

Comparison of Long-Term Renal Functions after Partial versus Radical Nephrectomy In a Turkish Patient Population with cT1 Renal Tumors: A Multicenter Study of the Urooncology Association, Turkey

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Abstract

Abstract Purpose: To compare the functional outcomes of patients who underwent partial (PN) or radical nephrectomy (RN) for clinical T1 (cT1) renal tumors using the Kidney Cancer Database of the Urooncology Association, Turkey. **Methods:** We retrospectively reviewed 1004 patients who underwent PN and RN for cT1 renal tumors at multiple academic tertiary centers between 2000 and 2018. Patients with preoperative end-stage chronic kidney disease and/or metastatic disease were excluded. **Results:** There were 452 patients in the PN group and 552 patients in the RN group. The eGFR was significantly reduced in both groups on postoperative day one (PN=13.7 vs. RN=19.1 ml/min/1.73 m²: p<0.001). In the PN group, eGFR showed a tendency to recover according to a quadratic pattern and reached preoperative levels in the first and third years (95.6±28.8 ml/min/1.73 m² and 96.9±28.9 ml/min/1.73 m², respectively), with no significant difference between the eGFRs in the 1st and 3rd years (p=0.710). To define groups at risk, different cut-off values for the GFR were considered. Among patients with a baseline GFR<90, the RN cohort had significantly lower eGFRs in the first and third years than the PN cohort (p=0.02). Logistic regression showed that comorbidities, coronary artery disease, diabetes and hypertension had no adverse impacts on the changes in the eGFR (p=0.60, p=0.13, and p=0.13, respectively). **Conclusion:** For the treatment of stage T1 kidney tumors, the first choice should be open or laparoscopic partial nephrectomy due to the superior long-term preservation of renal function and overall survival, regardless of age and comorbidities.

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Running Title: Comparison of Long-Term Renal Functions after Partial versus Radical Nephrectomy

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Abstract

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Methods: We retrospectively reviewed 1004 patients who underwent PN and RN for cT1 renal tumors at multiple academic tertiary centers between 2000 and 2018. Patients with preoperative end-stage chronic kidney disease and/or metastatic disease were excluded.

Results: There were 452 patients in the PN group and 552 patients in the RN group. The eGFR was significantly reduced in both groups on postoperative day one (PN=13.7 vs. RN=19.1 ml/min/1.73 m²: $p < 0.001$). In the PN group, eGFR showed a tendency to recover according to a quadratic pattern and reached preoperative levels in the first and third years (95.6±28.8 ml/min/1.73 m² and 96.9±28.9 ml/min/1.73 m², respectively), with no significant difference between the eGFRs in the 1st and 3rd years ($p=0.710$). To define groups at risk, different cut-off values for the GFR were considered. Among patients with a baseline GFR<90, the RN cohort had significantly lower eGFRs in the first and third years than the PN cohort ($p=0.02$). Logistic regression showed that comorbidities, coronary artery disease, diabetes and hypertension had no adverse impacts on the changes in the eGFR ($p = 0.60$, $p = 0.13$, and $p = 0.13$, respectively).

Conclusion: For the treatment of stage T1 kidney tumors, the first choice should be open or laparoscopic partial nephrectomy due to the superior long-term preservation of renal function and overall survival, regardless of age and comorbidities.

Keywords: Kidney cancer, Renal cell carcinoma, Nephrectomy, Kidney function, Glomerular filtration rate.

What Is Known?

The partial nephrectomy is preferable management due to preserving renal function. However, studies still show controversial results. The prospective randomized controlled trial by the EORTC suggested that RN resulted in superior overall survival compared with PN. There are factors described for preserving renal function, such as the preoperative parenchymal quality, the volume of the preserved parenchyma, and ischemia time and type.

What Is New?

