Radical Nephrectomy Provides a Worse Prognosis Than Partial Nephrectomy in T3aN0M0 Renal Cancer of Small (≤ 4 cm) Size and No Invasion of Perisinus Fat

Shiliang Liu

Huazhong University of Science and Technology

Zhixian Wang

Huazhong University of Science and Technology

Chang Liu (✉ liuchangtjh@163.com)

Huazhong University of Science and Technology

Research Article

Keywords: Renal cell carcinoma, Partial nephrectomy, Radical nephrectomy, SEER, Surgery, Outcome

Posted Date: December 8th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-116412/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: Radical nephrectomy (RN) is the recommended treatment for T3aN0M0 renal cell carcinoma (RCC). However, it is not necessarily the best treatment for small T3aN0M0 RCCs. We evaluated the effect of tumor size combined with consideration of anatomic types of extrarenal-fat invasion on the surgical decision-making between partial nephrectomy (PN) vs. RN in T3aN0M0 RCC.

Methods: Data were obtained from the Surveillance, Epidemiology, and End Results database (2004 to 2015) with 6125 patients suffering from T3aN0M0 RCC. Cox and Fine and Gray models were used for survival analyses. Propensity-score matching was used for PN vs. RN.

Results: A larger T3aN0M0 RCC was associated with higher risk of mortality (hazard ratio (HR)_{all-cause mortality}: 1.07, 95% confidence interval (CI): 1.02–1.13, $P = 0.011$; HR_{RCC-cause mortality}: 1.13, 95%CI: 1.06–1.21, $P < 0.001$) compared with a small T3aN0M0 RCC. After propensity-score matching, in T3aN0M0 ≤ 4 cm, RN compared with PN significantly increased the risk of death (HR: 1.77; 95%CI: 1.14–2.74, $P = 0.011$) and offered no significant difference in RCC-specific survival (HR: 1.57, 95%CI: 0.74–3.36, $P = 0.240$). However, RN and PN showed no significant difference in overall survival in T3aN0M0 RCC >4 cm (HR: 0.98; 95%CI: 0.59–1.62, $P = 0.929$) or in T3aN0M0 RCC with sinus/perisinus-fat invasion (HR: 1.18; 95%CI: 0.61–2.27, $P = 0.631$).

Conclusion: PN provided better overall survival compared with RN for small (≤ 4 cm) T3aN0M0 RCCs without sinus/perisinus-fat invasion. Focusing only on anatomic-invasion characteristics rather than type and tumor size is not sufficient for treatment decisions in T3aN0M0 RCC.

Background

With the widespread use of partial nephrectomy (PN) in T1 renal cell carcinoma (RCC)[1], numerous patients with T1 RCC have undergone pathologic upgrades to T3aN0M0 after PN[2-4]. This action has led to a treatment-strategy dilemma (i.e., clinical observation or conversion to radical nephrectomy (RN) for such pathologic upstaging post-PN). In clinical practice, RN is preferred because there is not sufficient evidence to show the value of PN in T3aN0M0 RCC. However, some patients with RN might not obtain a better survival outcome. Besides, how to select patients suitable for PN is not known. Some studies have indicated that the prognosis of PN for small T3aN0M0 RCCs is satisfactory[4-7]. Those studies showed the limitation of heterogeneity and small sample sizes. Whether PN can provide a better prognosis in select cases of T3aN0M0 RCC and whether patients with small tumors and a certain type of fat invasion (perirenal fat vs. sinus/perisinus fat) can impact the choice of PN is not known[8-10]. Further studies are needed to address these important questions for surgical decision-making. We used data from the Surveillance, Epidemiology, and End Results (SEER) database and literature review to evaluate the impact of tumor size and fat-invasion types on the prognosis and factors associated with surgical decision-making in patients with T3aN0M0 RCC.

