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# **Nephron-Sparing Surgery for the Treatment of Renal Cell Carcinoma 4 to 7 cm in Size**

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## **1. Introduction**

The incidence of kidney cancer is gradually increasing over the past 2–3 decades [1]. 60 920 new cases of RCC have been diagnosed in the US in 2011 and 13 120 died of cancer [2]. The widespread use of modern radiological studies has substantially changed clinical presentation of the renal tumors. Currently, there is a trend towards more frequent diagnosis of asymptomatic, incidental, smaller lesions [1, 3]. Nephron sparing surgery (NSS) was initially used in the treatment of renal cell carcinoma (RCC) only for absolute and relative indications [4]. Excellent oncological outcome and reduced morbidity after NSS have led to more frequent use of organ preserving surgery in many centers [4–7]. Elective NSS is currently the treatment of choice for T1a tumors (<4 cm) in the patients with a normal contralateral kidney. Its safety and oncological results have been evaluated in numerous studies [3, 8–10].

The role of NSS in the tumors of 4–7 cm in size is less evaluated and controversial. It could be technically challenging as well [10]. The existing studies suggest that this policy might be feasible and safe. In this paper we present our single centre experience in using the NSS for RCC of 4–7 cm in size.

## **2. Technique of nephron-sparing surgery**

All patients were operated through extraperitoneal, extrapleural incision above the 12<sup>th</sup> rib in 38 cases and above the 11<sup>th</sup> rib in 19 cases. The kidney was completely mobilized to exclude the presence of satellite tumors. Peritumoral fat was left in situ. Sharp incision of the

renal capsule was performed 2 to 3 mm away from the tumor margin. The renal pedicle was isolated completely and the renal artery was clamped just before beginning the incision on the renal capsule. The venous clamping was not used in any case. For diminishing the outcomes of renal ischemia vigorous hydration, infusion of Mannitol before the arterial clamping, and renal hypothermia was adopted in all cases. Tumors were enucleated without a layer of normal parenchyma in 17 cases and enucleoresection was performed in 40 cases. Tumor bed was inspected very carefully on the presence of residual tissue. Intraoperative frozen section of tumor bed was routinely performed. The results of frozen section were negative in all cases. The data of the patients who underwent nephrectomy due to positive margins on the frozen section were not included in the study. The visible bleeding vessels and opened calices were closed using running sutures. Finally, tumor bed was coagulated carefully for haemostatic and partly for oncological reasons. The coagulation was performed by means of diathermy. The parenchymal defect was closed using absorbable interrupted sutures. In case of large capsular defect it was covered with free peritoneal graft.

The stained slides from all tumor specimens were reviewed by urological pathologist. Shortly, the resected kidneys were evaluated macroscopically. The maximal tumor size was measured and 1.5 x 2cm tissue samples were taken for further assessment. Specimens were fixed, stained and evaluated by the same pathologist according to conventional technique. Pathological tumor staging was performed according to the 2002 TNM staging system [11] and nuclear grade was assigned according to the Furhman's grading system [12]. The removed tumor specimen was always inspected by pathologists and the surgical margins were inked.

Patients were followed with renal functional tests, chest X-ray, abdominal ultrasound or CT every 3 months during the first year, once in 6 months for the next two years and annually thereafter. In terms of statistical analysis the probability of cumulative and cancer-specific survival was estimated by the Kaplan-Meier method using the whole number of events.

### 3. Results

We retrospectively reviewed the records of 57 patients who underwent NSS at our institution from 1994 to 2011. The table 1 describes the clinical and pathological features of 57 patients operated at our institution. All patients were carefully evaluated to exclude the presence of distant metastases. Preoperative evaluation included: ultrasonography of the kidney, CT of the abdomen and chest X-ray in all patients. Renal function was assessed by measuring serum creatinine level and creatinine clearance.

