

Nephron sparing surgery as the treatment of choice in renal cell carcinoma

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Introduction. Advances in imaging diagnostics have contributed to the frequent detection of small kidney tumours both at an early stage and of low grade. Although radical nephrectomy is still the gold standard in Renal Cell Carcinoma (RCC) treatment, yet it slowly ceases to be the standard approach and open or laparoscopic Nephron Sparing Surgery (NSS) is becoming more and more common.

Aim. The purpose of the study was to determine the functional and oncological outcomes of NSS for RCC basing on an analysis of 108 patients.

Material and methods. The patients were divided into two groups: T1a (≤ 4 cm) and T1b ($\geq 4 \leq 7$ cm). We performed an analysis of all patients with a minimal follow-up time of 24 months. In the majority of patients the diagnosis was clear-cell carcinoma (83.9%).

Results. G2 tumours were the most common (51.7%). The cumulative proportion of survivors without local relapse within the operated kidney and/or in the local lymph nodes and without distant metastases after 2 and 3 years was 99% and 93%, respectively. Our results support the fact that in pT1a and pT1b patients NSS is a safe and effective procedure. The size of pT1 tumours has no bearing on 2-year and 3-year recurrence-free survivals.

Conclusion. Intraoperative ultrasound allows for further identification of additional neoplastic foci and for the use of the best surgical approach. Intraoperative ultrasound is useful in NSS, and especially in those cases, where the tumor lies in the central part of the kidney.

Key words: renal cell carcinoma, nephron sparing surgery, risk factors, results of treatment

Introduction

Kidney malignant tumours, including renal cell carcinoma (RCC) account for 3% of all adult malignant tumours. They are more frequent in men (with a male: female ratio of 1.5:1) [1, 2].

Epidemiological data reveal a constant increase in the incidence of RCC. In the years 1990 and 2005, in Poland, the incidence of RCC was 3624 and 3749, respectively; with a respective death rate of 2256 and 2442. Advances in imaging diagnostics allow to detect smaller kidney tumours in the early staging and low grading. Although radical nephrectomy still remains the gold standard in RCC treatment yet, gradually it ceases to be the standard treatment applied. Nephron sparing surgery (both open or laparoscopic) is becoming a more common approach [3-7].

Aim

To determine the functional and oncological outcomes of nephron sparing surgery (NSS) in patients with renal cell carcinoma (RCC) basing on the analysis of a database of 108 RCC patients.

Material and methods

Between 1999 and 2007 we performed 108 NSS procedures in patients with kidney tumours. The detection of the kidney tumour and TNM staging was determined basing on ultrasound, computer tomography (CT) scans or magnetic resonance imaging (MRI). The size of the tumour was assessed in the postoperative specimens as the greatest dimension of the tumour. TNM staging and pathological grading was established according to the classification of Union Internationale Centre le Cancer (UICC) incl. the 2002 amendments [8]. The tumours were divided acc. to the WHO classification (2004), i.e. modified Heidelberg classification [9]. Histopathological grading was based on the Fuhrman nuclear grade [10, 11]. All patients underwent intraoperative ultrasound with a 7.5 MHz linear probe in order to evaluate coexisting cancerous foci within the operated kidney and to estimate the adequate line of tumour resection with a margin of no less than 5 mm. Tumour resection was performed after main vessel clamping. The duration of clampage varied from 3 to 20 minutes (mean time 9.2 ± 4.6 min.). In 9 patients (10.3%) the NSS procedure was performed

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within the single kidney. In 4 cases the previous nephrectomy was performed due to the presence of a tumour, whereas in the other 5 cases – due to non-oncology. In case of 5 patients intraoperative ultrasound revealed the presence of additional neoplastic foci and therefore operative qualification was changed from NSS to radical nephrectomy. The patients with pathologically confirmed T1 stage (2002) were divided into two subgroups: group T1a (the greatest dimension of the tumour ≤ 4 cm) and group T1b (the greatest dimension of the tumour $\geq 4 \leq 7$ cm). Follow-up was performed acc. to EAU Guidelines. We performed an analysis of all the patients who completed a 24 month follow-up. The end point of the analysis was set to be November 30th 2008 (n=108).