Methods

Patient cohorts

We screened 18 registries in the SEER database to identify cases of T3aN0M0 RCC with the kidney parenchyma as the primary site (ICD-O-3 code C64.9) between 2004-20105 after obtaining permission to access research data files. The SEER database covers ~28% of the population in the USA. The characteristics of the SEER population are comparable with those of the general population (<https://seer.cancer.gov/>). **Supplementary Figure 1** shows a flowchart with detailed information describing data selection from the SEER database. All tumors included in the present study were

≤15 cm in size. All patients were aged ≥18 years and had undergone PN or RN. Moreover, histology-confirmed clear cell, papillary, and chromophobe tumors were included. Patients were excluded if: (i) they had other types of primary malignancy or multiple RCCs; (ii) their information was missing or did not include the specific cause of death. RCC with sarcomatoid dedifferentiation was also excluded because it carries a high risk of mortality by RCC, and RN was the best treatment. Also, we excluded patients who were followed for <3 months, and those who died within 30 days.

Outcome and variables for analyses

The primary outcomes of interest were all- and RCC-cause mortality. The SEER Cause of Death Recode was used to identify the cause of death. Patients who died from RCC were identified as “RCC-cause mortality,” those who died from other causes were designated as “competing events before RCC-cause mortality,” whereas any cause of death was considered “all-cause mortality.” “Duration of survival” was defined as the time from the date of diagnosis to the date of death or last contact. We collated a range of demographic variables for our study: year of diagnosis; age at diagnosis; sex; ethnicity (White and Others [Black, American Indian/Alaska Native, Asian Native, and Asian/Pacific Islander]). We also collated a range of data related to tumors: tumor size (cm) and histology cell type for RCC (clear cell, and nonclear cell [papillary and chromophobe]); tumor grade (“well-differentiated” [grade 1], “moderately differentiated” [grade 2], “poorly differentiated” [grade 3], and “undifferentiated” [grade 4]); invasion features (sinus/perisinus invasion and perinephric-fat invasion; in the SEER database, such characteristics were recoded after 2010).

Statistical analyses

Continuous variables are described as the mean (standard deviation [SD]) if they have a normal distribution compared with a Student’s *t*-test or as the median (interquartile range [IQR]) if they did not have a normal distribution compared with a Wilcoxon rank-sum test. Categorical variables are presented as frequencies (%) and were compared using a chi-square test. Overall survival (OS) was compared using the Kaplan–Meier method for survival function along with the log-rank test. Multivariable Cox proportional hazards regression models were conducted. Fine and Gray competing risk proportional hazard regression models were fitted to assess mortality caused by RCC and other competing events[11]. To evaluate the choice of surgical method (PN or RN) for T3aN0M0 RCC, we conducted matching of the propensity score using the “nearest-neighbor” method for the likelihood of carrying out PN[12]. Propensity scores were calculated using a multivariable logistic regression model for each patient based on all covariables for T3aN0M0 RCC (year and age at diagnosis, sex, ethnicity, tumor size, tumor grade, and tumor histology). Although tumor grade and tumor histology were histology features obtained postoperatively, they continued to impact the surgical choice in clinical practice for T3aN0M0 RCC. Therefore, they were also included in propensity-score matching. This practice balanced variables and reduced the risk of a selection bias, which may have exerted influence over the association between the surgical method and outcomes. Patients were matched at a 1:1 ratio based on those propensity scores. A sensitivity analysis accounting for the invasion type of T3aN0M0 was carried out using the total dataset with information on the invasion type of T3aN0M0 after 2010 (because the feature of fat invasion beyond the renal capsule was only included in the SEER database then). All analyses were conducted using the R v.3.5.2 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). All *P* values are two-sided, and *P* < 0.05 was considered significant.

Results

Demographic characteristics

The clinicopathologic characteristics of the entire cohort (N = 6125) are provided in **Supplementary Table 1**. The mean age was 62.6 (SD, 11.8; median, 63; IQR, 55–71) years. The mean tumor size was 6.9 (SD, 3.1; median, 6.5; IQR, 4.5–

9.0) cm. To compare PN vs. RN, 1:1 propensity-score matching is presented in **Table 1**. Before propensity-score matching, compared with RCC treated by PN, RCC treated with RN exhibited a larger tumor size (mean 7.34 vs. 4.21 cm, $P < 0.001$), higher tumor grade (III/IV 53.5% vs. I/II 41.9%, $P < 0.001$), higher prevalence of clear-cell RCC (88.8% vs. 69.0%, $P < 0.001$), and older age (62.8 vs. 61.5, $P = 0.001$). After propensity-score matching, the RN group and PN group exhibited an excellent balance of patient characteristics at baseline. All standard mean differences were $<10\%$, except for tumor size in the cohort of T3aN0M0 >7 cm, which remained larger in RN, but showed no significant difference (9.19 vs. 9.46 cm, $P = 0.292$, with a standard mean difference of 15.4%).

