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Comparison of oncologic outcomes between elective partial and radical nephrectomy in patients with renal cell carcinoma in CT1B stadium

Poređenje onkoloških ishoda između elektivne parcijalne i radikalne nefrektomije kod bolesnika sa karcinomom bubrežnih ćelija CT1B stadijuma

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Abstract

Background/Aim. In renal cell carcinoma (RCC), the choice of surgical technique, radical (RN) or partial nephrectomy (PN), is still center-dependent because there are still no absolute recommendations for this approach. The aim of this study was to analyze the oncological aspects, time until recurrent disease appears, and cancer-specific survival in patients with RCC in T1bN0M0 stadium depending on the type of surgical procedure, PN or RN technique. **Methods.** In a clinical observational study, data of 154 patients operated at the Clinic for Urology, Military Medical Academy, Belgrade, Serbia with a mean follow-up period of no less than five years were analyzed. Patients were divided into two groups; a group of patients with RN and a group of patients with PN. The inclusion criteria were: renal tumors 4–7 cm, histopathological confirmation of RCC, absence of metastasis, and normal serum creatinine. Exclusion criteria included: the presence of other malignancies, solitary functional kidney or comorbidities that can compromise renal function, bilateral tumors, or unilateral multiple tumors. **Results.** The study analyzed data from 154 patients, 97 (63%) RNs, and 57 (37%) patients that underwent PN. Analyzing cancer-specific survival in four patients with RN, there was a disease advancement that led to a lethal outcome, and one PN patient died as a result of local relapse and distant metastasis. **Conclusion.** Based on our results, PN is a good and safe treatment option for patients with RCC in T1b stadium. PN offers a similar tumor control and better cancer-specific survival.

Key words:
carcinoma, renal cell; kidney neoplasms; neoplasm metastasis; neoplasms staging; nephrectomy; urologic surgical procedures.

Apstrakt

Uvod/Cilj. Kod karcinoma bubrežnih ćelija (KBĆ) izbor hirurške tehnike – radikalne (RN) ili parcijalne nefrektomije (PN) i dalje zavisi od centra gde se resekcija vrši, jer i dalje nema apsolutnih preporuka u vezi sa izborom pristupa. Cilj studije bio je da se analiziraju onkološki aspekti bolesnika sa KBĆ u stadijumu T1bN0M0 u zavisnosti od tipa primenjene hirurške procedure – PN ili RN. **Metode.** Kliničkom opservacionom studijom tipa serije slučajeva analizirani su podaci 154 bolesnika koji su operisani na Klinici za urologiju Vojnomedicinske akademije, Beograd, Srbija, sa prosečnim periodom praćenja ne kraćim od 5 godina. Bolesnici su bili podeljeni u dve grupe: grupu bolesnika sa RN i grupu bolesnika sa PN. Kriterijumi za uključivanje u studiju bili su: tumori bubrega veličine 4–7 cm, patohistološki postavljena dijagnoza KBĆ, odsustvo metastaza i vrednosti serumskog kreatinina u referentnim granicama. Kriterijumi za isključivanje bolesnika iz kliničkog ispitivanja bili su: prisustvo drugih maligniteta, prisustvo drugog funkcionalnog bubrega ili oboljenja koja mogu kompromitovati bubrežnu funkciju, bilateralni tumori i više tumora na jednom bubregu. **Rezultati.** U studiji su analizirani podaci od ukupno 154 bolesnika, 97 (63%) sa RN i 57 (37%) sa PN. Analizirajući preživljavanje bolesnika, u zavisnosti od tumora, utvrđeno je da je kod četiri bolesnika sa RN došlo do smrtnog ishoda zbog napredovanja bolesti, dok je kod jednog bolesnika sa PN smrtni ishod nastupio kao posledica lokalnog recidiva tumora i udaljenih metastaza. **Zaključak.** Na osnovu naših rezultata, PN je dobar i siguran izbor u lečenju bolesnika sa KBĆ u T1b stadijumu. Parcijalne nefrektomije nudi sličnu kontrolu tumora i bolje preživljavanje obolelih od KBĆ.