Statistical analysis

We used Statistica v.7 for statistical analysis. Evaluation of quality variables was performed with the the Shapiro–Wilk test, whereas groups T1a and T1b using Student’s t-Test and the Mann–Whitney U test. Spearman’s Rank Correlation test was used for determining relations between some variables. Recurrence-free survival was assessed using the Kaplan–Meier method. The survival curves in groups T1a and T1b were compared using the Gehan–Wilcoxon test. The differences between the quality variables were determined using Pearson’s chi-square (χ^2) test or with an accurate Fisher’s test with Yates’s modification.

Results

Between 1999 and 2008 NSS was performed in 113 kidney tumour patients. In five cases conversion to radical nephrectomy was necessary in the course of the procedure because additional neoplastic foci were found in the course of intraoperative ultrasound. In 87 patients the diagnosis of RCC was confirmed in the course of pathological examination; in the remaining 21 cases (19.4%) benign tumours were diagnosed, such as benign lesions (12/108), cysts (6/108) and inflammatory infiltrations imitating PCC in CT scans (3/108). In 9 cases (10.3%) NSS was the procedure of choice due to previous nephrectomy performed due to either oncological (4/9) or benign causes (5/9). In a majority of our patients we found single tumours; only in 2 cases we found multifocal tumours before surgery. In these two cases, we performed heminephrectomy because the secondary neoplastic foci were located in the same segment of the kidney as the main tumour. In 5 patients with additional neoplastic foci diagnosed with the use of intraoperative ultrasound and located in other kidney segments than main tumour, we decided to perform radical nephrectomy, providing the other kidney was free from neoplastic lesions and functioned properly. The mean age of our patients was 61.04 ± 12.2 years (range: 27 – 83 years). The mean size of the tumour was 36.1 ± 11.1 mm (range: 12 – 70 mm). In those patients who had undergone previous radical nephrectomy for RCC the mean duration to the performance of NSS within the second kidney was 66.2 ± 42.6 months (range: 18 – 155 months). Clear cell renal carcinoma (CCRC) was the most common diagnosis, with 73 cases (83.9%) followed by chromophobic type 8 (9.1%) and papillary tumours 6 (6.9%). G2 tumours (acc. to Fuhrman) were

the most common 45 (51.7%) – 31 (52.5%) in T1a and 14 (50.0%) in T1b stage. G1 tumours were found in 33 cases (37.9%) – 23 (38.9%) in T1a and 10 (35.7%) in T1b. G3 tumours were observed in 9 cases (10.3%) – 5 (8.5%) in T1a and 4 (14.3%) in T1b. Among the 87 tumour removed in the course of NSS 41 (47.2%) were localised within the lower pole, 26 (29.9%) in the central area of kidney and 20 (22.9%) within the upper pool. Basing on the analysis of ambulatory charts ending on 30.11.2008, we confirmed that all the operated patients survived, however in 2 cases (2.3%) we observed local relapse without lymph node and/or distant metastases. In one patient with a pT1a tumour local relapse was diagnosed after 44 months, and in the other case, that of a patient with a pT1b tumour, after 79 months (median: 57 months). Among the patients with no metastases we assessed also those, who had previously undergone nephrectomy for RCC and the sole patient who did not experience recurrence on the operated side, but rather in the second kidney. In all the operated patients we observed no distant metastases; nevertheless, in one case after 42 months, we diagnosed tumour of 4 centimetres in the second kidney and the patient was referred for NSS. Neoplastic cells within the operated area after tumour excision were observed in 3 (3.4%) cases. All these patients underwent secondary nephrectomy after 1.3 ± 0.57 months and were assessed pathologically as stage pT1a. The mean time of vessel clamping of the kidney was 9.2 ± 4.6 min. (range: 3 – 20 min.). Mean follow-up time was 52.1 ± 20.7 months (range: 25 – 122 months). We operated 45 (51.7 %) men and 42 (48.3 %) women. There were 59 (67.8 %) tumours in stage pT1a (37 men and 22 women) and 28 (32.2 %) in stage pT1b (8 men and 30 women) stage. We observed no significant differences in the mean age between groups pT1a and pT1b (59.6 ± 12.5 vs. 64.1 ± 11.3 years, $p = 0.58$). The pT1a and pT1b groups contained 59 patients (67.8%) and 29 (32.2%), respectively. The mean size of pT1a and pT1b tumours was 29.1 ± 6.4 mm and 47.8 ± 7.2 mm, respectively. The mean follow-up time in both groups was almost the same (pT1a: 45.05 ± 22.8 months, pT1b: 48.00 ± 27.8 ; $p=0.208$). The analysis revealed no statistically significant correlations between tumour size and grade ($R=0.130$; $p=0.227$), patient age and Fuhrman’s nuclear grading ($R=0.083$; $p=0.440$) and age and tumour size ($R=0.182$; $p=0.09$). Cumulative proportion of survivors without local relapse within the operated kidney and/or in the local lymph nodes or distant metastases after 2 and 3 years was 99% and 93%, respectively. (Figure 1).

