Can we consider temporary, preoperative active observation in patients with kidney tumors up to 3 cm in order to decrease the number of patients over-treated with NSS – nephron sparing surgery?

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KEY WORDS

small kidney tumors ◗ pT1 ◗ benign disorders ◗ non-cancerous disorders ◗ NSS

ABSTRACT

Introduction. The increasing number of benign and non-cancerous tumors has resulted in the common use of NSS for the treatment of pT1 tumors. However, this kind of treatment did not reduce the number of unnecessary operations.

Material and methods. Two-hundred nineteen patients with pT1 tumors treated with NSS were analyzed retrospectively. The mean time of observation was 77.9 months. The patients were divided into groups depending on tumor size and the degree of cellular differentiation of the tumor – DCTD (according to Fuhrman).

Results. Statistical analysis revealed that an increase in tumor diameter accompanied a decrease in the percentage of patients with tumors staged pT1 as well as those graded G1 and G0 (according to Fuhrmann). Mean survival time also decreases. While the percentage of tumors graded G3, those staged pT3, unconventional varieties of renal cell carcinoma (RCC), local recurrence, as well as renal insufficiency all increase together with increases in tumor diameter.

Conclusions. In patients with tumors up to 3 cm, the risk of surgical overtreatment increases. In patients with pT1 increases: the risk of unconventional varieties of RCC, cancerous progression, and death along with the increase in the size of the tumor and DCTD. Along with the size of pT1 tumors, a decrease in the number of benign and non-cancerous tumors as well as 5-years survival after NSS is observed. The dynamics of cancerous changes in the tumors up to 2 cm is similar to the dynamics observed in the tumors up to 3 cm, whereas those of 4 cm act similarly as the tumors of 5 cm diameter.

INTRODUCTION

The dilemma of the last 20 years was how to reconcile oncological safety with minimum interference to the parenchyma of the kidney in the patients with benign tumors and simultaneously minimize the risk of unnecessary surgeries. It seems that the introduction of NSS (nephron-sparing surgery) could solve that problem to a large extent [1]. Statistical data from recent years demonstrate a significant fall in the size of operated kidney tumors and a considerable rise in the number of pT1 tumors. Nevertheless, the average survival has not changed for many years [2, 3]. The increasing number of patients treated with NSS allowed the presentation of a disproportionately high percentage of benign and non-cancerous changes in histopathological examinations [4, 5, 6].

The precise preoperative assessment of benign, often heterogeneous, tumors is still far from perfect. The latest achievements of radiological diagnostics and percutaneous biopsy, which is burdened with a large number of false negative results, as well as more and more sensitive and common molecular and genetic diagnostics still cannot guarantee a correct diagnosis [5, 7, 8].

Long-term analysis of the results of NSS in patients with pT1a tumors shows, in the majority of cases, smaller progression of cancerous changes and a higher rate of survival. On the other hand, active observation of patients with tumors of the same size results in similar findings where the time of the observation currently does not exceed 3 years [8, 9]. Therefore a question arises – does the risk of earlier surgery in patients with pT_{1a} tumors of advanced age, often with coexisting diseases, lead to the phenomenon of overtreatment?

MATERIAL AND METHODS

Two-hundred nineteen patients, aged 25 to 85 (mean 61.7), with pT1 tumors (operated between 1988 and 2009 with NSS) were enrolled in the study. The group consisted of 101 (46.1%) women and 118 (53.9%) men. The basis of qualification for NSS was a CT scan of the kidneys. In most cases the patients also underwent: an NMR examination, 37 patients (16.9%); vascular examination of the kidneys, 22 (10%); and PET, 7 (3.2%). Both before and after the operation, all the patients underwent a routine laboratory and radiological examination in accordance with EORTC recommendations. According to the diameter of the tumor the patients were divided into three groups. The tumor was measured in the post-operative preparation using a caliper or tailor's tape measure. The first group (n – 97) consisted of the patients with a tumor up to 3 cm, the second (n – 80) with a tumor between 3 and 5cm, and the third (n – 42) with a tumor larger than 5 cm. Other groups included: Ia (n – 52) with a tumor up to 2 cm and IIa (n – 50) with a tumor up to 4 cm, subdivided from groups 1 and 2, respectively.