Tumor size is a predictor for survival from T3aN0M0 RCC

Supplementary Table 2 suggests that, after adjustment for other covariables, tumor size was a significant risk factor for mortality (hazard ratio (HR)_{all mortality} 1.07, 95% confidence interval (CI): 1.02–1.13, $P = 0.011$; sub-distribution HR [sHR]_{RCC-caused mortality} 1.13, 95%CI: 1.06–1.21, $P < 0.001$). For T3a RCC of size ≤ 4 cm, tumor size was not an independent predictor of survival function (HR_{all mortality} 0.84, 95%CI: 0.59–1.19, $P = 0.316$; sHR_{RCC-caused mortality} 0.57, 95%CI: 0.31–1.05, $P = 0.070$). However, for tumor size >4 cm, tumor size increased the risk of mortality (HR 1.10, 95%CI: 1.05–1.15, $P < 0.001$, **Supplementary Table 3**).

Outcomes of PN vs. RN based on tumor size

Figure 1 presents the results of the Kaplan–Meier survival curve for PN vs. RN. In patients with T3aN0M0 (≤ 4 cm) RCC, PN was associated with improved OS compared with RN ($P_{\text{unmatched data}} < 0.001$; $P_{\text{matched data}} = 0.006$). **Table 2** shows that RN in patients with tumor size ≤ 4 cm was associated with a significantly higher risk for all-cause mortality adjusted for covariates (HR_{unmatched data}: 1.65, 95%CI: 1.09–2.51, $P = 0.019$; HR_{matched data}: 1.77, 95%CI: 1.14–2.74, $P = 0.01$); however, the type of surgical procedure was not an independent risk predictor of RCC-specific mortality (HR_{unmatched data}: 1.42, 95%CI: 0.66–3.05, $P = 0.370$; HR_{matched data}: 1.57, 95%CI: 0.74–3.36, $P = 0.24$) for T3aN0M0 (≤ 4 cm) RCC. PN did not provide a significant outcome benefit compared with RN in patients with T3aN0M0 RCC of size >4 cm after adjustment for clinicopathological characteristics (**Table 2**).

Outcomes of PN vs. RN based on different types of extrarenal fat invasion

The type of extrarenal fat invasion impacted the benefit of surgical decision-making significantly (**Figure 2**). PN vs. RN showed a different OS across all tumor sizes (HR_{all size group}: 1.18, 95%CI: 0.61–2.27, $P = 0.631$; HR _{≤ 4 cm group}: 2.08, 95%CI: 0.44–9.77, $P = 0.352$; HR _{>4 cm group}: 0.67, 95%CI: 0.32–1.39, $P = 0.282$). Moreover, for all tumor sizes >4 cm, OS showed no significant difference between PN and RN irrespective of the type of extrarenal-fat invasion (HR_{all type group}: 0.98, 95%CI: 0.59–1.62, $P = 0.929$; HR_{perirenal fat invasion group}: 1.34, 95%CI: 0.6–2.69, $P = 0.419$; HR_{perisinus invasion group}: 0.67, 95%CI: 0.32–1.39, $P = 0.282$). However, for T3aN0M0 RCC of size ≤ 4 cm and perirenal-fat invasion, PN improved OS significantly compared with that for RN (HR 5.91, 95%CI: 1.83–19.0, $P = 0.003$).

