KIDNEY FUNCTION RELATION TO SIZE OF THE TUMOR IN RENAL CELL CANCINOMA

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Resume. In this work authors aimed to research the influence if the tumor and specifically tumor size on kidney function. They analyzed results of investigation of patients with verified renal cell carcinoma and studied kidney function in those patients. Gromerular filtration rate, that is usually approximately calculated with formulas for approximation, but in this study authors used nephroscintigraphy that allowed to estimate GRF separately in each kidney. Authors concluded that with increase in size of the tumors kidney function decreases. There was a significant difference in kidney function between kidneys harboring tumors below and over 7cm.

Key words: renal cell carcinoma, partial nephrectomy, kidney function, kidney insufficiency

Introduction. Renal cell carcinoma (RCC) accounts 4% of the total number of neoplasms of malignant genesis and is diagnosed increasingly in conditions of application the method of ultrasound diagnosis [1]. Currently, due to the increase in the number of diagnosed cases of RCC is growing interest in anatomical and functional changes in the kidney under the influence of neoplasm. In the world there is a trend to increase the number of detected forms of RCC and increase the number of surgical procedures on kidneys [2]. The main methods of surgical treatment of RCC remain radical and fractional nephrectomy. However, despite the significant increase in the number of performed fractional nephrectomies, due to the development of surgical techniques and increased surgeon experience, there is still a tendency of dominance the organ deferent surgical procedures in RCC [3]. Today in the world and national literature is not well studied the influence of the tumor on the function of affected kidney. The main difficulty is the lack of standardized method of

measuring renal function in conditions of diagnosis the RCC. On the other hand, with age in the patients are registered the general decline in renal functions. Especially acute, this problem is in patients after radical nephrectomy, where the development of renal failure and subsequent complications may lead to reduction overall survival in patients with RCC [4].

In international practice, is used the method of assessment the renal function by calculating formulas in which are used the patient's body weight and level of blood creatinine. The disadvantage of these methods is the instability of level of creatinine over time and dependence of this level on many factors [5]. Compensatory increase of function the contralateral kidney may mask the onset of chronic renal failure, and, as a consequence of the first, the development of cardiovascular disease. Given all the above, we set the goal - study the effect of tumor size of kidney on its function in patients with RCC.

Materials and methods

In the Clinic of Plastic and Reconstructive oncourology of the National Cancer Institute between 2008 and 2012 were examined and treated 749 patients with renal cell carcinoma. All patients were subjected to a comprehensive survey, which included the collection of anamnestic data, physical examination and clinical laboratory and X-ray radiological methods of investigation. The final analysis included 334 patients with histologically verified RCC, unilateral tumor and also the main point of inclusion the patient into work was the implementation of dynamic kidney scan in the preoperative stage. To the exclusion criteria were referred multiple renal tumors, the presence of bilateral renal tumors and histological types, which did not meet the RCC.

Function of kidney as GFR was calculated by dynamic kidney scan, which allows us to estimate separately the function of each kidney.

After taking into account all factors of inclusion and exclusion, in the analysis were involved 334 patients. The data for each patient was filled to the database and was made the analysis of the acquired information. In the analysis has been used: clinical information about the disease, age, sex, histological type of the tumor, stage of disease, tumor diameter based on CT scans. Patients were also stratified into

groups based on tumor size, the first group included tumors up to 4cm (correspond clinical stage T1a), the second group comprised formations with maximum diameter of 4 to 7cm (clinical group T1b), the third - 7-10cm (clinically corresponds to the stage T2a) and the fourth group consisted of patients with formations over 10cm in diameter (group T2b with localized RCC). The assessment of function change was made in the studied groups. During comparison in groups was used the assessment of normal distributions according to Shapiro-Wilk test, and was subsequently performed pairwise comparison of groups using t-test. We also managed to take the opportunity to compare the function of the affected kidney with contralateral unaffected kidney.

Results

Average age of the total group was 54,7 ± 10,4 years; average maximum size of the tumor for the group was 61,1 ± 31,9 mm; total GFR 85,8 ± 19,8 ml / min and an average value of GFR in the affected kidney was 40 7 ± 12,8 ml / min. The results of indicators of descriptive statistics of the general group and individually stratified by size are shown in Table 1.

