymal tumors - angiomyolipomas – were among the more frequently discovered benign tumors.

The treatment tactics and the survival prognosis of RCC depend on the differentiation of tumor cells (G): the higher G (and lower differentiation), the worse the prognosis. The more unfavorable and aggressive variants of RCC are papillary cancer, chromophobe renal cell carcinoma involving the renal pelvis and mucinous cancer. Multilocular renal cell carcinoma is considered to be a variant with a more favorable prognosis.

Deaths from RCC were associated with late hospitalization and resulting late diagnosis, low differentiation (G 3-4), presence of invasion into surrounding tissues and metastasis. We have determined a mean survival rate of 2 years and 4 months after diagnosis.

In conclusion, it has been found that the comprehensive study of renal tumors is of significant importance due to the increased incidence of this disease, late diagnosis of malignant tumors, and the aggressive course and unfavorable prognosis of the disease. Early diagnosis, precise morphological characteristics and proper treatment of kidney tumors will help improve the quality of life of patients and reduce morbidity and mortality rates.

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PROSTAGLANDIN DYNAMICS IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND LESIONS OF THE STOMACH MUCOSA

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Introduction. Today it is known that prostaglandins (PG), including PgE2,PgI2, are able to contribute to the rehabilitation of damaged gastric mucosa (GM) that positively influence on the morphological changes, regression of rebuilding changes, the proliferative activity of epithelial cells and the depth of occurrence of Helicobacter pylori (HP)-simultaneously affect several elements of pathogenesis [1,6,7,12,13].

All processes in the stomach ,which are under the influence of Hp ,are systemic in nature and show a direct pathogenic effect on the kidneys in patients with chronic kidney disease (CKD).

The damaging effects of aggressive systemic factors increase and cause acceleration of progression of CKD with the increasing degree of it. [4.13].

The increase of the excretion of inflammatory mediators is observed in patients with CKD with the presence of erosive and ulcerative lesions of the stomach (EULS)- renal prostanoids (prostaglandins and thromboxanes), arachidonic acid, histamine, bradykinin and others. Some of them, especially PgE2, enhances mucus in GM and some other effects that are widely discussed in the literature and cause conflicting conclusions [1,3,7,8,16].

A respond of mucous membrane of renal pelvises and cups on pathogenic properties of microorganisms, as during colonization of gastric mucosa with Hp, are characterized by activation of proinflammatory cytokines of blood (precursor of arachidonic acid), macrophages (mast cells or labrocytes), lymphocytes, neutrophils and monocytes, which promotes the expression of inflammatory mediators - renal prostanoids (prostaglandins including prostaglandin E2 and thromboxane), arachidonic acid [9,14,15].

Renal prostanoids (prostaglandins and thromboxanes) are involved in regulating renal hemodynamics, tubular transport of ions and renin secretion. In addition, they can be active participants as mediators of inflammation by the action of damaging factors (inflammatory substances, toxic changes at CKD) [2,3,4,9].

Two forms of cyclooxygenase(COG)are expressed in the kidneys:

1. Structural (COG - 1).

2. Induced (COG - 2).

COG - 1 is synthesized in the body constantly under normal conditions and provides production of prostoglandin PgE2, PgI2 that are improving the protective properties of gastric mucosa [7,9]. PgE2 increases the secretion of mucous helium and bicarbonates, inhibits secretion of hydrochloric acid. PgI2 supports optimal level of hemodynamics in the microcirculation, normalizes the state of labrocytes and lysosomes membranes, regulates the function of vascular epithelium, activates cell proliferation in normal processes of regeneration and inhibits the production of free radicals and enzymes by neutrophils.

COG - 2 is produced during the inflammation in the large quantities. It provides a synthesis of proinflammatory prostaglandins, causing its characteristic features - vasospasm of microcirculation, exudation in the inflammatory focus, pain and fever [5,8,9,10].

Consequently, there is a close relationship between the development of erosive and ulcerative gastroduodenal lesions and progression of CKD. It should be noted that the progression of both pathological processes are interrelated, Hp infection causes a number of systemic effects (activation of proinflammatory cytokines, apoptosis, selection of biologically active substances that enhance ischemia, hypoxia of the affected tissue, activation of the hemostatic platelet level) that detect pathogenic effects on kidneys and progression of CKD. On the other hand, kidney disease, especially in reducing their function, are reduced the processes of COX-1 activation, resulting in reduced production of prostaglandins, which are important to support both local and systemic hemodynamics in normal and, in particular, take part in protecting the stomach from aggression factors (increased mucus, bicarbonate excretion, etc.). [5,10,13,16].

The aim was to study the dynamics of the systemic and local content of prostaglandin E2 in patients with chronic kidney disease stage II and III, due to a long course of chronic recurrent pyelonephritis with the presence erosive and ulcerative lesions of the stomach under the influence of mukohen.