Ključne reči:
karcinom bubrežnog parenhima; bubreg, neoplazme; neoplazme, metastaze; neoplazme, određivanje stadijuma; nefrektomija; hirurgija, urološka, procedure.

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Introduction

Renal cell carcinoma (RCC) presents the third most frequent urological malignancy, 2–3% of all adult malignancies and 80–85% of all primary renal carcinomas [1]. It is the most frequent solid renal tumor whose prevalence increases in Europe and North America [2]. Worldwide, over 350,000 new cases of RCC have been diagnosed annually, with over 140,000 kidney cancer-related deaths (mortality rate around 40%). Therefore, these patients represent a significant health issue [3, 4]. In the European Union, just in 2012, 84,499 new cases of RCC have been diagnosed with 34,700 cancer-related deaths [5].

Surgical treatment is the usual management option for a patient with RCC. Surgical resection is the standard treatment option in patients with localized RCC. Historically [6], radical nephrectomy (RN) has been the benchmark surgical treatment of organ-confined RCC. Partial nephrectomy (PN) has taken primacy in treating RCC up to 4 cm. In selected cases with tumors from 4 to 7 cm, it has proven to be as reliable as RN, even though there are available guidelines recommending that PN be applied even in tumors that exceed 7 cm [7]. So far, a unified and definitive position on the role of PN in clinical-stage T1bN0M0 of RCC has not been proposed when there is no absolute indication for this type of surgery. Most relevant studies specify from the oncological point of view that PN is equally reliable as RN when referring to "cancer-free survival" [8]. In addition, the European Association of Urology (EAU) guideline from 2016 recommends that patients in the T1a clinical stage of RCC should be treated with PN and that PN should be applied whenever possible in patients in T1b clinical stage of the tumor [9].

The aim of this study was to analyze the oncological aspects, such as the time to tumor recurrence and cancer specific survival for patients with RCC in clinical-stage T1bN0M0 depending on the type of surgical treatment, PN or RN.

Methods

The study was adopted as a case series clinical observational study and was conducted on patients that underwent surgical treatment at the Clinic for Urology, Military Medical Academy, Belgrade, Serbia for renal tumors with the histological confirmation of RCC as a result of PN or RN.

Patients were divided into two groups by type of surgical resection: RN group and PN group.

Patients were recruited depending on inclusion and exclusion criteria. The two analyzed groups consisted of patients aged 18–80 years who underwent surgical treatment for renal tumors either by PN or RN from 2006 to 2013. In all patients, RCC was confirmed by histopathology. All significant variables of the disease were registered. The surveillance period was from 2006 to 2018, with a median follow-up period of no less than five years, which depended on the patient's survival following nephrectomy or if there was no lethal outcome.

The inclusion criteria were: renal tumors 4–7 cm, histopathological confirmation of RCC, absence of distant metastasis, and normal serum creatinine level.

The exclusion criteria were: the presence of other malignancies, one functional kidney or other conditions that may compromise renal function in the future, bilateral tumors, and multiple unilateral tumors.

Preoperative diagnostic evaluation in all cases consisted of determining the size of the tumor, absence or presence of metastasis, function, and morphology of the contralateral kidney and was conducted using multi-slice computed tomography (MSCT). This imaging was performed not only in our institution but also in other medical institutions. In some instances, if the MSCT scan was inconclusive, it was repeated in our institution. The contralateral kidney was defined as normal if the serum creatine level and MSCT scan were normal.

Following surgical treatment, the histopathological analysis was performed to determine the tumor grade, vascular or lymphatic invasion, histopathological RCC subtype, and histopathological Tumor-Nodes-Metastasis (TNM) stage.