Our study suggested that the significant predictive factor for renal preservation is the volume of the preserved parenchyma and the radical nephrectomy is the worse predictive factor. However, our study also showed that the dialysis rate, which impairs patients' quality of life, was similar between the two groups in the long-term follow-up. Our study also demonstrated that the age, gender, and presence of comorbidities, including coronary artery disease, diabetes, and hypertension, had no adverse impacts on the changes in the eGFR. Another important finding of our study is that the parenchymal quality is another critical factor for GFR change. Our study showed that GFR change was more significant in patients who had any level of kidney disease (preoperative GFR below 90 ml/min/1.73 m²).

Introduction

The detection of early-stage localized T1 renal tumors has increased due to the widespread use of modern imaging procedures. This has led to higher utilization of partial nephrectomy (PN), although radical nephrectomy (RN) remains the most commonly performed procedure for the excision of renal tumors (1,2).

According to the recent American and European guidelines, PN has become the standard treatment modality for T1 renal masses, and compared with RN, PN yields similar oncological results, superior preservation of renal function and minimization of the long-term risks associated with renal insufficiency when it is technically feasible (3-5). Despite these advantages, PN is technically challenging and carries a higher risk of perioperative complications than RN; thus, RN is still chosen for some patients (6-8). However, it is essential to preserve long-term function to avoid chronic kidney disease (CKD), which may be associated with adverse events such as the development of cardiovascular disease. Currently, few studies have reported the prediction of short-term postoperative renal function, and the results of these studies were inconsistent in terms of the preservation of renal function after PN and RN (9-15). More recently, researchers have attempted to identify which patients will benefit more from PN, which may help clinicians select the appropriate surgery. Preserving renal function (RF) depends on factors such as the preoperative parenchymal quality, the volume of the preserved parenchyma, and ischemia time and type (10).

In this study, long-term renal function and patient and surgeon parameters significantly affecting the outcomes of PN and RN were investigated using the kidney cancer database of the Turkish Urooncology Society.

Materials and Methods

The Kidney Cancer Database of the Turkish Urooncology Association was interrogated, and 3400 patients presenting between 2000 and 2018 were retrospectively identified from the Redcap Database. Of those, 1004 patients with cT1N0M0 renal masses who underwent either PN or RN with open and/or laparoscopic approaches were included in the study cohort. Patients with a solitary kidney, a bilateral tumor, metastatic disease, and/or a preoperative eGFR < 15 ml/min/1.73 m² were excluded. All procedures were performed by eight experienced surgeons from six different institutions. Patients were divided into two groups depending on whether they underwent PN or RN. Demographic parameters, including age; sex; the presence of diabetes, coronary artery disease, and hypertension; and operative data including surgical approach, ischemia type and time, histopathological evaluation, renal function assessments, and complications were recorded and analyzed. The Institutional Review Board of the University of Cukurova approved the study (52/March-2019).

Follow-up and data collection

Patients were generally assessed in terms of renal function on postoperative day one and subsequently every 12 months. Preoperative and postoperative serum creatinine concentrations were obtained from the

medical records. This study's primary endpoint, the eGFR, was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and overall survival (OS) was defined as death from any cause after surgery. CKD was staged according to the National Kidney Foundation guidelines, and the baseline GFR was calculated using the preoperative creatinine levels.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0. (IBM Inc., Armonk, N, USA). The statistical level of significance for all tests was $p < 0.05$. To evaluate the changes in the measurements obtained at different time points, repeated measures analysis was adopted, and the LSD test was used for multiple comparisons. The Bonferroni-adjusted Student's t-test was used to assess whether there was a difference between the PN and RN groups for each repeated measurement. Logistic regression analysis was performed to determine significant risk factors, and renal function decline was defined as the decrease between the baseline value and that obtained in the 3rd postoperative year. In univariate analysis, overall survival (OS) was calculated by the Kaplan-Meier method, and the log-rank test was performed. Cox regression analysis was performed to identify significant prognostic factors. Variables significant at the $p < 0.2$ level in univariate analysis and variables considered clinically significant were entered into the Cox regression analysis.