Discussion

T3a RCC is classified only by local extension (involvement of perirenal veins, fat invasion, or invasion of the pelvicalyceal system) regardless of tumor size. The potential role of tumor size and type of invasion for prognostication and treatment decision-making in patients with T3aN0M0 RCC is controversial but deserves increased attention[13, 14]. Our study led to two important findings. First, in patients with T3aN0M0 RCC, tumor size was identified as an independent prognostic predictor. Our data suggest that it is reasonable to stratify small and large T3aN0M0 RCC tumors in a manner that is not based solely on extrarenal invasion. Second, patients with small (≤ 4

cm) T3aN0M0 RCC without the presence of sinus-fat invasion could benefit more from PN than from RN. However, PN did not yield any significant benefits to patients with T3aN0M0 RCC of tumor size >4 cm and besides, PN was not beneficial for RCC with sinus-fat invasion across all tumor sizes. These findings may have critical implications for the next revision of the TNM staging system. Our findings may also provide clinicians with important guidelines for prognostication and surgery decision-making (PN vs. RN) based on tumor size and different types of extrarenal-fat invasion in T3aN0M0 RCC (**Figure 3**).

Although tumor size is not considered a parameter for TNM staging in patients with T3aN0M0 RCC, resection is based mostly on preoperative tumor diameter as well as other factors (i.e., tumor diameter, tumor location, renal-vein invasion, and surgeon experience) in clinical practice. Wide use of PN in T1 RCC has led to an overall increase in the prevalence of T3aN0M0 upstaging from T1 after PN. The prevalence of pathologic upstaging from clinical T1 reported in contemporary studies is 5%–14%[4, 9, 15, 16]. Pathologic upstaging post-PN poses a dilemma to surgeons regarding the choice of surgical approach (clinic observation following PN or conversion to RN), considering that conventional imaging methods are limited in terms of detecting features relating to perirenal-fat invasion.

RN is considered to be standard treatment for small T3aN0M0. However, treatment of small T3aN0M0 with PN has not yielded inferior results and has drawn increased attention[2, 5-10, 15-21] (**Table 3**). It seems clear that the prognosis of T3aN0M0 disease may be determined by the biological characteristics of the tumor rather than just the type of surgical procedure. Hence, T3aN0M0 RCC should not deter surgeons from undertaking PN. Also, treatment of advanced RCC with drugs (e.g., targeted therapy and immunotherapy) has been shown to prolong progression-free survival[22], which further provides the possibility of PN in patients with T3aN0M0 RCC.

Smaller tumors (<4 cm) that have been upstaged to T3aN0M0 should be considered for PN because PN can provide comparable DSS, lower noncancer-specific mortality, and better OS. In our study, PN was associated with longer OS in patients with T3aN0M0 RCC (≤ 4 cm) compared with that using RN. RN for small RCCs could increase the risk of chronic kidney diseases and threaten OS. However, this observation was not seen in patients with tumor size >4 cm; in addition, RN increased the risk of mortality by other competing events (sHR: 1.78, 95%CI 1.05–3.00, $P = 0.032$) for patients with RCCs <4 cm. Lee et al.[8] conducted a retrospective study in which 6.3% (215/3,431) of patients were upstaged from clinical T1 to T3aN0M0. Subgroup analyses of T3aN0M0 RCC in their study showed that the PN group did not show significant differences in terms of recurrence-free survival, DSS, or OS compared with those in the RN group. In a study conducted by Jong and colleagues[7], 63 and 142 patients were upstaged to T3aN0M0 from T1a and T1b, respectively. Those authors concluded that PN provided a recurrence-free survival outcome similar to that observed for RN in patients with small T3aN0M0 RCC.

While differentiating T3aN0M0 based on size seems logical for deciding on PN vs. RN, the propensity of invasion into sinus fat and/or the renal vein is important. Invasion into perirenal fat has been shown to not increase RCC-specific mortality. Conversely, invasion into sinus fat portends a worse prognosis than perirenal-fat invasion even though both are classified as T3aN0M0[23-25]. We found that RCC presenting with sinus/perisinus-fat invasion could not benefit from PN regardless of tumor size. Our results show that we must be alert to invasion of extrarenal sinus fat across all tumor sizes, and that RN should be suggested for patients with pT3a RCC of such histologic features because PN did not provide better OS for those patients.