Postoperative assessment of the patients was performed in an outpatient setting for a month and then six months subsequently following the surgical treatment. All of them included physical examination, laboratory analysis, ultrasound of the abdomen and pelvis minor, chest X-ray, and annual MSCT. Determining the presence of postoperative metastasis and local relapse involved an ultrasound scan, chest X-ray, and MSCT. All of these examinations were performed by a radiologist.

Statistical data analysis was performed by PASW Statistics version 18 statistical software. The χ^2 test was used for statistical analysis between some categories, and the Mann-Whitney *U* test for assessing differences in the continual variables. The value of $p < 0.05$ was considered statistically significant.

The principles of the International Council for Harmonization Good Clinical Practice were strictly followed, and the approval from the Ethics Committee of the Military Medical Academy from December 07, 2016 was obtained.

Results

This study analyzed data from 154 patients, 97 (63%) patients with RN and 57 (37%) patients with PN (Table 1). The male/female ratio was nearly 3/1 (115 vs. 39, respective-

Table 1

Demographic characteristics of patients operated due to renal cell carcinoma

Variable	Nephrectomy		*p*-value
	RN (n = 97)	PN (n = 57)	
Male/female	65 (67.0)/32 (33.0)	50 (87.7)/7 (12.3)	0.008*
Age	61.00 (49.50–68.0)	55.00 (46.50–61.50)	0.027**
Age male	62.00 (54.00–67.50)	56.00 (45.50–63.00)	0.010**
Age female	53.50 (47.00–68.75)	55.00 (48.00–60.00)	0.929**
p-value	0.219**	0.877**	

Results are shown as a number (%) or median (interquartile range).

PN – partial nephrectomy; RN – radical nephrectomy.

***– χ^2 test; **– Mann-Whitney test.**

ly). Furthermore, males were more represented in both groups of patients, but the frequency was statistically more significant in the PN group compared to the RN group (87.7% vs. 67.0%, respectively). When comparing the age of the patients at the time of diagnosing RCC in the analyzed groups, there was a statistically significant difference in the median age in the RN group.

More than 74% of patients in both groups were asymptomatic (Table 2). If present, the most frequent symptom in both groups was pain.

Regarding the histopathological characteristics of the tumors, initially, at the time of surgical treatment, all patients were in the clinical T1bN0M0 stage (Stage I). Table 3 presents the largest diameter of the tumor mass in the PN and RN group; between the groups, there was a statistically significant difference ($p < 0.001$). In the RN group, the mean tumor diameter was 53.00 mm, while in the PN group, it was 43.00 mm. Evaluating the tumor localization, no statistically significant difference in the RN and PN groups was registered. In over 80% of patients in both groups, the confirmed histopathological diagnosis was the clear-cell subtype of RCC.

The ipsilateral adrenal gland in the PN group during tumor resection was left intact, while in the RN group, it was removed in nearly 60% of patients. Once removed, there were nearly no cases of tumor involvement except for two patients in the RN group.

Following surgical tumor resection, a histopathological analysis was performed by defining the tumor grade (Table 4).

Table 2

Symptoms associated with radical and partial nephrectomy

Symptoms	Nephrectomy		*p*-value*
	Radical	Partial	
None	72 (74.2)	47 (82.5)	
Pain	15 (15.5)	8 (14.0)	
Haematuria	8 (8.2)	1 (1.8)	0.323
Hyperkalemia	1 (1.0)	–	
Anemia	1 (1.0)	–	

Results are shown as a number (%).
***– χ^2 test.**

Table 3

Anatomical localization and histopathological characteristics of the tumor

Variable	RN	PN	*p*-value
Diameter (mm)	53.00 (45.00–60.00)	43.00 (40.00–50.00)	< 0.001*
Localization			
upper pole	36 (37.1)	16 (28.1)	0.104**
lower pole	27 (27.8)	25 (43.8)	
interpolar region	34 (35.1)	16 (28.1)	
Histopathological characteristics			
clear-cell	70 (87.5)	43 (82.7)	0.196**
papillary	3 (3.8)	6 (11.5)	
chromophobe	7 (8.8)	3 (5.8)	