Another division comprised four groups of patients qualified according to the degree of tumor cell differentiation (DCTD). The first group (n – 81) consisted of patients with DCTD G1 (according to Fuhrmann), the second group (n – 92) with DCTD G2, the third (n – 15) with DCTD G3 – 4, and the fourth group (n – 31) included patients with benign or non-cancerous changes that were marked as G0. Twenty-nine patients with variations of RCC different from clear cell renal cell carcinoma (cRCC) were analyzed separately. Each group was assessed in terms of the cancer progression, overall survival (OS), disease-specific survival (DSS), progression-free survival (PFS), and the occurrence of post-operative renal insufficiency.

Table 1. The analysis of the three groups, where the basis of division was tumor diameter.

Diameter of the tumor	Sex		Degree of cellular tumor diversification	Varietes of RCC	Death rate	Local recurrence	Metastases	Follow up (months)
	F	M						
Under 3 cm n = 97 44.3%	54 55.7%	43 44.3%	G1 – 44 = 45.4% G2 – 31 = 31.9% G3-4 – 6 = 3.1% G0 – 8 = 19.6%	3 3.1%	4 4.1%	4 4.1%	1 1.0%	78.3
3-5 cm n = 80 36.5%	32 40%	48 60%	G1 – 29 = 36.3% G2 – 37 = 46.2% G3-4 – 6 = 7.5% G0 – 6 = 10%	18 22.5%	7 8.7%	8 10.0%	3 3.7%	87.4
Above 5 cm n = 42 19.2%	15 35.7%	27 64.3%	G1 – 8 = 19.1% G2 – 24 = 57.1% G3-4 – 6 = 14.3% G0 – 4 = 9.5%	8 19.0%	7 16.7%	6 14.3%	3 7.1%	69.4
Total 219	101	118		29 13.2%	18 8.2%	18 8,2%	7 3.2%	77.9
Statistical difference	0.04		0.007	0.002	0.04	0.04	0.16	0.04

The observation time was 5–247 months (mean 77.9).

All the patients except for 36 (16.5%) underwent retroperitoneal laparoscopic NSS. The determinant of renal insufficiency was the concentration of creatinine in blood of 1.5 mg (132 µm/l). The statistical analysis was conducted with Statistica Statsoft 8.0. Chi-square and the exact bilateral Fischer tests were used. The PFS rate was assessed on the basis of Kaplan-Meyer analysis and regarded as statistically significant if $p < 0.05$.

RESULTS

The first group, observed for 78.3 months, consisting of 54 (55.7%) women and 43 (44.3%) men with no significant age difference, revealed the lowest general death rate – 4 (4.1%) and DSS – 3 (3.1%) in comparison to the other groups ($p < 0.04$). Local recurrence appeared in 4 patients (4.1%), while metastasis in 1 patient (1%). Considering DCTD in this group, G3 constituted 3.1%, G2 – 31.9%, G1 – 45.4%, and G0 – 19.6%. The patients with cRCC constituted 77.3% and patients with unconventional varieties of RCC 3.1%. The left kidney was operated in 36 patients (37.1%), the right one in 59 (60.8%), whereas bilateral operations were carried out in 2 patients (2.1%). In the marked off subgroup, Ia, the patients with a G1 tumor constituted 46.1%, G2 – 21.3%, and no G3 tumors were found. The general death rate in the second subgroup amounted to 2 (3.8%), while local recurrence appeared in 1 patient (1.9%); which did not make any significant statistic difference in regards to the whole of group one.

In the second group, tumors between 3 and 5 cm were mostly found in men – 60%. The mean observation time was 87.4 months. The average age of the operated was 56.7 years and was not statistically different from group I. The left kidney was operated in case of 54.3% of patients, the right one in 41.9%, and a bilateral operation was conducted in 3.6% of the patients. DTCD G3 was diagnosed in 7.5% of patients, G2 – 46.2%, G1 – 36.3%, and G0 – 10% ($p = 0.007$). Patients diagnosed with cRCC equaled 67.3% and those with variations of RCC amounted to 22.2% of the all diagnoses in that group ($p < 0.002$). The rate of local recurrence (10%), metastases (3.7%), as well as OS and DFS (8.7 and 6.2%, respectively) were statistically higher in comparison to group I. In subgroup IIa (tumors up to 4 cm), men composed the majority (66.1%). Local recurrence was found in 4 patients (16.1%) and death in 5 (9.5%). Patients with G3-4 amounted to 7.8%, G2 – 48%, G1 – 36%, and G0 – 10%; there is no difference between these patients and the patients from group II. The only difference was a lower rate of RCC variations in 12% ($p = 0.048$) (Tab. 1).