Considering the fact that the patients were divided into two groups acc. to the pT1 stage, there was no significant difference in the cumulative proportion of those surviving without recurrence after 2 and 3 years (100% vs. 93% and 100% vs. 96%). (Figure 2).

The results show that up to 7 cm in diameter the size of the tumour has no bearing on the time to the appearance of metastases. Three patients were excluded from further evaluation: in 1 of these cases nephrectomy

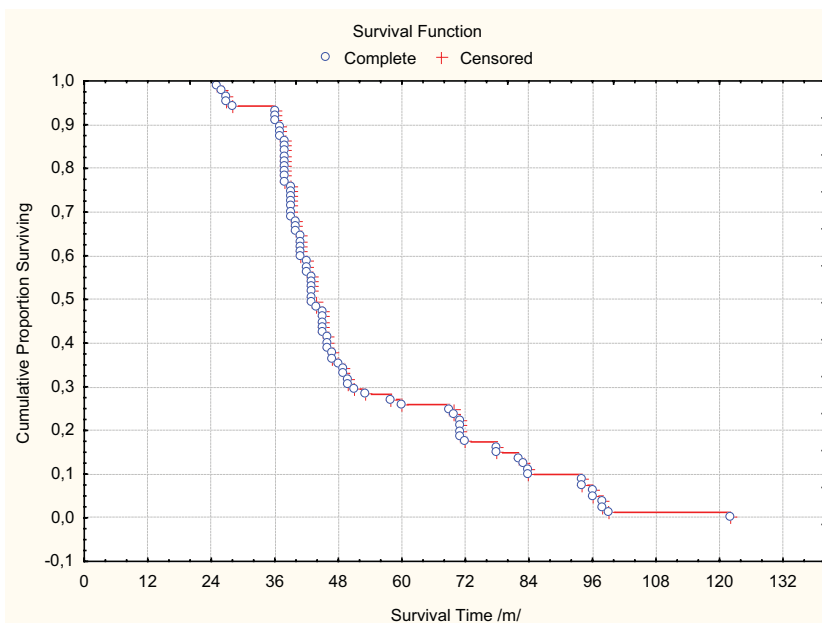


Figure 1. Cumulative Proportion Progression-Free Survivals; RCC patients after NSS