Results are shown as a number (%) or median (interquartile range) value.
PN – partial nephrectomy; RN – radical nephrectomy.
***– Mann-Whitney test; **– χ^2 test.**

Table 4

Tumor grade, local invasion and histopathological stage

Variable	RN	PN	*p*-value*
Grade (G)			
G1	2 (2.1)	1 (1.8)	
G2	56 (58.9)	37 (64.9)	0.670
G3	35 (36.8)	19 (33.3)	
G4	2 (2.1)	–	
Lymphatic invasion			
no	23 (29.9)	26 (50.0)	0.034
yes	54 (70.1)	26 (50.0)	
Vascular invasion			
no	19 (25.0)	30 (58.8)	< 0.001
yes	57 (75.0)	21 (41.2)	
T stage			
T1a	11 (11.5)	19 (33.3)	
T1b	43 (44.8)	33 (57.9)	
T2	2 (2.1)	2 (3.5)	< 0.001
T3a	38 (39.6)	3 (5.3)	
T3b	2 (2.1)	–	

Results are shown as a number (%).
PN – partial nephrectomy; RN – radical nephrectomy.
***– χ^2 test.**

Table 5

Clinical progression-free survival of RCC patients subjected to radical or partial nephrectomy

Nephrectomy	Tumor relapse	Clinical progression-free survival (days), mean (95% CI)
Radical	6	1,470.29 (997.56–1,943.01)
Partial	2	1,142.50 (0.00–2,311.64)

RCC – renal cell carcinoma; CI – confidence interval.

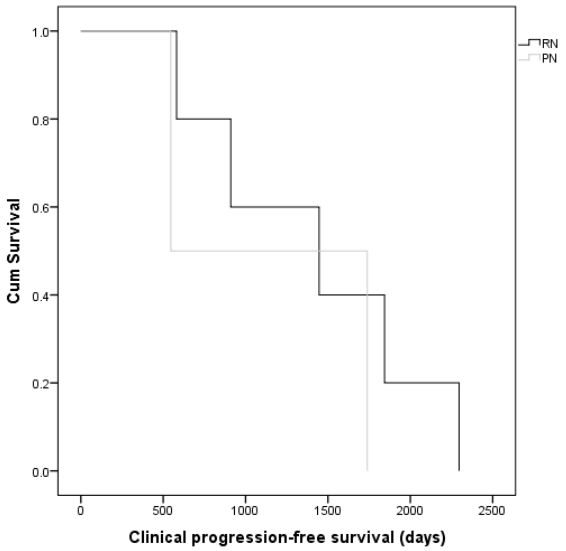

Fig. 1 – Clinical progression-free survival according to the type of surgical resection. PN – partial nephrectomy; RN – radical nephrectomy. Log Rank (Mantel-Cox) test, $p = 0.436$.

No statistically significant difference concerning the tumor grade between the RN and PN group was established ($p = 0.670$). The most frequent tumor grade in both groups was grade 2 and 3 (in over 95%). The lymphatic invasion was statistically significantly more frequent in the RN group in over 70.1% of cases compared to the PN group, where it was present in 50.0% of cases. The same was with vascular invasion in 75% of cases in the RN group, while in the PN group, it was present in 41.2% of cases.

However, considering the histopathological stage of the tumor, a statistically significant difference was established between the RN and PN groups ($p < 0.001$). In the RN group, it was mostly in the T1b and T3a stages, while in the PN group, it was in the T1a and T1b stages (Table 4).