In the third group, the percentage of men was found to be even higher in comparison to group I ($p = 0.04$). The average age was 58.4 years. There were 71.5% of patients with cRCC, while RCC variations constituted 19% ($p = 0.002$). DCTD G3 was 14.3%, G2 – 7.1%, G1 – 19.1%, and G0 – 9.5%. During the 68.4 months of observation the death rate was 16.7%, DSS – 14.3%, local recurrence – 14.3%, and metastases – 7.1%; which in comparison to group I makes a statistical significance ($p = 0.004$). A significant increase in the size of the tumor in men was also apparent ($p = 0.02$) (Tab. 2).

In the analyzed group, during the observation time after 77.6 months, the OS reached 91.8%, DSS – 93.6%, and PFS – 85.7%. The differences between group III and groups I and II were statistically significant ($p = 0.04$ and $p = 0.03$ respectively). PFS dependent on tumor diameter is shown in figure 1.

The analysis of the four groups, where the basis of division was DCTD (see table 3), indicates significant discrepancies between the groups.

Table 2. The percentage rate of six-year survival after NSS depending on the tumor diameter.

Survival	Group I n – 97	Group II n – 80	Group III n – 42	Total n – 219	p value
Overall Survival (OS)	95.9%	91.5%	83.3%	91.8%	0.04
Disease-Specific Survival (DSS)	96.9%	93.8%	85.7%	93.6%	0.04
Progression-Free Survival (PFS)	92.6%	85.1%	69.1%	85.7%	0.03

Table 3. The analysis of the four groups, where the basis of division was DCTD.

Grading	Sex		Varietes of RCC	Death rate	Local recurrence	Metastases	Follow up (months)
	F	M					
G1 n – 81 37.0%	33 40.7%	48 59.3%	71 RCC 87.7% 10 varietes 12.3%	2 2.3%	3 3.7%	–	85.2
G2 n – 92 42.0%	43 46.7%	49 53.3%	77 RCC 83,7% 15 varietes 16.3%	10 10.9%	9 9.8%	5 5.4%	74.4
G3-4 n - 15 6.8%	6 40%	9 60%	11 RCC 73.3% 4 varietes 26.7%	6 40%	5 33.3%	2 13.3%	70.1
G0 n - 31 14,2%	19 61.3%	12 38.7%	–	–	1 3.2%	–	61.2
Total n - 219	101 46.3%	118 53.9%	29 13.2%	18 8.2%	18 8.2%	7 3.2%	77.9
Statistical difference	0.21		0.69	0.004	0.003	0.02	0.82

The observation time in group G1 (n – 81) was 85.2 months. The general death rate was 2.3% and DSS was 1.2%. Local recurrence was found in 3.7% of the patients. cRCC was found in 87.7% of the patients, while the unconventional variations of RCC constituted 12.3%.

In group G2 (n – 92), with the average observation time of 74.4 months, the death rate amounted to 10.9% and DSS was 9.8%. Local recurrence was found in 9.8% and metastases in 5.4% of the patients (p = 0.03 in comparison to group I). The percentage of RCC variations was 16.3% and cRCC 83.7% (p = 0.69 in comparison to group G2 and G3-4).

In group G3-4, for 70.1 months of observation, the general death rate amounted to 40% and DSS was 26.7% (p = 0.004). Local recurrence was found in 33.3% and metastases in 13.3% of the patients (p = 0.003). cRCC was found in 73.3% and variations of RCC in 26.7% (p = 0.03).

In group G0, with the observation time of 61.2 months, local recurrence was found in one patient (3.2%). No death or metastases were found. The ratio of men and women was 38.7% to 61.3% (p = 0.04 in comparison to the other groups). Apart from this group, the sex did not affect the NSS results. The only patient with progression in this group was a 58-year-old man with a 1.5 cm tumor, in whom, after the laparoscopic NSS, a kidney infarction was found. After 10 months a follow-up, examination revealed a 3 cm tumor. After the kidney removal, cRCC G2 was found. In this group (G0) histopathological examination revealed: angiomyolipoma (AML) in 10 (36%) patients, a non-cancerous cyst in 8 (25.8), oncocytoma in 6 (19.4%), and individual cases of lipoma, adipose tissue, xantogranulomatosis, abscess, calcification, or infarction in the remaining 22.6%.

