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ORIGINAL ARTICLE

Partial versus radical nephrectomy for pT1a renal cancer in Serbia

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Summary

Purpose: *To assess the treatment outcome of pT1a renal tumors, comparing overall survival (OS) in patients treated with radical nephrectomy (RN) and partial nephrectomy (PN), and to examine the rate of utilization of PN in a tertiary institution in Serbia.*

Methods: *Included were patients treated for pT1a kidney tumors with open RN or open PN during 1996-2013. The inclusion criterion was the pathological tumor stage T1a. Exclusion criteria were higher pathological stages, metastatic presentation, or imperative indications for partial nephrectomy. Patients were followed-up every 3 to 4 months for the first year after surgery, every 6 months until the 5th year, and annually thereafter.*

Results: *286 patients were included in the study, and PN was performed in 177 (61.9%) of them, whereas RN was performed in the remaining 109 (38.1%). The median follow-up for the entire group was 42.0 months (interquartile range 74.5). There were no statistically significant differences between groups in cancer-specific survival (CSS) (log-rank=0.506; p=0.477). Patients selected for RN were more likely to be older, symptomatic at presentation, and have larger tumors. There was no statistically significant difference in OS between the two groups (log-rank=2.616; p=0.106). In 1996, 20% of the patients were treated with PN; this number increased to 88% in 2013.*

Conclusion: *We did not find OS advantage for PN compared to RN in the setting of a developing country. The use of PN is increasing and is now utilized for ~90% of pT1a renal tumors.*

Key words: *nephron-sparing surgery, pT1a, partial nephrectomy, radical nephrectomy, small renal masses*

Introduction

With the advent of high-definition abdominal imaging, there is an increasing detection rate of small renal masses (SRMs), a fact that has led to stage migration of renal cancer [1]. Historically, the treatment modality used for the vast majority of SRMs was RN. However, in the past decade, the usage of PN has increased substantially [2]. Observational retrospective studies have shown that in comparison with RN, PN provides improved renal function, a lower risk of cardiovascular events, and OS benefits [3-5]. As a result of these studies, there are strong recommendations in the guidelines for the utilization of PN for SRMs [6,7].

However, most of the studies concerning the benefits of PN are conducted in developed countries. Cardiovascular disease (CVD) mortality in Eastern European countries is much higher than the European average [8], and in Serbia, 48% of premature mortality is related to CVD [9]. There is no data comparing the impact of PN vs RN on OS

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in this setting.

Despite all the potential benefits of PN and the guidelines' recommendations, large national databases have suggested underutilization of PN in the USA [10] and only recently a steady increase in PN utilization has been observed in this country [2]. The data on usage of PN in developing countries however is scarce.

The purpose of this study was to assess the experience in a tertiary institution in Serbia, as a developing country, with the treatment of pT1a renal tumors, comparing OS in patients treated with RN and PN, and to examine the rate of utilization of PN.

Methods

Patient assessment

The records of patients treated for pT1a kidney tumors in the Clinical Center of Serbia's Clinic of Urology with open RN or open PN during the period from 1996 to 2013 were analyzed. The inclusion criterion was the pathological tumor stage T1a. Exclusion criteria were higher pathological stages, metastatic presentation, or imperative indications for PN (solitary kidney or an atrophic contralateral kidney, and impaired renal function - estimated glomerular filtration rate (eGFR) <45 ml). Preoperative patient staging included history, physical examination, routine blood tests and serum biochemistry studies, chest X-ray, and abdominal CT scan. The option for the type of surgery was left to the surgeon's and patient's consideration after accounting for the size of the tumor, radiographic characteristics, life expectancy, and surgeon's comfort. Patients were considered symptomatic if presented with a palpable flank or abdominal mass and/or pain, gross hematuria, acute onset varicocele or constitutional symptoms (anorexia, weight loss, night sweats, fatigue). Comorbidity was evaluated using the Charlson Comorbidity Index (CCI) [11]. eGFR was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study equation [12]. Patients were followed-up every 3 to 4 months for the first year after surgery, every 6 months until the fifth year; and annually thereafter.