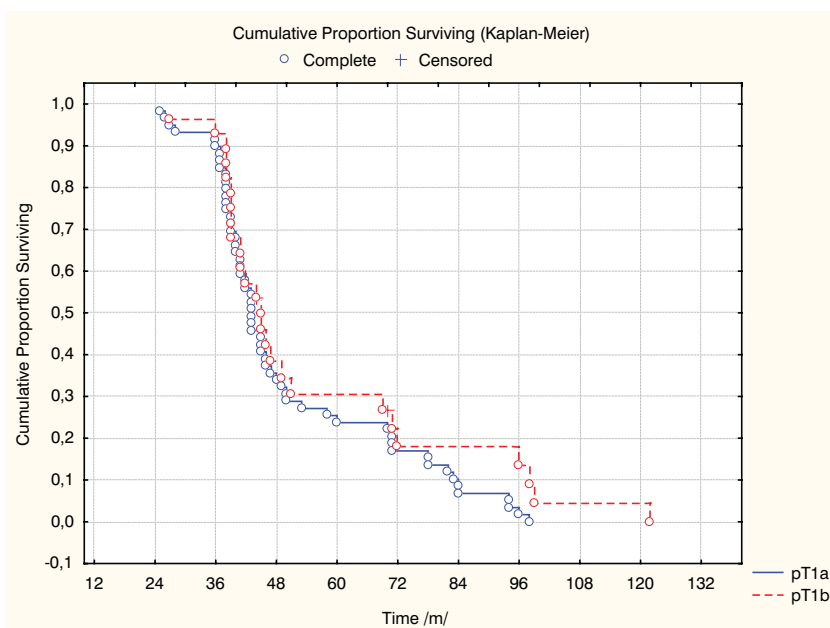


Figure 2. Cumulative Proportion Progression-Free Survivals; RCC patients after NSS; in relation to tumour size ($p=0.4618$)

was performed as a result of early postoperative massive bleeding. 5 patients underwent blood transfusion.

Discussion

A metaanalysis of surgeries performed in patients with kidney tumours in different institutions reveal a high ratio of benign tumours (up to 34 % of lesions), especially those small in size [12]. In the analysis of Pankhurst et al. [13] performed on 349 patients benign tumours account for 16%. The ratio of malignant tumours was higher in case of tumours exceeding 7 cm in diameter (93.7%), as compared to smaller tumours < 2 cm (72.1%). It shows that the risk of malignancy increases with the

size of the tumour (OR 1.39; 95% CI 1.17-1.65). 73.9% tumours were diagnosed accidentally, and were basically asymptomatic. The mean size of asymptomatic tumours was 3.7 cm, while in case of symptomatic tumours (at least one symptom) – 6.2 cm. These tumours were of lower grading [13]. In our material this ratio was approx. 10.6%, but when considering pseudotumours and cysts type Bosniack III the ratio becomes higher (19.4%). The size of benign tumours was significantly smaller than that of RCC tumours (27.4 ± 9.8 vs. 36.1 ± 11.1 mm, $p=0.004$). However, in 2/87 cases (2.3%) we observed local relapse within the operated kidney and cumulative proportion of those surviving without local relapse within the operated kidney and/or in the local lymph nodes or without distant

metastases was 93% after 3 years; the probability of 5-years metastases-free survival was low – only 26%. Such a low 5-year survival rate without local metastases probably arises from the fact that our patient group was small and achieved a low median of 43 months. We would like to define the term “local metastases: which we used in the course of our analysis. In our study patients without local relapse, but with a confirmed tumour within the other kidney were excluded from the group of patients with local metastases. If we were to analyse these patients the incidence of metastases would increase to 3.4%. The tumour size remains the most important prognostic factor in RCC patients. Bell was the first author to stress the correlation between tumour size and the possibility of lymph nodes metastases [14] and set the borderline size of the tumour at 3 cm. Because the ratio of recurrence-free survivals in the years 2 and 3 of follow-up in both the pT1a group and the pT1b group did not differ significantly it may be stated that the size of the operated tumours (up to 7 cm) has no significant influence on the time to recurrence. International, multicenter studies analysing over 700 cases of NSS procedures in selected patient groups with T1 tumours revealed no statistically significant differences in the survival rate between tumours ≤ 4 and > 4 cm in size. Additionally, in case of tumours exceeding 4 cm there were no significantly more frequent occurrences of positive margins, local relapse and systemic metastases [15]. A European multicenter clinical study performed by Ficarra et al. [16] revealed that 5- and 10-year survivals are significantly more frequent in case of patients with pT1a tumours (91.4% and 83.4%), as compared to pT1b (81.6% and 75.2%) ($p < 0.001$). Hafez et al. [17] analysed the results of 485 NSSs in patients with T1 tumours and found that in case of tumours < 4 cm 5-year survival was significantly more frequent as compared to that of patients with larger tumours (> 4 cm) (96% and 86%, $p = 0.0001$). Lapini et al. [18] in a group of 107 patients with T1a tumours (mean size of tumour: 2.7cm; mean follow-up: 84 months) showed that 5- and 10-year progression-free survivals occurred in 98.1% and 94.7%, respectively. Only 3 patients (2.8%) presented with progression (2 patients – local and 1 patient – systemic progression). Antonelli et al. [19] recommend limiting NSS to the treatment for tumours < 4 cm. On the other hand, many studies have reported increased indications for NSS in case of larger tumours up to 7cm [20, 21]. The data of EAU Guidelines (2007) show, that in case of patients with small tumours radical nephrectomy is still performed [22]. The natural history of kidney tumours of small size was rarely analysed, because of the relatively short time relapse between diagnosis and surgical treatment. Bosniak et al. [23] performed a retrospective analysis of 40 patients with tumours < 3.5 cm (mean observation was 3.25 years, range: 1.75 – 8.5 years). In 26 cases the tumours were operated after an average of 3.8 years after diagnosis (range: 1.8 – 8.5 yrs). In 84.6% this was clear RCC. The mean annual growth of tumour was 0.36 cm per year (range: 0 – 1.1 cm/yr). In all these cases no