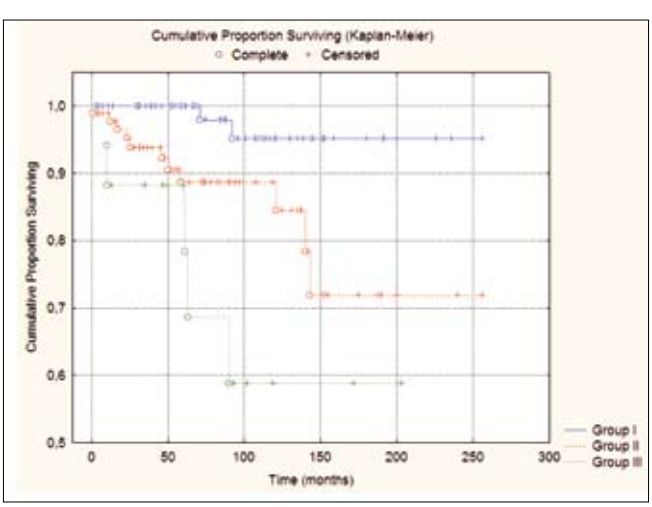

Fig. 1. Progression-free survival in patients after NSS divided into groups according to tumor diameter.

The rate of six-year survival indicates significant statistical differences depending on DCTD (p = 0.008; p = 0.0005; p = 0.0004) (see table 4).

Among all the analyzed groups there were 29 (12.2%) patients with unconventional RCC, such as: papillary RCC – 16 (55%), chromophobe RCC – 5 (17.2%), cystic RCC – 4 (13.8%), sarcomatoid RCC – 2 (6.9%), and liposarcoma in 2 (6.9%) patients. The average survival in this group reached 70.1 months. Death and local recurrence were found in 10.3% of the patients. No metastases were found. The patients from this group do not differ statistically from the remaining 159 patients with cRCC. The DCTD was quite similar, that is; G3 – 10.3%, G2 – 48.3%, and G1 – 41.4%.

In 41 (16.7%) patients the NSS was conducted under imperative indications. Within 58.7 months of observation OS of those patients amounted to 80.3%, DSS was 85.4%, and PFS was 77.8%. In 178 (81.7%) of the remaining patients operated under elective indications within 81.2 months of observation OS amounted to 94.8%, DSS – 96.5%, and PFS –91.1% (p = 0.03; p = 0.004)

The comparative analysis of the result of women and men after the observation for 81 and 69.6 months respectively, showed OS 92.2% *vs.* 90.7%, PFS 85.1% *vs.* 92.4%, and DSS 98.7% *vs.* 95.8%; making no significant statistical difference p = 0.69. The women outnumbered men only in group G0. Among the operated patients aged up to 45 years, 20.6% were found in group I, 16.2% in group II, and 16.6% in III (p = 0.068).

In 27.4% of patients, before performing NSS, tumors other than cRCC were suspected, but only after the operation was cRCC diagnosed. Renal insufficiency before NSS was found in 6 (2.2%) of the patients and after NSS in 11 (5%), however 10 of them had only one kidney (bilateral asynchronous tumors). In group I, renal

Table 4. The percentage rate of six-year survival after NSS depending on DCTD (degree of tumor cell differentiation).

Survival	Group I n – 81	Group II n – 92	Group III n – 15	Group IV n – 31	p value
Overall Survival	97.5%	89.1%	60.0%	100%	0.008
Disease-Specific Survival	98.8%	90.2%	73.3%	100%	0.0005
Progression-Free Survival	95.1%	79.3%	46.7%	96.8%	0.0004

insufficiency was found in 1 (1%) patient, in II – 4 (4.9%) patients, and in III – 6 (14.3%) of the patients.

DISCUSSION

The progress in the diagnostics of kidney tumors caused an increasing rate of their diagnosis up from 7.7% in 1983 to 10.9% in 2002 per 100,000 population. In that time, the rate of benign tumors (pT1) increased from 0.9% to 3.6% per 100,000 population [2]. Kane et al. stated that in 1993-2003 the diagnosis rate of tumors up to 2 cm increased from 7.7% to 12.1%, tumors with diameter of 2.5 cm up from 14.8% to 28.4%, whereas tumors up to 3 cm in size up from 31.2% to 41.3% [4]. Cooperberg et al. pronounced that in 1993-2004 the diagnosis rate of tumors up to 3 cm increased from 32.5% to 43.5%, while the number of patients with pT1 increased from 42.9% to 56.2% [3]. In the analyzed group, the largest was the group of patients with tumors up to 3 cm (44.3%). It also turned out that increases in tumor size accompanied increases in the number of patients with low DCTD (G3), whereas G1 and G0 decrease (p = 0.007).