Results

Demographic data

Of the 1004 patients, 452 (45.1%) underwent PN, and 552 (54.9%) underwent RN. The rate of PN for cT1 tumors increased from 5% in 2000 to 45% in 2018. The mean tumor sizes were 3.3 cm and 4.6 cm in the PN and RN groups, respectively, and the difference was significant ($p = 0.001$) (see Table 1). The mean \pm SD preoperative eGFR was similar between the two groups: 100.7 ± 26.4 and 96.9 ± 34.6 ml/min/1.73 m² in the PN and RN groups, respectively ($p = 0.72$).

Renal function outcome

The eGFR was significantly reduced in both groups on postoperative day one (13.7 vs. 19.1 ml/min/1.73 m² for PN and RN, respectively; $p < 0.001$). In the PN group, the eGFR showed a tendency to recover and followed a quadratic pattern during follow-up. The mean eGFR in the PN group reached preoperative levels in the first and third years (95.6 ± 28.8 and 96.9 ± 28.9 ml/min/1.73 m², respectively), with no significant difference between those values ($p = 0.710$). However, in the RN group, the eGFR did not recover to baseline, and compared to the preoperative levels, the reduction was significant at the end of the third year ($p < 0.001$; see Table 2). RN increased the risk of renal function decline three-fold compared with PN ($p < 0.05$). Additionally, there was a significant difference between repeated measures of eGFR according to operation type ($p < 0.001$; see figure 1).

Assuming an arbitrary cut-off value for the eGFR of 90 ml/min/1.73 m², among patients with a preoperative GFR > 90 , the eGFR decreased similarly in the first year in the two groups (15.9 vs. 21.2 ml/min/1.73 m² for PN and RN, respectively). Statistical analysis showed that the significant decline in the eGFR was parallel in the two groups ($p = 0.04$). Furthermore, in patients with a baseline eGFR < 90 , renal function was significantly better preserved in the PN cohort, and the difference between the PN and RN groups was more pronounced ($p = 0.02$). The eGFR level recovered almost to the baseline level in the third postoperative year in the PN group (see figure 2 a-b). The proportions of patients in the two groups requiring hemodialysis did not differ (PN=2.8% vs. RN=3.7%; $p = 0.29$).

Logistic regression analysis was performed to identify the significant risk factors for renal function decline, and the results are shown in Table 3. The presence of coronary artery disease, diabetes, and hypertension had no adverse impacts on the changes in the eGFR ($p = 0.60$, $p = 0.13$, and $p = 0.13$, respectively).

Operative outcomes

The open approach was selected more frequently in the RN group than in the laparoscopic arm (69.7% vs. 30.3%, respectively, $p < 0.001$). In the PN cohort, the perioperative complications and operation time were significantly higher in those undergoing the laparoscopic approach than in those undergoing the open approach ($p = 0.02$, and $p < 0.001$, respectively). In the RN cohort, only blood loss was significantly higher when using the open approach ($p = 0.01$) (see Table 4).

The perioperative and postoperative complication rates and the blood transfusion rate were significantly higher in the PN cohort ($p = 0.001$, $p = 0.02$, and $p = 0.004$, respectively). Histopathological evaluation showed clear cell carcinoma as the most common histological type. Benign pathology was present in 7.6% of the patients who underwent RN and 11.1% of the patients who underwent PN.

Survival outcome

OS was significantly longer in PN patients than in the RN cohort (see Figure 3). The mean OS times were 165.3 and 159.9 (95% CI: 162.6-168.0 vs. 155.6-164.2; $p < 0.05$) months in the PN and RN groups, respectively. There was no significant difference in mortality between groups when the patients were divided by age (< 49 , 50-64, and ≥ 65 ; $p = 0.12$). Although the mean OS was shorter in patients with comorbidities, including hypertension, diabetes mellitus, coronary artery disease, and hyperlipidemia, than in those without comorbidities (160.2 vs. 164.2 months), this difference was not statistically significant ($p = 0.41$; see Table 5).

A Cox proportional hazards model was used to evaluate the potential predictors, and the results are shown in Table 6. Univariate analysis revealed that OS was significantly associated with RN (HR: 3.3, 95% CI: 1.1-9.8; $p = 0.03$). In multivariate analysis, RN was an independent negative prognostic factor for OS (HR: 6.3, 95% CI: 1.4-27.9; $p = 0.01$).