The overall surveillance period in the RN group was 2,343 days (365–4,297 days), while in the PN group, it was 2,175 days (868–4,045 days). The evaluation of the clinical progression-free survival in patients with RCC had shown a low rate of tumor relapse (Table 5). Of the overall number of patients in the RN group, a relapse of the tumor was registered only in 6 patients, while in the PN group, it was registered in two patients. The average time for relapse to occur in the RN group was 1,470 days and 1,142 days in the PN group. This has proven not to be statistically significant [Log Rank (Mantel-Cox) test, $p = 0.436$] (Figure 1).

When analyzing the cause of death in five patients, the occurrence of tumor relapse or the appearance of metastasis were connected to the lethal outcome (Table 6). In all other patients, the leading cause of death was not related to the operated RCC but rather to other comorbidities (cerebrovascular or cardiovascular).

When analyzing the cancer-specific survival, or the mortality from RCC as the single cause of death, we registered that in four patients, the lethal outcome was the result of metastasis, while one patient died because of local relapse and distant metastasis (Table 6, Figure 2).

Table 6

Cancer-specific survival of RCC patients subjected to radical or partial nephrectomy

Nephrectomy	Patients		
	total number	died	censored, number (%)
Radical	95	4	91 (95.8)
Partial	55	1	54 (98.2)

RCC – renal cell carcinoma.

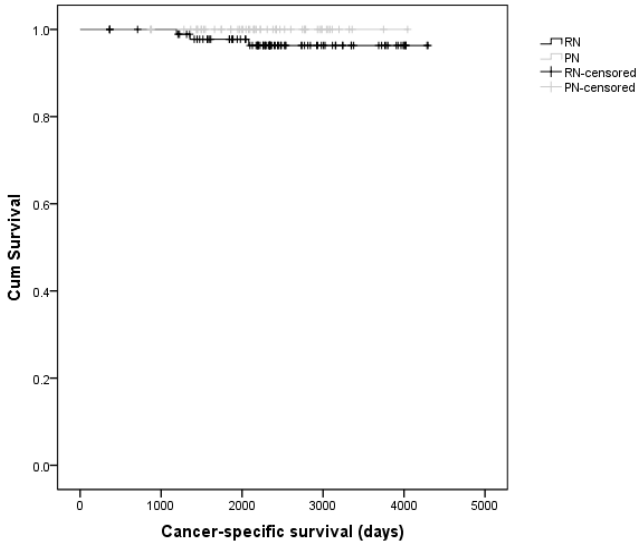

Fig. 2 – Cancer-specific survival according to the type of surgical resection.
PN – partial nephrectomy; RN – radical nephrectomy.
Log Rank (Mantel-Cox) test; p = 0.459.

Discussion

Based on a global assessment of data from 167 countries in 2017, RCC was the seventh most frequent malignancy and represented 3.3% of all newly detected carcinomas [10]. An estimated increase of new cases of RCC was 22% by 2020 [3]. Obesity, smoking, and hypertension are known risk factors for RCC. With the global population aging, there is also an increase in the prevalence of this malignancy [11]. RCC represents around 90–95% of all kidney tumors, and at the time of diagnosis, 25–30% of patients already have metastatic disease [10].

Surgical treatment of RCC is still the gold standard in treating this malignancy [12, 13]. In the early stages of RCC, when the lesions are small and surgical resection is possible, several surgical modalities are available. In the previous decade, an offset occurred from RN towards the necessity of nephron-sparing techniques PN. Preservation surgical techniques have a goal to preserve renal function and, at the same time, have identical oncological results as in RNs [14, 15]. Moreover, when considering the quality of life, renal function, and overall survival, the majority of studies agree that PN has a significant advantage over RN [16–19]. Additionally, an offset from open to laparoscopic and robot-assisted surgery occurred [20]. Now in the leading countries in the world, PN is performed mostly laparoscopically or by robot-assisted techniques.