The strengths of the SEER database are its sample size, established quality-assurance program, as well as internal and external validity, but there are some drawbacks to using the SEER database[26]. The data included in our study was obtained from the SEER database and this was a retrospective study. Hence, the retrospective nature of this investigation is an inherent limitation. Second, the SEER database does not detail the features of renal-vein invasion, and the latter portends a worse prognosis than perirenal-fat invasion. Tumors with renal-vein thrombi are, in general,

treated with RN instead of PN, so our results might skew risk assessment. There was some missing information for one or more variables that were excluded from our study, which might have led to a selection bias. Therefore, a sensitivity analysis was conducted on the subset of cases diagnosed between 2010 and 2015 (the period in which the T3aN0M0 invasion type was included). Marked differences in results were not observed, which suggested that missing data did not cause a significant analytical bias.

Conclusion

For better clinical practice, selected patients with small T3aN0M0 RCCs (≤ 4 cm) without sinus/perisinus-fat invasion could receive PN, instead of RN only, because this practice may prolong OS. Tumor size is an independent prognostic predictor and should be considered for improved survival stratification. Surgical decision-making when selecting PN or RN for T3aN0M0 RCC should be based on tumor size and presentation of fat-invasion types.

Abbreviations

CI: Confidence interval; DSS: Disease specific survival; HR: Hazard ratio; IQR: Interquartile range; OS: Overall survival; PN: Partial nephrectomy; RCC: Renal cell carcinoma; RN: Radical nephrectomy; SEER: Surveillance, Epidemiology, and End Results; SD: Standard deviation.

Declarations

Acknowledgments

Not applicable

Authors' contributions

All authors read and approved the final manuscript. SL, ZW and CL participated in research design and data analysis. ZW and CL participated in data collection; SL and ZW drafted the manuscript.

Funding

Not applicable

Availability of data and materials

The raw data of this study are derived from the SEER database (<https://seer.cancer.gov/>), which is a publicly available database. All detailed data included in the study are available upon request by contact with the corresponding author.

Ethics approval and consent to participate

Since SEER data are anonymized, the need for institutional review board approval was waived. No administrative permission and/or licenses is acquired by this study to access the original data used in this research.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹ Department of Urology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, China. ² Department of integrated medical services, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, China

References

1. Ljungberg B, Albiges L, Abu-Ghanem Y, Bensalah K, Dabestani S, Fernandez-Pello S, Giles RH, Hofmann F, Hora M, Kuczyk MA *et al*: **European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update**. *Eur Urol* 2019, **75**(5):799-810.
2. Ramaswamy K, Kheterpal E, Pham H, Mohan S, Stifelman M, Taneja S, Huang WC: **Significance of Pathologic T3a Upstaging in Clinical T1 Renal Masses Undergoing Nephrectomy**. *Clin Genitourin Cancer* 2015, **13**(4):344-349.
3. Veccia A, Falagario U, Martini A, Marchioni M, Antonelli A, Simeone C, Cormio L, Capitanio U, Mir MC, Derweesh I *et al*: **Upstaging to pT3a in Patients Undergoing Partial or Radical Nephrectomy for cT1 Renal Tumors: A Systematic Review and Meta-analysis of Outcomes and Predictive Factors**. *Eur Urol Focus* 2020.
4. Gorin MA, Ball MW, Pierorazio PM, Tanagho YS, Bhayani SB, Kaouk JH, Rogers CG, Stifelman MD, Khalifeh A, Kumar R *et al*: **Outcomes and predictors of clinical T1 to pathological T3a tumor up-staging after robotic partial nephrectomy: a multi-institutional analysis**. *J Urol* 2013, **190**(5):1907-1911.
5. Weight CJ, Lythgoe C, Unnikrishnan R, Lane BR, Campbell SC, Fergany AF: **Partial nephrectomy does not compromise survival in patients with pathologic upstaging to pT2/pT3 or high-grade renal tumors compared with radical nephrectomy**. *Urology* 2011, **77**(5):1142-1146.
6. Andrade HS, Zargar H, Akca O, Kara O, Caputo PA, Ramirez D, Andres G, Stein RJ, Chueh SJ, Kaouk JH: **Is Robotic Partial Nephrectomy Safe for T3a Renal Cell Carcinoma? Experience of a High-Volume Center**. *J Endourol* 2017, **31**(2):153-157.
7. Oh JJ, Byun SS, Lee SE, Hong SK, Lee ES, Kim HH, Kwak C, Ku JH, Jeong CW, Kim YJ *et al*: **Partial nephrectomy versus radical nephrectomy for non-metastatic pathological T3a renal cell carcinoma: a multi-institutional comparative analysis**. *Int J Urol* 2014, **21**(4):352-357.
8. Lee H, Lee M, Lee SE, Byun SS, Kim HH, Kwak C, Hong SK: **Outcomes of pathologic stage T3a renal cell carcinoma up-staged from small renal tumor: emphasis on partial nephrectomy**. *BMC Cancer* 2018, **18**(1):427.
9. Shah PH, Moreira DM, Patel VR, Gaunay G, George AK, Alom M, Kozel Z, Yaskiv O, Hall SJ, Schwartz MJ *et al*: **Partial Nephrectomy is Associated with Higher Risk of Relapse Compared with Radical Nephrectomy for Clinical Stage T1 Renal Cell Carcinoma Pathologically Up Staged to T3a**. *J Urol* 2017, **198**(2):289-296.
10. Mouracade P, Kara O, Dagenais J, Maurice MJ, Nelson RJ, Malkoc E, Kaouk JH: **Perioperative morbidity, oncological outcomes and predictors of pT3a upstaging for patients undergoing partial nephrectomy for cT1 tumors**. *World J Urol* 2017, **35**(9):1425-1433.
11. Austin PC, Fine JP: **Practical recommendations for reporting Fine-Gray model analyses for competing risk data**. *Stat Med* 2017, **36**(27):4391-4400.
12. D'Agostino RB, Jr.: **Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group**. *Stat Med* 1998, **17**(19):2265-2281.
13. Sugiyama Y, Yatsuda J, Murakami Y, Ito N, Yamasaki T, Mikami Y, Ogawa O, Kamba T: **Impact of tumor size on patient survival after radical nephrectomy for pathological T3a renal cell carcinoma**. *Jpn J Clin Oncol* 2019,