Table 1. Parameters of descriptive statistics for study groups of patients

Parametr/Group	1 (under 4cm)	2(4-7cm)	3(7-10cm)	4 (>10cm)	Total
Number (N)	105	135	57	37	334
Age (years)	54.6±10.6	55±10.2	54.6±10.9	54±10	54.7±10.4
Male/female	67/38	77/58	32/25	23/14	199/135
Total GFR (ml/min)	89.3±19.4	86.7±19.8	82.7±20.4	77.7±18,3	85.9±19.9
GFR affected kidney (ml/min)	44.1±10.2	42.3±11.9	36.9±14.2	31.5±15	40.7±12.8
Max.diametr	31.2±7.6	55.9±8.6	84.3±9.1	129.7±21.5	61.8±31.9

The test groups were statistically matched by age and sex using the method x^2, p = 0,57 and p = 0,6 respectively. When assessing total GFR in groups was not diagnosed statistically significant differences in assessing renal function between compared groups, although the marked tendency of reduction in function. Average

values of total GFR for 4 groups were 89,3 ± 19,4 ml / min; 86,7 ± 19,8 ml / min; 82,7 ± 20,4 ml / min and 77,7 ± 18,32 ml / min respectively. Despite a tendency of reducing the total GFR in groups, statistically significant difference in pair-wise comparison (1st to 2nd, 2nd to 3rd, 3rd to 4th) was not detected. Data of pair-wise comparison of total GFR is shown in Table 2.

Table 2. Results of the pair-wise comparison of total GFR in study groups

Comparison groups	1 and 2	2 and 3	3 and 4	1 and 3	1 and 4	2 and 4
Significance	0.31	0.2	0.2	0.04	0.001	0.01

As can be seen from the Table 2, statistical reliability appeared only when were compared the groups that do not stand close; t-test revealed a significant difference between the patients of the first group in relation to group 3 (p =0.04), and in relation to group 4 (p =0.001). There was also found a significant difference between groups 2 and 4 (p =0.01). This can be explained by small sample of patients or compensatory mechanisms which lead to increase of GFR in the opposite kidney. So during the transition from one stage to another stage, decline of the total function is not so critical. However, sharp decline of the total GFR in the group proves the hypothesis about the possible effects of neoplastic process on renal function.

The next step was made the analysis of above groups, taking into account the function of affected kidney. Average value of GFR of the affected kidney in groups under investigation was 44,1 ± 10,3 ml / min; 42,3 ± 11,9 ml / min; 36,9 ± 14,2 ml / min and 31,5 ± 15ml/min respectively. Here, indexes of statistical validity improved and, despite the tendency, appeared statistically significant difference when comparing the groups 2 and 3 (p = 0.007). It was also close to the reliability difference among groups 3 and 4 (p = 0.07). The comparison of not standing along groups has only reinforced already existed before validity. Data of pair-wise comparison of GFR of the affected kidney are presented in Table 3.

Table 3. Results of the pair-wise comparison of GFR of the affected kidney in study groups

Comparison groups	1 and 2	2 and 3	3 and 4	1 and 3	1 and 4	2 and 4
Significance	0.2	0.007	0.07	0.0003	0.00001	0.00001

The next stage we analyzed the tumors that according to the 2010 classification are classified as T1 and compared them with the remaining group of patients. So, we formed groups stratified by tumor size less than 7 cm and the formation more than 7cm. Analytical data of these groups are presented in Table 4.

Table 4. Results of the pair-wise comparison of total GFR and GFR of the affected kidney among groups of tumors up to 7 cm and more than 7 cm

Parametr/Group	1 + 2 (<7cm)	2+3 (>7cm)	Total	P
Number (N)	240	94	334	
Total GFR (ml/min)	87.8±19.6	80.7±19.6	85.9±19.9	0.003
GFR affected kidney (ml/min)	43.1±11.2	34.7±11.9	40.7±12.8	0.0001

Was noted the high statistically significant difference in the function between patients of these two groups, so for the total GFR p = 0.003 and during the analysis of GFR of the affected kidney the accuracy was still higher than p = 0.00001.

To test our theory, we pair-wise compared the function of affected and unaffected kidneys for each patient in groups under investigation. The results are shown in Table 5.

Table 5. Results of the pair-wise comparison of GFR in the affected kidney and the contralateral kidney

Group (number of cases)	GFR of affected kidney (ml/min)	GFR of contralateral kidney (ml/min)	Significance (p)
1 (105)	44.1±10.2	45.1±12.8	0.53
2 (135)	42.3±11.9	44.4±12.2	0.14
3(57)	36.9±14.2	45.7±11.6	0.0004
4 (37)	31.5±15	46.3±12.3	0.00001

In groups 1 and 2 was not showed statistically significant difference between the function of affected and contralateral kidney (p = 0.53 and p = 0.14). Increasing the size of tumor more than 7cm has given the difference between the groups statistical validity. So, in groups of tumors 7-10cm average values were 36,9 ± 14,2 ml / min vs. 45,7 ± 13,6 ml / min (p = 0.0004). For tumors more than 10cm, these values were 31,5 ± 15ml/min vs. 46,2 ± 12,2 ml / min (p = 0.00001).

After assessment of relationship with the calculation of pair correlation coefficients we have presented the dependence of GFR of the affected kidney on the size of the tumor and represented in the form of graph. As it can be seen from Figure, there is correlation between the function of the affected kidney and tumor size.