The classical triad of symptoms (flank pain, macroscopic haematuria, and palpable mass) is present in around 6–10% of cases, but when present, it raises doubt on RCC [21]. In both of our groups, more than 74% of patients were asymptomatic. That is similar to the majority of studies that show that RCC has a devious development, so in most cases, it is incidentally detected [22, 23]. In our study, the most frequent symptom in both groups was abdominal pain (in around 15% of patients). Haematuria was present only in 9 patients. This is explained by the fact that the tumor was low grade and developed pain but not haematuria, anaemia, or other symptoms.

Available literature has shown that tumor size has a major significance and influences patients' survival following tumor resection [24]. The larger the size (especially over 30 mm), the shorter the survival. In tumors smaller than 30 mm, distant metastases are rare. In a study that analyzed 740 patients, Herrlinger et al. [24] reported that distant metastasis was present in only one patient, in whom the tumor size was less than 30 mm. In the PN group, the tumors were, on average, 10 mm smaller than in the RN group (43 mm vs. 53 mm, respectively). At the time of the operation, all patients had the tumo in clinical stage T1bN0M0 (Stage I).

The Corona and Saturn project study [25] has shown that the size of the tumor of 75 mm assessed by computed tomography at the time of diagnosis is the border value and those tumors whose diameter exceeds this value correlate with the appearance of distant bone metastasis. This study also showed that in 1,712 patients, the tumor recurrence of more than 5 years was related to the mean size of the tumor of 60 mm, while the mean tumor diameter of 70 mm was related to the tumor recurrence period less than 5 years following the operation. In tumors 40–70 mm in diameter, there is a probability that 6% of patients have already regional or distant metastasis at the time of diagnosis [26]. Results of these studies can have a role in selecting patients into subgroups as candidates for more aggressive treatments because of the probability of distant metastasis appearance or tumor recurrence following tumor resection.

RN was performed in our patients with tumors mostly localized in the upper pole of the kidney and somewhat lesser in the interpolar region. PN was performed in our patients with tumors mostly localized in the lower pole of the kidney.

An easier anatomical approach to the tumors localized in the lower pole can explain why PN is mostly the opted treatment in these cases and why RN is more frequent in tumors localized in the upper pole or interpolar.

After tumor resection, the protocol is followed by a histopathological examination that determines the tumor tissue differentiation or tumor grade, vascular and lymphatic invasion, tumor histological subtype, and TNM stage. Published studies have shown a direct connection between tumor size and its differentiation, so that increase in tumor diameter increases the volume of patients who have higher tumor grade [26]. The most frequent tumor grade in both of our groups was the grade 2 and 3 in over 95% of cases.

In the RN group, the lymphatic invasion was significantly more frequent than in the PN group (70.1% vs. 50.0%, respectively). It is the same case with vascular invasion, which was more frequent in the RN group (75.0%) than in the PN group (41.2%). The microvascular invasion is defined as the presence of malignant cells that invade the wall of the blood vessel or neoplastic emboluses in the intratumor blood vessels; it is present in 13.6–44.6% of RCC [27]. It is more frequent in higher grades of RCC and larger tumors. This is a significant prognostic factor, but the results in many studies are still controversial [28, 29].

In both analyzed groups, clear-cell RCC (ccRCC) was the most frequent histological subtype of RCC (in over 82% of patients). Similar results have been presented in other published studies [18, 26] because it is a known fact that ccRCC is the most commonly encountered histological subtype of RCC and is present in over 75% of patients, while the others are significantly less common [2, 30].

However, when analyzing the histopathological T stage, a significant difference in patients in the RN and PN groups was established. In the RN group, the T1b and T3a stages were most common, while in the PN group, the T1a and T1b stages dominated. Since one of the inclusion criteria to enter the study was that all of the patients be in the clinical T1b stage, in the RN group, this stage had been confirmed only in 44.8% of cases, while in the PN group, it was more present (57.9%). In the RN group, the rest of the patients had a lower, or more commonly, higher stage. In the PN group, the lower stage was mostly present, and only 5 patients had the higher stage. Data from published studies are similar concerning the difference in pre and postoperative stages [30], with an established difference in T and N stages at around 35%. Most commonly, an error was made in measuring the size of the tumor in 92% of cases and in assessing the local tumor invasion of perirenal fat. The N stage was assessed adequately in 94% of patients. However, the MSCT scan still represents the best method for identifying and assessing the preoperative stage of RCC. The major limitation is assessing the tumor size and local expansion in suspected borderline cases [30].