Statistics

Differences in investigated continuous variables were assessed using ANOVA, while x^2 test was used for categorical variables. Survival analysis was performed separately in the two subgroups of patients, and Kaplan-Meier curves were generated to estimate the cumulative survival probability. Log-rank test was performed for the assessment of differences in survival according to the different categories' events. Variables associated with type of surgery (gender, age, year of surgery, tumor size, and CCI) were assessed by Cox proportional hazard regression model. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 17.0; SPSS Inc, Chicago, Ill, USA).

Results

286 patients were finally included into this study. PN was performed in 177 patients (61.9%), whereas RN was performed in 109 (38.1%). The median follow-up for the entire group was 42.0 months (interquartile range-IQR=74.5). The median follow-up for PN patients was 28.0 months (IQR=44.0) and 82.0 months (IQR=83.0) for the RN group. Five-year CSS rates were 95.4±2.7% for PN and 93.2±2.9% for RN groups, respectively (log-

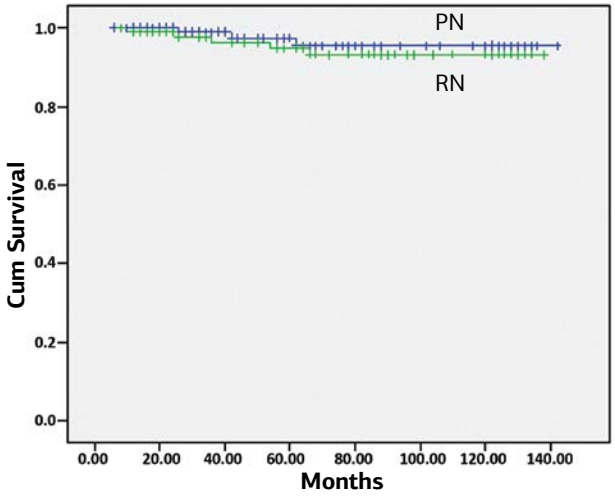

Figure 1. Kaplan-Meier estimates for cancer specific survival in all patients after partial nephrectomy (PN) and radical nephrectomy (RN) (log-rank, p=0.477).

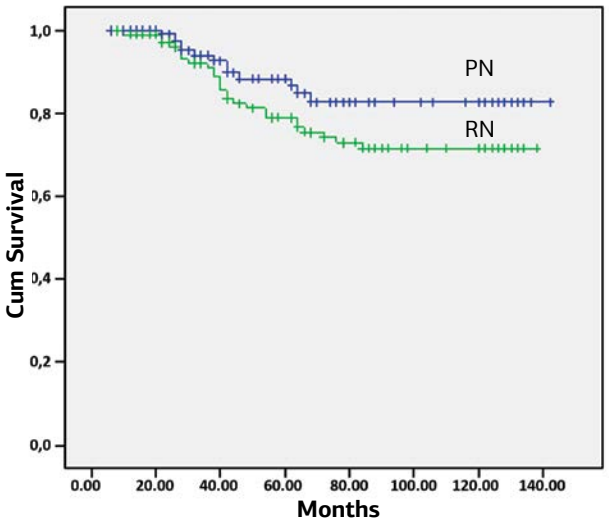

Figure 2. Kaplan-Meier estimates for overall survival in all patients after partial nephrectomy (PN) and radical nephrectomy (RN) (log-rank, p=0.106).