49(5):465-472.

14. Chevinsky M, Imnadze M, Sankin A, Winer A, Mano R, Jakubowski C, Mashni J, Sjoberg DD, Chen YB, Tickoo SK *et al*: **Pathological Stage T3a Significantly Increases Disease Recurrence across All Tumor Sizes in Renal Cell Carcinoma.** *J Urol* 2015, **194**(2):310-315.
15. Nayak JG, Patel P, Saarela O, Liu Z, Kapoor A, Finelli A, Tanguay S, Rendon R, Moore R, Black PC *et al*: **Pathological Upstaging of Clinical T1 to Pathological T3a Renal Cell Carcinoma: A Multi-institutional Analysis of Short-term Outcomes.** *Urology* 2016, **94**:154-160.
16. Jeong SH, Kim JK, Park J, Jeon HJ, Yoon MY, Jeong CW, Ku JH, Kim HH, Kwak C: **Pathological T3a Upstaging of Clinical T1 Renal Cell Carcinoma: Outcomes According to Surgical Technique and Predictors of Upstaging.** *PLoS One* 2016, **11**(11):e0166183.
17. Shvero A, Nativ O, Abu-Ghanem Y, Zilberman D, Zaher B, Levitt M, Fridman E, Portnoy O, Ramon J, Dotan ZA: **Oncologic Outcomes of Partial Nephrectomy for Stage T3a Renal Cell Cancer.** *Clin Genitourin Cancer* 2018, **16**(3):e613-e617.
18. Capitanio U, Stewart GD, Klatte T, Akdogan B, Roscigno M, Marszalek M, Dell'Oglio P, Zaffuto E, Rodriguez Faba O, Salagierski M *et al*: **Does the Unexpected Presence of Non-organ-confined Disease at Final Pathology Undermine Cancer Control in Patients with Clinical T1N0M0 Renal Cell Carcinoma Who Underwent Partial Nephrectomy?** *Eur Urol Focus* 2018, **4**(6):972-977.
19. Peng D, He ZS, Li XS, Tang Q, Zhang L, Yang KW, Yu XT, Zhang CJ, Zhou LQ: **Partial nephrectomy for T3aN0M0 renal cell carcinoma: shall we step forward?** *Int Braz J Urol* 2017, **43**(5):849-856.
20. Bertolo R, Garisto J, Sagalovich D, Dagenais J, Agudelo J, Kaouk J: **Achieving tumour control when suspecting sinus fat involvement during robot-assisted partial nephrectomy: step-by-step.** *BJU Int* 2019, **123**(3):548-556.
21. Russell CM, Lebastchi AH, Chipollini J, Niemann A, Mehra R, Morgan TM, Miller DC, Palapattu GS, Hafez KS, Sexton WJ *et al*: **Multi-institutional Survival Analysis of Incidental Pathologic T3a Upstaging in Clinical T1 Renal Cell Carcinoma Following Partial Nephrectomy.** *Urology* 2018, **117**:95-100.
22. Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, Venugopal B, Kollmannsberger C, Negrier S, Uemura M *et al*: **Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma.** *N Engl J Med* 2019, **380**(12):1103-1115.