The ipsilateral adrenal gland was removed only in the RN group – out of nearly 60% of patients, tumor involvement is found in two cases.

Analyzing data in 1,179 patients with RCC, Antonelli et al. [31] showed that preservation of the ipsilateral adrenal gland is recommended only in patients with tumors smaller than 4 cm. They also showed that local expansion and the size of RCC are the best risk predictors of the presence of metastasis in the adrenal gland. Siemer et al. [32] presented similar results and emphasized that the tumor diameter of 4 cm is crucial for deciding whether to perform ipsilateral adrenalectomy or not. The incidence of diagnosing metastasis in the adrenal gland is significantly higher in autopsy studies (6–29%) compared to clinical diagnosis (2–10%) [32–35]. A 19% involvement of the ipsilateral adrenal gland is present in autopsies and 5.5% in urology studies, while even up to 11% of the contralateral adrenal gland involvement is reported [36]. Moreover, it is relevant to take into consideration the possibility of metastasis in other organs, for example, the thyroid gland, lungs, bone metastasis, or other locations, because they are common, especially in higher stages [23]. The EAU Guidelines do not recommend ipsilateral adrenalectomy if there are no clear signs of adrenal gland involvement [37].

When analyzing the cancer-specific survival, our study showed that RCC was the cause of death in 4 patients in the RN group, where metastasis led directly to a lethal outcome, while in the PN group, this was the cause of death in one patient. Our study showed significantly better results than other studies. In a study by Jang et al. [18], a significant difference was not established in the 10-year cancer-specific survival in RCC patients with PN and RNs (85.7% vs. 84.4%, respectively). Similar conclusions were made by other authors who did not prove the advantage of PN to RN based on cancer-specific survival [8, 38, 39]. However, a recent study showed a major difference in the cancer-specific survival rate between laparoscopic PN and RN, where the overall survival, cancer-specific survival, and metastasis-free survival were significantly better in RN patients [40]. Compared with the RN group, patients of the PN group had a 1.9-fold overall survival, 2.9-fold cancer-specific survival, and 2.3-fold metastasis-free survival [40].

In the PN group, both relapses were local. In the first patient, the reoperation was performed 5 years after PN, where the initial tumor was 47 × 45 mm in diameter and localized at the lower pole. The recurrent tumor was 36 mm localized at the site of the previous resection. This was the only PN patient in whom the resection margin was positive. This patient is alive, without tumor recurrence. In the other patient, the tumor at the time of resection was 50 × 45 mm in diameter and localized in the interpolar region of the left kidney in the pT3a stage, with vascular and lymphatic invasion. In less than a year, the patient developed local tumor relapse, and after nephrectomy, also less than a year, developed metastatic disease and shortly after died. In the RN group, no local relapse was detected, but the patients developed distant pulmonary and cerebral metastasis. In a systematic review and meta-analysis of comparative studies, which involved 21 studies and included over 11,000 patients, it was concluded that PN is a sustainable treatment option for large renal tumors because it provides acceptable surgical morbidity, equivalent cancer control, and better preservation of renal function compared to RN with a potential for better overall survival of patients [41].

Conclusion

RNs and PNs are benchmark methods in the treatment of localized RCC. However, PN is a method that preserves the renal parenchyma, hence PN vs. RN provides better postoperative renal function. The results of our study strongly suggest that in patients in clinical-stage T1b of RCC, PN provides the same cancer control as RN. Taking this into consideration, when planning surgical treatment in this clinical stage, elective PN represents the standard treatment method and must be offered to the patient as an effective and safe option.

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