Table 1. Clinical and pathological features of patients stratified by treatment modality

	PN *N (%)*	*RN* *N (%)*	*p value*
Number patients	177 (61.9)	109 (38.1)	
Age at surgery, years (mean±SD)	57.08±11.8	60.3±10.8	0.024
Sex			
M	99 (55.9)	63 (57.8)	0.757
F	78 (54.1)	46 (42.2)	
CCI			
0-1	148 (83.6)	82 (75.2)	0.083
≥2	29 (16.4)	27 (24.8)	
Preoperative eGFR			
>60	154 (87.7)	91 (83.5)	0.409
45-59	23 (13.0)	18 (16.5)	
Symptomatic at presentation	34 (19.2)	41 (37.6)	0.001
Tumor size (mm) (mean±SD)	35.8±4.8	38.1±3.2	0.001
Tumor subtype			
CC	138 (78.5)	81 (75.2)	0.587
Non CC	29 (16.4)	20 (18.3)	
Benign	9 (5.1)	7 (6.5)	
Tumor grade			
G1-2	106 (59.9)	70 (64.2)	0.302
G3-4	71 (40.1)	39 (35.8)	
No. diabetic pts	24	13	0.689

PN: partial nephrectomy, RN: radical nephrectomy, M: male, F: female, CCI: Charlson Comorbidity Index, eGFR: estimated glomerular filtration rate, CC: clear cell renal cell carcinoma, pts: patients

rank=0.506; p=0.477) (Figure 1). The clinical and pathological features of all patients are shown in Table 1. Patients selected for RN were more likely to be older, symptomatic at presentation, and have larger tumors. There was no statistically significant difference in OS between the two groups (log-rank=2.616; p=0.106) (Figure 2).

The analysis of the trend of the usage of PN is shown in Figure 3. In 1996, 20% of the patients were treated with PN; this number increased to 88% in 2013. Features predicting the use of PN were patient age (HR-hazard ratio=1.02; 95% CI 1.00–1.05; p=0.020), year of operation (HR=0.82; 95% CI 0.78–0.87; p=0.001), and tumor size (HR=1.15; 95% CI 1.08–1.23; p=0.001).

Discussion

For many years, RN has been used as a standard form of treatment for SRMs [13]. Recently, there has been an increased use of PN, for imperative as well as elective indications in the therapy of SRMs, owing to advancements in surgical techniques. PN has proven to be a safe surgical procedure with comparable oncologic results and only a slightly higher complication rate compared to RN such as urinary leak and the reintervention rate [14]. Additionally, knowing that up to 20% of SRMs are benign [15], RN could represent overtreatment in this patient group. In our series of renal masses smaller than 4 cm, the percentage of benign lesions was 5.6%.

Many retrospective observational studies found that PN is associated with better OS and the authors have hypothesized that this result is attributable to better preservation of renal function. One of the first studies from USA has concluded that that compared with PN, RN may be associated with decreased OS in younger patients with small renal tumors [16]. Kim et al. [17] performed a sys-