metastases were observed. It is advisable to indicate, basing on the prospective research of the threshold of tumour size and the increase of the tumour mass, which would contribute to choosing the right treatment. Although the tumour size is a very important prognostic factor, yet it is not the most reliable. Obviously many pathological and molecular markers are used, however none of them is sensitive and specific enough, and thus it cannot be applied in daily urological practice [24]. It appears that modern functional imaging techniques and the molecular and genetic estimations of specimens after biopsy of small tumours allow for the evaluation of their aggressive and invasive potential [25]. There is some evidence that the recognition of the profile of genetic expression allows for the identification of different subtypes of renal clear cell carcinoma, permitting the prognosis of treatment results [24]. Intraoperative ultrasound, especially using a 5 – 7.5 MHz linear probe allows for the proper identification of the multifocal tumours, especially small in size, which were not found in the course of preoperative visual techniques. It also allows for the proper design of the surgical approach with optimal margins, simultaneously sparing the healthy parts of the kidney. This is of utmost importance in case of single kidney surgery or in the case of bilateral tumours. In our material 9 patients underwent NSS of the single kidney and only in 4 of these patients did we observed a slight increase of plasma creatinin level (< 5 mg %). Dimarco et al. analysed 2373 nephrectomy patients and reported that multifocal tumours are more frequent in case of papillary type of RCC. 29 multifocal tumours of an overall number of 266 papillary RCC accounted for 10.9%, compared to 2.0% in case of clear RCC and 1.9% in chromophobic RCC. Clear RCC single tumours were larger when compared to multifocal or papillary tumours. However, the patients with multifocal tumours were at a higher risk of developing a tumour in the second kidney [26].

The multifocality of the tumour has no significant influence of the survival rate [27]. In our material multifocal tumours were observed in 4 cases of clear RCC. In 7 cases the pathological examination revealed neoplastic infiltrations close to the surgical margin. Many authors report similar results of tumour resection or enucleation; this seems to be the result of deep coagulation within the tumour site. Enucleation of tumours up to 4 cm in diameter is as effective as partial resection of the kidney and yet allows for the maximal sparing of kidney. At the same time there is no increased risk of local relapse and of decreased survival [12, 21]. The low ratio of intra-, postoperative and late complications renders NSS a safe surgical procedure [28, 29].

Conclusions

1. Nephron sparing surgery (NSS) in case of pT1a and pT1b tumours is a safe and effective procedure.
2. The size of pT1 tumours has no influence on recurrence-free 2-year and 3-year survivals.

3. The intraoperative ultrasound enables the further identification of additional neoplastic foci and proper choice of surgical cutting.
4. The intraoperative ultrasound is useful in nephron sparing surgery especially in case of tumours localized within the central part of the kidney.

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