The current indirect measure of cancerous aggression of a tumor, as well as an independent factor for the progression risk, is the size of the tumor [10, 11]. Only a few authors are dubious about it [12, 13]. For many years the assessment of the clinical progression of a tumor has been based on its diameter [TNM] similarly to nomograms estimating the risk of progression (for instance SSING, UNCLA) [14]. The vast majority of authors confirm the correlation between the size of the tumor and DCTD [15]. Hong et al. in the tumor up to 4 cm and larger found an increasing rate of pT3 5.2% *vs.* 27.5% respectively, while DCTD G3 from 26.7% to 50.3% [16]. Ross et al. in the tumors 1-2 cm, 2-3 cm, and 3-4 cm observed pT3 in 3%, 5.1%, and 12.1% respectively, whereas G3 in 7.5%, 9.0%, and 14.6% of the cases [17]. Pahernik et al., in the tumors of the same size, observed pT3 in 3%, 5.1%, and 13.6%, while G3 in 1.1%, 8%, and 15% of the cases [10]. The percentage of these factors coincides almost entirely with the data of the analyzed group. In addition, the dynamics of the tumor up to 2 cm and up to 3 cm was the same, similarly for the tumor up to 3-4 cm and 5 cm. Some authors, like Jeldres et al., state bigger differences in the patients with DCTD G3 0.94%, 3.7%, 11.2%, and 15.9% in the tumors from 1 cm up to 4 cm respectively, while in the tumor larger than 7 cm in 30.3% of the cases [18]. Ratman et al. observed an increase of DCTD by 13% for each additional centimeter of tumor diameter [19] and Frank et al. estimated 17% for each extra centimeter [6].

Another factor confirming the activity of a tumor is metastases. In general, their percentage increases proportionally to the diameter of the tumor. For instance, in the tumors up to 2 cm, 2-3 cm, and 3-4 cm Ross et al. estimated them in 3%, 2.8%, and 6.2% respectively. Similarly Ramzi estimated them in 4.2%, 14.2%, and 36.2% and Pahernik in 3%, 5.4%, and 12.1% respectively [10, 11, 17]. On the other hand Nguyen et al., similarly to Klate et al., observed 1% more metastases in tumors of 1-2 cm in diameter than in tumors of 2-3 cm (5.2% *vs.* 4.7%) [12, 13]. These differences may arise from the large heterogeneity of benign tumors as well as a small number of patients in the analyzed groups. Kunkle et al. stated that each additional centimeter of a tumor increases the risk of metastasis by 22% [22]. In case of the tumors of the same size the rate of metastases was as follows: 1%, 3.7%, and 7.1%, which agrees with the data by Ross and Kunkle [17, 22]. The presented facts demonstrate a clear correlation between the analyzed factors and the size of a tumor.

An element observed much earlier, which turned into a clinical problem due to popularization of NSS, is the increasing number of benign and non-cancerous tumors, especially small ones [6, 21]. The discrepancy regarding the frequency of their occurrence is significant from 4.8% up to 34% [8, 13, 22, 23]. The observation becomes crucial that the increasing size of a tumor is accompanied by falls in the number of the benign and non-cancerous changes in kidneys. Pahernik et al. diagnosed 25% of such changes in the tumors up to 2 cm, in 18.9% of tumors up to 2-3 cm, and in 11.8% of tumors 3-4 cm, whereas only 4.5% in tumors above 4 cm [10]. Hong et al. found as many as 64.5% of benign changes in tumors up to 1 cm, in 22% of tumors up to 2 cm in diameter, in 10.7% of tumors up to 3 cm, and in 8.1% of tumors up to 4 cm [16]. These observations are confirmed by other authors [1, 19, 20]. In the analyzed group of patients, the G0 changes were found from group I – III in case of 19.6%, 10%, and 9.5% respectively. It is worth paying attention to the prevailing number of women in group I, while groups II and III are dominated by men proportionally to the size of the tumor (p <0.03). This fact of a higher rate of the G0 changes in women has been confirmed by many authors. Simer et al. discovered 41% of such changes in women and 20% in men; Fuji et al. – 28.1% *vs.* 5.3%; and Eggener 36% *vs.* 9.5%, respectively [23, 24, 28].

Young age predisposes to changes of the histopathological composition of the tumors. A higher percentage of papillary RCC tumors with a lower extent of clinical progression are mostly observed up to the age of 45 [10, 11, 26, 27], however this has not been confirmed by our observations.