The mean follow-up was 70.1 months (range: 10-157 months). Out of the 57 patients 35 (61.4%) were male and 22 (38.6%) were female. The median patient age was 53.1 years (range: 37-68 years). Left side tumor was detected in 34 (59.6%) cases and right side in 23 (40.4 %) cases. The tumor was located in the upper pole in 21 (36.8 %), in the mid kidney in 7 (12.2 %) and in the lower pole in 29 (51%) patients. Tumors were located peripherally in 46 (80.7%) cases and the central tumor location was detected in 11 (19.3%) cases. The peripheral location was defined as: peripherally located and enveloped by cortical parenchyma tumor,

without extension into the renal sinus. At the diagnosis 53 (92.9 %) tumors were detected incidentally and 4 (7.1%) were associated with microscopic haematuria. The NSS was performed for absolute indications in 5 (8.7%) and for relative indications in 11 (19.9%) cases. 41 (71.9%) patients underwent NSS for elective indications.

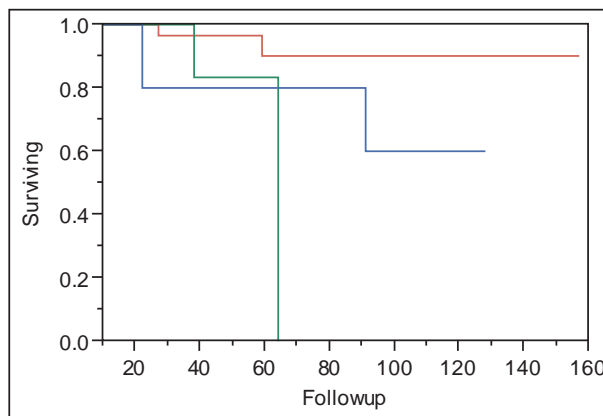
<b>Age at surgery (years)</b>	53.1 (37-68)
<b>Gender</b>	
Male	35 (61.4 %)
Female	22 (38.6 %)
<b>Tumor location</b>	
Left	34 (59.6%)
Right	23 (40.4 %)
Upper pole	21 (36.8 %)
Mid kidney	7 (12.2 %)
Lower pole	29 (51%)
Central	11 (19.3%)
Peripheral	46 (80.7%)
<b>Clinical presentation</b>	
Incidental	53 (93%)
Presented by haematuria, pain etc.	4 (7%)
<b>Tumor size (mm.)</b>	48.1 (41-70)
<b>Stage</b>	
pT1b	53 (93%)
pT3a	4 (7%)
<b>Fuhrman grade</b>	
G1	22 (38.6 %)
G2	27 (47.4 %)
G3	8 (14 %)
<b>Histological subtype (%)</b>	
Clear cell	49 (85.9 %)
Pappilary	5 (8.7 %)
Chromophobe	2 (3.7 %)
Cystic RCC	1 (1.75 %)
<b>Surgical complications</b>	
Bleeding	1(1.75 %)
Urinary leakage	4 (7%)
<b>Disease Recurrence</b>	
Local recurrence	2 (3.5 %)
Distant metastases	4 (7%)

**Table 1.** Clinico-pathological characteristics of 57 patients operated with NSS.

The mean tumour size was 48.1 mm. (range: 41-70 mm.). The mean tumor size in the patients who underwent NSS for elective indications was 44.7 mm. and in the patients who underwent NSS for absolute and relative indications was 65.8 mm ( $p < 0.04$ ). The difference between the later two groups was not significant. Fifty three out of 57 tumors were pT1b (92.9 %) and 4 (7.1%) were pT3a. Pathological T3a stage was confirmed by tumor microinvasion into the perirenal fat. The final pathological evaluation did not reveal any case of tumor extension out of the inked area of the surgical specimens. Grade I tumor was diagnosed in 22 (38.6%), Grade 2 in 27 (47.4%) and Grade 3 in 8 (14%) cases. Morphological evaluation revealed 49 (85.9%) clear cell, 5 papillary (8.7%), 2 chromophobe (3.7%) and 1 cystic (1.75%) RCCs.