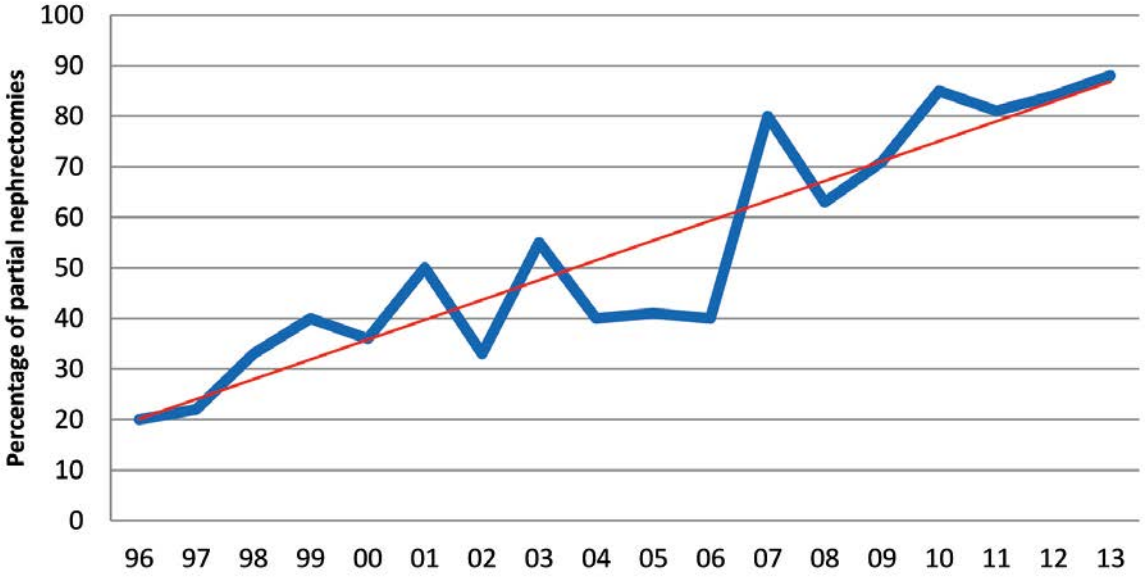

Figure 3. The trend of utilization of partial nephrectomy from 1996 to 2013.

tematic review and meta-analysis and included over 41,000 patients undergoing PN (23%) or RN (77%). PN correlated with a 19% reduction in all-cause mortality compared with RN. A large German multicenter study found that in patients with localized renal cell carcinoma, PN might be associated with better OS than RN [18]. Takagi et al. [19] reported that in Japanese patients with pre-existing chronic kidney disease (CKD) with eGFR at 45–59 mL, PN could successfully prevent the development of late stage CKD in comparison with RN. There is only one randomized controlled trial regarding RN vs PN in the elective setting. During a median follow-up of more than 9 years, no survival advantage was found in patients who underwent PN. However, this study had several limitations [20].

Most of the data regarding the benefits of PN in terms of OS are coming from developed, high-income countries with well-organized healthcare and health education. The Serbian population is specific if compared to other European countries because over the past two decades, the Republic of Serbia has experienced political instability, war in neighboring countries, economic sanctions by the United Nations, isolation, hyperinflation, refugee immigration and professional emigration which has resulted in radical changes in socioeconomic standards, employment, and inequalities in the utilization of healthcare services and worsening health habits [21]. As a consequence, Serbia has a much higher CVD mortality than the European average [8]. There are no studies on the influence of PN on OS in this setting. In contrast with most of the retrospective studies from developed countries, we have found no statistically significant difference in OS between patients treated with PN vs RN (Figure 2).

These results could be specific to the setting in which our study was performed. However, Tobert et al. [22] recently postulated that better OS in patients treated with PN can be explained by selection bias and absence of confounding control, and that PN seems to have less of a benefit over RN than once believed. Furthermore, they stated that CKD caused by surgery might not be associated with the same risk of progression and mortality as CKD caused by renal disease, and similarly, that in kidney recipients there is no increased risk of mortality compared with healthy controls [23].

In our study, patients undergoing PN had smaller tumors, and few of them were symptomatic at presentation, implying that there was a selection bias regarding tumor characteristics. However, there were no statistically significant differences in CCI and preoperative renal function between the groups, and these factors probably have a more profound impact on OS.

There has been a steep increase in the use of PN in our institution over the years. In the last year of our study, almost 90% of patients with tumors smaller than 4 cm were treated with PN. This result is comparable to the most influential institutions in the world [24]. In our group, the determinants for PN usage were smaller tumor size, younger age, and more recent year of the surgery. These findings are similar to studies from the developed world. However, we did not find male sex to be associated with the use of PN, conversely to previously reported results [24,25]. There is also still the problem of underutilization of laparoscopic surgery in our institution due to equipment availability and cost.

There are several limitations in this study. It is a retrospective analysis of a database from a single institution, and the results are subject to the inherent biases associated with high-volume tertiary care centers. The results also are potentially limited by the small patient numbers, selection bias, and a relatively short median follow-up time, especially for the PN group. These results may also not be reflective of other institutions in developing countries.

In conclusion, we have not found an OS advantage for PN compared to RN in the setting of a developing country. The use of PN is increasing and is now utilized in ~90% of patients with tumors smaller than 4 cm in our institution. We maintain that there is a need for more studies regarding these topics from non-high-income countries.

Conflict of interests

The authors declare no conflict of interests.

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