23. Wang Z, Yu K, Zhu Y, Feng C, Liu C, Liu S, Wang J, Zeng X: **Multiple Patterns of Perirenal Fat Invasion Are Associated With a Poorer Prognosis Compared With Isolated Invasion: A Proposal for a Revision of T3aN0M0 TNM Staging System.** *Front Oncol* 2020, **10**:336.
24. Bertini R, Roscigno M, Freschi M, Strada E, Petralia G, Pasta A, Matloob R, Sozzi F, Da Pozzo L, Colombo R *et al*: **Renal sinus fat invasion in pT3a clear cell renal cell carcinoma affects outcomes of patients without nodal involvement or distant metastases.** *J Urol* 2009, **181**(5):2027-2032.
25. Shah PH, Lyon TD, Lohse CM, Cheville JC, Leibovich BC, Boorjian SA, Thompson RH: **Prognostic evaluation of perinephric fat, renal sinus fat, and renal vein invasion for patients with pathological stage T3a clear-cell renal cell carcinoma.** *BJU Int* 2019, **123**(2):270-276.
26. Cates JMM: **The AJCC 8th Edition Staging System for Soft Tissue Sarcoma of the Extremities or Trunk: A Cohort Study of the SEER Database.** *J Natl Compr Canc Netw* 2018, **16**(2):144-152.

Tables

TABLE 1. Patient characteristics stratified by surgery type								
	Unmatched T3aN0M0 cohort				Matched T3aN0M0 cohort			
	PN group	RN group	P	SMD	PN group	RN group	P	SMD
All cohort								
Number of patients	911	5214			911	911		
Year at diagnosis. N (%)			0.007	9.9%			0.956	0.5%
2004–2009/2010–2015	216/695 (23.7/76.3)	1463/3751 (28.1/71.9)			216/695 (23.7/76.3)	218/693 (23.9/76.1)		
Age at diagnosis, years. Mean (SD)	61.5 (1.16)	62.8 (1.18)	0.001	11.6%	61.5 (1.16)	6.2 (1.22)	0.371	4.2%
Ethnicity: white/other. N (%)	775/136 (85.1/14.9)	4545/669 (87.2/12.8)	0.094	6.1%	775/136 (85.1/14.9)	777/134 (85.3/14.7)	0.947	0.6%
Sex: female/male. N (%)	246/665 (27.0/73.0)	1617/3597 (31.0/69.0)	0.017	8.8%	246/665 (27.0/73.0)	276/635 (30.3/69.7)	0.133	7.3%
Histology: ccRCC/nccRCC. N (%)	629/282 (69.0/31.0)	4628/586 (88.8/11.2)	<0.001	49.8%	629/282 (69.0/31.0)	663/248 (72.8/27.2)	0.089	8.2%
Grade: I or II/III or IV	529/382 (58.1/41.9)	2422/2792 (46.5/53.5)	<0.001	23.4%	529/382 (58.1/41.9)	526/385 (57.7/42.3)	0.924	0.7%
Size, cm. Mean (SD)	4.21 (2.20)	7.34 (2.94)	<0.001	120.3%	4.2 (2.2)	4.4 (2.15)	0.053	9.1%
Tumor size. N (%)			<0.001	119.8%			0.401	6.3%
≤4 cm	525 (57.6)	701 (13.4)			525 (57.6)	498 (54.7)		
4 cm to 7 cm	292 (32.1)	1983 (38)			292 (32.1)	318 (34.9)		
>7 cm	94 (10.3)	2530 (48.5)			94 (10.3)	95 (10.4)		
Cohort of pT3a ≤4 cm								
Number of patients	525	701			413	413		
Year at diagnosis. N (%)								
2004–2009/2010–2015	141/384 (26.9/73.1)	266/435 (37.9/62.1)	<0.001	23.9%	126/287 (30.5/69.5)	120/293 (29.1/70.9)	0.704	3.2%