Discussion

The primary concern in the treatment of small renal masses with RN is the loss of kidney function. Thus, PN has become the gold standard approach when technically feasible. The literature supports the advantages of PN (9-13). Among Turkish patients, there are similar rates of PN and RN for cT1 renal masses, making this dataset suitable for analysis. This analysis has shown that there was a significant difference in OS between patients undergoing PN and RN. Furthermore, no significant adverse effect of age on OS was evident. The majority of studies have shown that renal function preservation is correlated with survival, and previous retrospective studies with large patient numbers suggested that renal function was an independent prognostic factor for non-cancer-related mortality. (2,17). In contrast, a prospective randomized controlled trial by the EORTC suggested that RN resulted in superior overall survival compared with PN (10-year overall survival: 81.1% vs. 75.7%; HR: 1.51, $p = 0.02$) (9). Furthermore, Liek *et al.* showed that significant survival benefits were only seen in male patients < 75 years treated with PN ($p = 0.0005$), and there was no significant difference between the groups among male patients > 75 years and female patients ($p = 0.736$, $p = 0.175$, and $p = 0.191$, respectively) (11). Conversely, Mir *et al.* compared PN and RN in very elderly (> 75 years) patients, and PN yielded a benefit with regard to cancer-specific mortality (HR: 0.19, 95% CI: 0.04-0.97; $p = 0.05$), but there was no significant benefit with regard to either overall mortality or non-cancer-specific mortality (18). In agreement with these results, in our study, we did not find an association between age (subgroups; < 49 , 50-64, and > 65 years) and OS.

In general, most of the studies published in the literature so far have shown that PN is associated with a lower risk of CKD and survival benefits (2,17). Tan *et al.* assessed patients under age 50 who were treated for renal masses with PN and RN and reported that there was no significant difference in overall survival between the groups (HR: 0.83, 95% CI: 0.63-1.10, $p = 0.196$) (19). Based on their findings, the authors claimed that surgically induced CKD, rather than medical CKD, is associated with a lower risk of progression of renal insufficiency (20,21).

The present study showed a significant difference in the decrease in the GFR between the PN and RN groups, regardless of age, sex, or comorbidities. Finally, PN for T1 tumors was the most significant factor

affecting the preservation of renal function. A recent study compared retroperitoneal laparoscopic partial and radical nephrectomy and showed similar preoperative and postoperative eGFR levels ($p=0.63$ and $p=0.15$, respectively). Nevertheless, the decrease in eGFR levels was significantly greater in the RN cohort, which agrees with our results (22). In contrast, Cooper *et al.* assessed the outcomes of percutaneous radiofrequency ablation, partial nephrectomy, and radical nephrectomy in cT1 renal cancer patients and demonstrated similar preoperative and postoperative eGFR values. There was no significant difference between PN and RN ($p =0.74$ and $p =0.73$, respectively) (23). Another important finding of the Cooper study was a similar need for dialysis in the two groups ($p=0.29$).

New evidence has shown that patients with a baseline eGFR below 85 ml/min were at risk for reduced renal function and higher cancer-specific mortality unless their postoperative eGFR was maintained above 60-65 mL/min, and PN should be selected for patients with any level of preoperative renal insufficiency (24). Additionally, published evidence has shown that the eGFR is an important prognostic factor and that the prognosis was worse when the eGFR fell below 45 mL/min/1.73 m² after surgery (21). Another study by Takagi *et al.* assessed 95 patients with renal insufficiency who underwent PN and RN for T1a-T2 renal cell carcinoma and demonstrated that PN resulted in significantly superior preservation of renal function than RN (absence of CKD 64% vs. 22% in PN and RN, respectively) (25). Our findings are in agreement with those of Takagi *et al.* When an arbitrary cut-off value of 90 mL/min/1.73 m² was used for the GFR, among patients with a baseline GFR <90 mL/min/1.73 m², renal function was significantly better preserved in the PN cohort, and the difference between the PN and RN cohorts became more significant. The eGFR level had returned to close to the baseline level by the third postoperative year in the PN cohort.