The mean duration of renal ischemia was 22 minutes (range: 18-35 mm.). No perioperative mortality and/or serious general complications (myocardial infarction, deep venous thrombosis etc.) have been observed. Postoperative complications occurred in 5 (8.8%) patients including: one (1.7%) postoperative bleeding and 4 (7%) urinary fistulas. The bleeding was observed in peripherally located, large (6 cm. in size) tumor operated for absolute indication. Urinary leakage occurred in two patients operated for centrally located (18.1%) and in two (4.2%) peripherally located tumors. This difference was statistically significant in favor of peripherally located tumors ( $p < 0.0001$ ). All patients required a double "J" stenting. Perirenal hematoma was observed in 2 (3.5%) cases but did not need any intervention and resolved spontaneously. Renal functions were stable in all patients during the follow-up period with a median postoperative creatinine level of 0.9 mg/dl (range: 0.7-1.4 mg/dl). The median hospital stay was 6 days (range: 4-15 days).

The tumor has recurred in 6 (10.5%) patients. Of them, local recurrence was detected in 2 (3.5%) and systemic recurrence in 4 (7%) patients. At the end of the follow-up overall survival was 85.8%, the disease-free survivals was 88.2 %. Both disease-free and overall survival were significantly better in groups of relative and elective indications as compared with absolute indication ( $p = 0.014$  and  $p = 0.023$ , respectively) (Figure 1).



**Figure 1.** Cancer-specific survival in the patients with elective, relative and absolute indications for NSS. — Elective; — Relative; — Absolute

## 4. Discussion

The widespread use of modern radiological modalities substantially changed clinical presentation of renal tumors in recent decades. Currently, there is a trend towards the diagnosis of asymptomatic, incidental, smaller lesions at lower stages [1, 3, 10]. The local disease recurrence is the major drawback of NSS mostly due to the incomplete resection of the primary tumor. In this due radical nephrectomy still remains the gold standard for the treatment of RCC [4, 10].

Improved diagnostic and surgical techniques have led to wider use of NSS. Uzzo RG. and Novick AC. in their review of the results of more than 1800 cases of NSS have showed that the true biological significance of multicentric renal tumors and its implications for NSS remains to be elucidated [3]. In a prospective, randomized EORTC (European Organisation for Research and Treatment of Cancer) phase 3 study comparing open partial nephrectomy (OPN) with open radical nephrectomy (ORN) in small renal tumors (< 5 cm.) found comparable oncological results in the both arms [8, 9]. Moreover, excellent 5 and 10 year disease-free survival rates of 98.5% and 96.7% have been reported after NSS in non-randomized studies [5-7]. These data are now widely accepted. Finally, the recent evidence favoring the NSS over radical nephrectomy in the prevention of chronic kidney disease and possibly linking it to a better overall survival will constitute a strong argument for wider use of NSS. On the other hand, NSS is technically more demanding than RN even for small renal tumors [13]. The previous report of the EORTC 30904 trial revealed that complication rate in NSS was slightly higher than in radical nephrectomy [8].

Based on the success of NSS in the tumors of  $\leq 4$  cm, it has been increasingly used for the treatment of 4-7 cm. tumors in case of a normal contralateral kidney. Leibovich BC. *Et al.* retrospectively compared the results of NSS and radical nephrectomy in the tumors of 4 to 7 cm in size. There were no statistically significant differences in cancer-specific survival and distant metastases-free survival after adjusting for important pathological features. Thus, the authors concluded that the NSS has excellent results for the treatment of 4 to 7 cm renal tumors in appropriately selected patients [14].

Dash A. *et al.* compared the outcomes of the patients who had an elective partial or radical nephrectomy for clear cell renal cell carcinoma of 4–7 cm. in size. With the median follow-up of 21 months the authors failed to show that radical nephrectomy was associated with a better cancer control than the NSS. In terms of functional results the authors found that the serum creatinine level 3 months after surgery was significantly lower in the patients who had NSS [15].