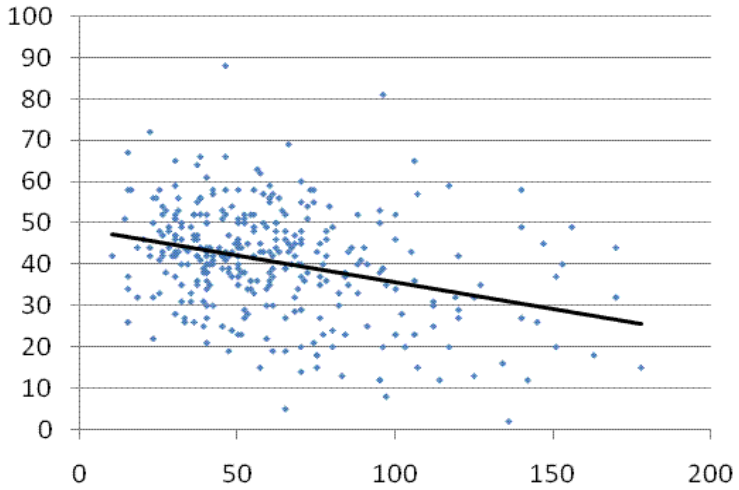

Figure. Correlation dependence of renal function from the size of the tumor

Discussion.

In this paper it was shown that the tumor size and the decrease of GFR independently correlate in patients with RCC. This information supports the theory about the relationship of decrease the renal function and tumor genesis and is the first work that has shown the direct correlation between increasing tumor size and decreased GFR [6]. There are several possible mechanisms that may explain this relationship and it is most likely the combination of several mechanisms lead to this association. One possible explanation can be that with increase in the size of the tumor turns out to be the destruction of renal tissue: either by direct invasion into the parenchyma, or mechanically changing the architecture of the kidney, compressing

the renal parenchyma, collector tubules, canaliculus and nephrons. Also tumor may secrete unknown factors that can inhibit the function of the kidney and with increase of tumor size the secretion of these factors can increase by decreasing GFR [7]. Both of these mechanisms determine the tumor as a primary pathology and chronic renal failure as a secondary phenomenon after the development of cancer.

The frequency of detection of RCC is increasing every year since the 70s of the last century. Partly this can be explained by identifying small symptomless tumors as a result of frequent use of the method of ultrasound diagnosis and CT in clinical practice [2]. However, these small formations can not fully explain the increase of the frequency of detection of RCC, because the increase of not localized forms of RCC also takes place [8]. Despite the early detection and treatment of small asymptomatic forms, stages of mortality from RCC continue to grow. This may suggest that either the methods of treatment of RCC have deteriorated in recent years (which are unlikely because of the higher detection rate and the possibility of an earlier treatment) or RCC has become more lethal in recent decades. It is likely that the nature of the tumor itself may change as a result of the increase, from an unknown carcinogenic factor. It is now impossible to say whether chronic kidney disease can be such a factor, but there are more evidence of links between kidney disease and RCC [9]. Additional studies are necessary for further study the characteristics of such a relationship. Size 7 cm is still critical to the RCC, we can clearly see from our work the difference in GFR between the group of patients with tumors up to 7 cm or more than 7cm.

Confirmation of these data was the analysis of the pair-wise comparison of the affected and unaffected kidneys, which also found a significant difference between the function of kidney beginning from tumors larger than 7 cm ($p = 0.0004$). Based on this, we can conclude that when the tumor size is 7cm, occurs anatomical and functional changes that lead to the initial changes in GFR of the affected kidney by tumor. This information may also be interesting because total difference in GFR between groups of patients with tumors up to 7 cm and more than 7 cm is not statistically significant ($p = 0.07$), and in theory this dependence can not be shown in studies that used the classic formula for calculating the estimated GFR based on

serum creatinine levels. Limiting factors in this study are: retrospective nature of the investigation which is held in one center and a small number of observations. The second disadvantage of this work may be that in the study in used information about patients who underwent surgical treatment, and therefore not considered a situation where surgery was not carried out due to the high anesthetic risk to the patient. Thus we can speak of a kind of selection bias in the group of patients who were included in the study. Another disadvantage of the study can be retrospective collection of information about patients' comorbidities, which may underestimate the true picture of comorbidity. Thus, the work is the first analysis of the dependence of renal function on the size of formation (tumor).

Conclusions

We have shown for the first time the correlation dependence of the effect of size of the kidney tumor on its functional state, namely, with the growing of size of the tumor, the renal function declines. Comparative assessment of the glomerular filtration rate in the healthy kidneys with the function of affected by the tumor kidney, after stratification by size on groups showed a significant ($p = 0.00001$) difference between the groups with tumors up to 7cm or more than 7cm, which corresponds to stages T1 and T2.

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