Several studies have attempted to identify the factors affecting changes in the eGFR and to predict who will benefit from PN or RN. Bhindi *et al.* reported that older age, diabetes, and a worse preoperative eGFR were associated with a worse postoperative eGFR in the RN cohort, but in the PN cohort, diabetes was not associated with a worse postoperative GFR ($p=0.4$) (16). Comorbidities were not associated with OS in our study because the duration of the disease was short, and patients with comorbidities were more likely to undergo PN. The authors emphasized that the sparing of nephrons alone is not sufficient to achieve this in the PN group, and optimal diabetes control is essential. Other studies indicated that preoperative parenchymal quality, the volume of the preserved parenchyma,(10) and ischemia duration are the most powerful factors affecting postoperative GFR levels (26). In this study, we showed that there was no statistically significant adverse effect of comorbidities such as coronary artery disease, diabetes, and hypertension on the change in the GFR in either group and the major loss of renal parenchyma in RN is the most important factor.

The surgical approach is another point of discussion. In the literature, the laparoscopic approach is reported to have advantages in terms of a fast recovery and reduced morbidity (27). Our study suggests that surgeons more often use minimally invasive procedures during PN. Surgeons prefer a more open approach during RN and for small early-stage masses. The surgical approach in the RN cohort was dictated mainly by the size and complexity of the tumor. Our study also demonstrated significantly greater blood loss with an open approach in both the PN and RN cohorts. However, there was no significant difference in the transfusion rate between the open and laparoscopic approaches in either group. In agreement with our findings, a meta-analysis reported that laparoscopic RN resulted in less blood loss and lower transfusion rates than open RN (blood loss: WMD =-201.02, 95% CI: -246.29 to-155.75, blood transfusion rate: OR =0.59, 95% CI: 0.43-0.81) (28).

Our study's limitations are the retrospective, nonrandomized study design and the possible presence of unidentified confounding variables. Another significant limitation was the performance of procedures by multiple surgeons in six different centers, as the individual learning curve and experience of each surgeon could be sources of bias. Additionally, the lack of nephrometry scores is another limitation; nomogram data have only recently been collected. The patients were treated over a long span of time, and it remains uncertain whether the changes in patient selection and quality of medical care influenced the results. Furthermore, in this study, all participants were followed according to the respective institutional protocols, and there was a lack of standardization of follow-up.

Conclusions

Our results support the benefits of PN in terms of renal function preservation in the postoperative period. The results of this study suggest that open or laparoscopic partial nephrectomy should be the treatment of choice for cT1 stage kidney cancer due to the advantages of long-term renal preservation and improved overall survival, regardless of age and comorbidities.

Author Disclosure Statement:

There is no competing financial interests.

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Ethics Approval:

The study was approved by the Ethics committee of Cukurova University (March 2019/52)

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Fig 1. GFR change of PN vs RN