Becker F. *et al.* reported the excellent results of NSS performed for elective indications. 69 patients with the tumor size of more than 4 cm. underwent NSS. After a mean follow-up of 6.2 years seven patients (10.1%) have died, none of them due to the tumor-related causes. Tumor recurrence was detected in four patients (5.8%). The 5-year overall survival was 94.9%. The 10-year and 15-year overall survival was 86.7%. Cancer-specific survival was 100% at 5, 10, and 15 years. The authors concluded that the selected patients with localized

RCC of > 4 cm. can be treated with elective NSS providing optimal long-term outcome. The surgeon's decision for organ-preserving surgery should depend on the tumor location and technical feasibility rather than on the tumor size [16].

Pahernick S. *et al.* compared the results of NSS for the tumors of less and more than 4 cm. in size. Out of 474 treated patients 102 had the tumor of more than 4 cm. The mean follow-up was 4.7 years. The 5 and 10-year cancer-specific survival for small and large tumors were: 97.9% and 95.8%, 94.9% and 95.8%, respectively. In contrast to the tumor size, stage pT3a was associated with a significantly higher risk of tumor related death. The authors advocated that the surgeon's decision with regard to the organ preservation should consider the tumor location and safe surgical resectability, rather than the tumor size [17]. This conclusion has been later supported by Antonelli A. *et al.* [18].

Joniau S. *et al.* presented their results of NSS for the patients with bigger than 4 cm renal tumors. The following data have been collected and analyzed: surgical indication, tumor characteristics, complications, serum creatinine level, time to recurrence and time to the patient death. Local cancer control has been achieved in the vast majority of patients. The renal function was preserved in the patients with elective indications. NSS for absolute indications was significantly correlated with the loss of renal function but not with a cancer-specific survival [19].

In our study the local disease recurrence was detected in 2 (3.5%) and the systemic recurrence in 4 (7%) patients. We could not reveal any changes in the serum creatinine level pre- and postoperatively in the both groups, despite cold ischemia which was used in all patients. Both, the cancer-specific and overall survival was significantly better in the groups of relative and elective indications as compared with the absolute indication ( $p < 0.014$  and  $p < 0.023$ , respectively). These data are similar to the results of the eight-institution multicentre review of 1048 NSS procedures [13].

It has been shown by Badalato GM. *et al.* in their recent publication that the oncological efficacy of NSS for pT1b renal tumors was comparable to that of radical nephrectomy [20]. The authors compared the NSS with radical nephrectomy in the patients with T1b RCC using a propensity scoring approach. 11 256 cases of 4-7 cm. tumors that underwent partial or radical nephrectomy have been evaluated. The propensity score analysis was used to adjust for the potential differences in the baseline characteristics of the patients between the two groups. Overall and disease-free survival of the patients was compared in stratified and adjusted analysis, controlling for propensity scores. For the entire patient cohort, no difference in the survivals was found in the NSS and radical nephrectomy groups. The survival difference between the groups in a propensity-adjusted cohort of patients could not be confirmed even when stratified by the tumor size and patient age.

We've observed that the NSS for centrally located tumors was associated with a higher complication rate. This goes in accordance with the data of Ficarra V. *et al.* who recently proposed a new tumor scoring system [21]. According to the authors this system can better predict the complications after NSS than linear tumor size.

The weak points of our study are retrospective nature and absence of control group consisting of RN patients. However, the prospective randomized study is very difficult to conduct especially in the era of minimally invasive approaches for the treatment of RCC.

## 5. Conclusion

In conclusion, the NSS is a feasible procedure for RCCs of 4-7 cm in size. The local cancer control can be achieved in most patients. Oncological outcome of the treatment is negatively related with the tumor size. Long-term prospective studies on the higher number of patients are required to prove the similar oncological efficacy of NSS and radical nephrectomy in the RCCs of 4-7 cm. in size.

## Author details

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