The results of the subgroup consisting of 29 patients with unconventional variations of RCC indicate that neither progression nor death rate nor the percentage of tumor up to 3 cm in diameter differed from the remaining 159 patients with cRCC. The variations of RCC are not the factors in growing risk of progression, despite the fact that their percentage increases along with the diameter of a tumor [21, 25]. The percentage of progression increases, while the rate of survival decreases proportionally to DCTD and the dynamics of the changes is higher than it was observed in case of the growing diameter of a tumor. These observations are also confirmed by other authors [21, 25].

Pahernik et al. observed that after 10 years, OS amounted to 80.8% in tumors up to 2 cm, 72.8% in tumor up to 3 cm, and 44.4% in tumors up to 4 cm [10]. Ficara et al., after the 5 years following NSS, observed OS of 100% in cases of tumors up to 2 cm, 83% in tumors 5-6 cm in diameter, and 0% in tumors above 10 cm [14].

Both analyzed factors (T and G) are strong and independent determinants of progression after NSS. However, they can be largely modulated by other factors of statistically less significance such as: only one kidney, renal insufficiency, and multifocal or imperative

recommendation for NSS; even then they affect the NSS results [6, 15, 16, 23].

A persistently growing number of notifications of the active observation of the patients with kidney tumors pT1 show that, approximately 30% grow very slowly or they do not grow at all [8, 29]. The annual growth most often correlates with the DCTD of a tumor. Kunkle et al., in case of tumor up to 2 cm, observed the annual growth of 0.47 cm a year, in tumors of 2-4 cm – 0.65 cm a year, while in case of tumors above 4 cm – 1.36 cm a year. In reference to the DCTD similarly to G1 the growth amounted to 0.34 cm a year, in G2 – 0.62 cm a year, and in G3 – 1.04 cm a year [22]. The histopathological composition of a tumor influences its growth – in RCC it amounted to 0.45 cm a year, while papillary RCC – 0.26 cm a year. Most authors, while observing the growth of kidney tumors, state that the rate of metastases does not exceed 2% with OS reaching 100%, DSS – 97% in case of tumors up to 4 cm, whereas in tumors above 4 cm – 81.3% and 77.3% respectively [8, 9]. The above quoted results are comparable with the results after NSS from group I analyzed by us. The only difference is the observation period that is 2-3 times longer in the group with the operated patients.

Enthusiasm for nephron-sparing surgery (NSS) has been stimulated by several trends, including advances in renal imaging, improved surgical techniques and methods to prevent ischemic renal injury, and better postoperative management, such as renal replacement therapy and long-term prospective cancer-free survival data [30]. This kind of surgery may be performed safely and cost-effectively with low morbidity, preservation of renal function, a low local recurrence rate, and high patient satisfaction [31, 32]. NSS does provide equivalent cancer control relative to radical nephrectomy, even in the presence of bad prognostic factors. No disease progression or deaths attributable to renal cell carcinoma were associated with positive surgical margins (PSMs) therefore total nephrectomy should be avoided as a response to PSMs [33]. All these important facts make nephron sparing surgery a preferable surgical technique, which is nowadays used not only in pT1 but also in higher grade tumors.

Another problem is the quality of life (QoL) in patients with kidney cancer. Previous papers showed that after the operation, independently of the technique, the patients' QoL remains high [34]. However, active surveillance of patients with small renal tumors surely may influence QoL which is the result of anxiety of progression. Unfortunately we lack the studies concerning that issue. According to similar papers about QoL in patients with cancers under active surveillance we may say that individuals who improved their lifestyle enhanced their QOL further [35]. It is possible that we will observe the same behavior in patients with small renal cancers. Further research is needed.

CONCLUSIONS

In patients with kidney tumors up to 3 cm in diameter, the action allowing reduction in the risk of overtreatment with no greater risk of progression is their watchful waiting. In patients with the pT1 kidney tumor the growth of their diameter is accompanied by a fall in the degree of the cellular tumor differentiation (G2, G3-4), which results in the increase in the cancerous progression and a drop in 5-year DSS after NSS. Along with the growth of a tumor the percentage of men and unconventional variations of RCC increases. However, the number of benign and non-cancerous tumors decreases. For the reason of a higher rate of benign tumors, including G0 in women, their results after NSS are non-statistically better. The dynamics of changes in tumors up to 2 cm is similar to those of 3 cm, whereas tumors up to 4 cm are similar to those of 5 cm.

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