Fig 2. a.) GFR>90 Comparison of PN and RN b.) GFR<90 Comparison of PN and RN

Fig 3. OS curves according to operation type

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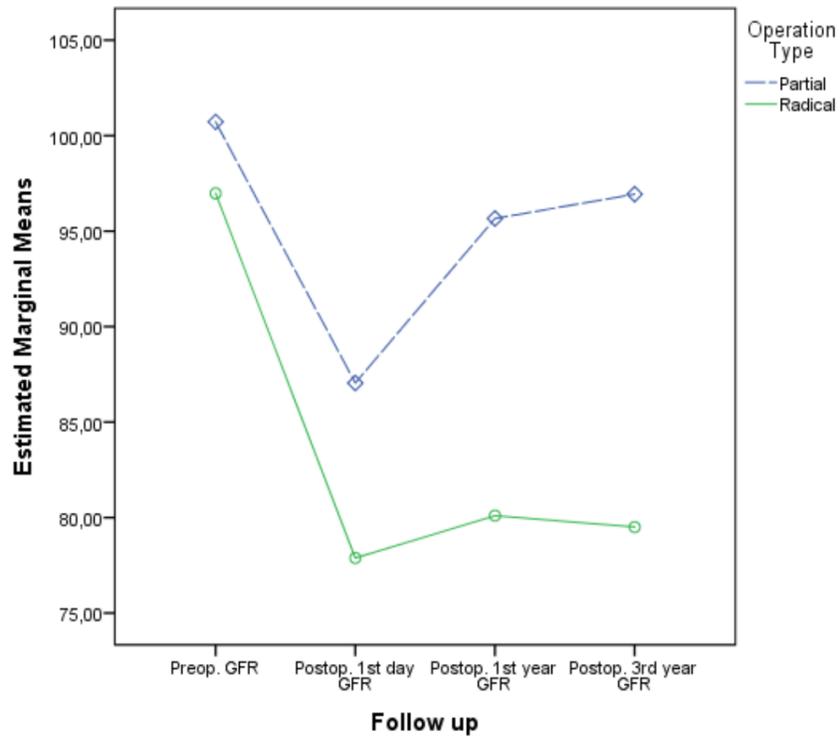


Fig 1. GFR change of PN vs RN

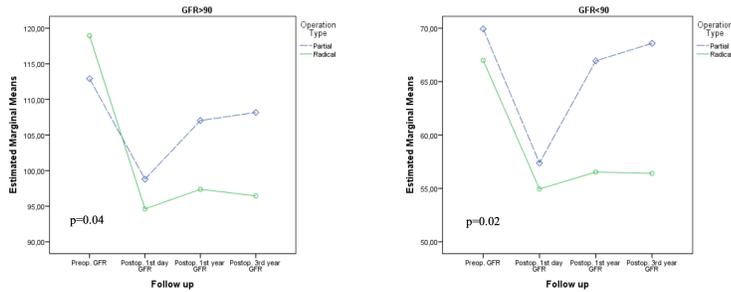


Fig 2. a.) GFR > 90 Comparison of PN and RN b.) GFR < 90 Comparison of PN and RN

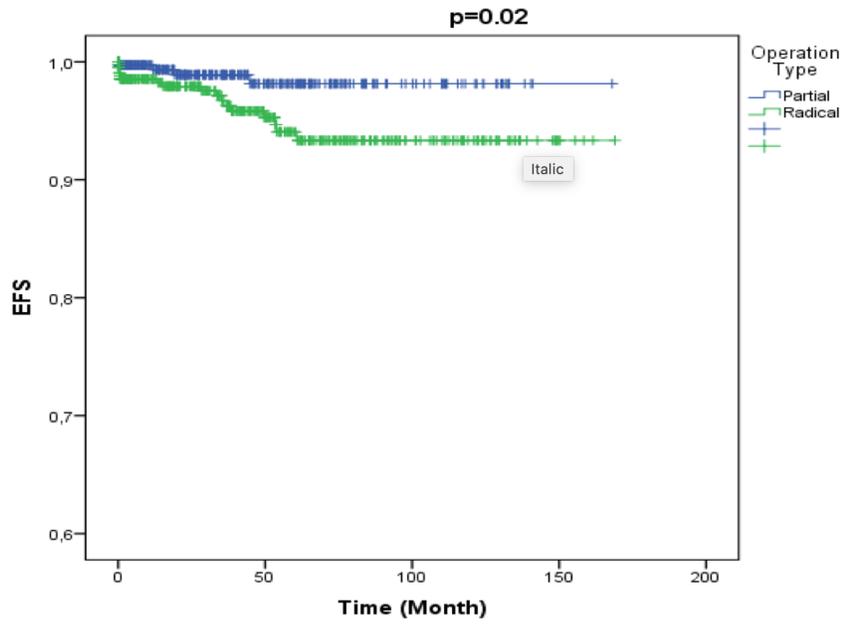


Fig 3. OS curves according to operation type