Age at diagnosis, years. Mean (SD)	60.4 (1.15)	63.9 (1.24)	<0.001	29.3%	61.5 (1.11)	61.3 (1.21)	0.802	1.7%
Ethnicity: white/other. N (%)	444/81 (84.6/15.4)	625/76 (89.2/10.8)	0.022	13.6%	356/57 (86.2/13.8)	359/54 (86.9/13.1)	0.838	2.1%
Sex: female/male. N (%)	143/382 (27.2/72.8)	253/448 (36.1/63.9)	0.001	19.1%	121/292 (29.3/70.7)	120/293 (29.1/70.9)	1.000	0.5%
Histology: ccRCC/nccRCC. N (%)	324/201 (61.7/38.3)	572/129 (81.6/18.4)	<0.001	45.2%	297/116 (71.9/28.1)	294/119 (71.2/28.8)	0.877	1.6%
Grade: I or II/III or IV	348/177 (66.3/33.7)	449/252 (64.1/35.9)	0.453	4.7%	269/144 (65.1/34.9)	265/148 (64.2/35.8)	0.827	2.0%
Size, cm. Mean (SD)	2.81 (0.79)	3.15 (0.77)	<0.001	43.4%	2.93 (0.76)	2.94 (0.83)	0.864	1.2%
Cohort of pT3a 4–7 cm								
Number of patients	292	1983			292	292		
Year at diagnosis. N (%)								
2004–2009/2010–2015	57/235 (19.5/80.5)	560/1423 (28.2/71.8)	0.002	20.6%	57/235 (19.5/80.5)	55/237 (18.8/81.2)	0.916	1.7%
Age at diagnosis, years. Mean (SD)	62.5 (1.15)	63.9 (1.18)	0.068	11.5%	62.5 (1.15)	62.0 (1.19)	0.569	4.7%
Ethnicity: white/other. N (%)	249/43 (85.3/14.7)	1744/239 (87.9/12.1)	0.230	7.9%	249/43 (85.3/14.7)	249/43 (85.3/14.7)	1.000	<0.1%
Sex: female/male. N (%)	79/213 (27.1/72.9)	621/1362 (31.3/68.7)	0.160	9.4%	79/213 (27.1/72.9)	80/212 (27.4/72.6)	1.000	0.8%
Histology: ccRCC/nccRCC. N (%)	222/70 (76.0/24.0)	1779/204 (89.7/10.3)	<0.001	36.9%	222/70 (76.0/24.0)	223/69 (76.4/23.6)	1.000	0.8%
Grade: I or II/III or IV	147/145 (50.3/49.7)	1008/975 (50.8/49.2)	0.925	1.0%	147/145 (50.3/49.7)	146/146 (50.0/50.0)	1.000	0.7%
Size, cm. Mean (SD)	5.13 (0.79)	5.69 (0.85)	<0.001	67.8%	5.13 (0.79)	5.16 (0.75)	0.643	3.8%
Cohort of pT3a >7 cm								
Number of patients	94	2530			94	94		

Year at diagnosis. N (%)								
2004–2009/2010–2015	18/76 (19.1/80.9)	637/1893 (25.2/74.8)	0.228	14.6%	18/76 (19.1/80.9)	15/79 (16.0/84.0)	0.701	8.4%
Age at diagnosis, years. Mean (SD)	64.4 (1.14)	61.7 (1.15)	0.027	23.4%	64.4 (1.14)	65.3 (1.11)	0.577	8.1%
Ethnicity: white/other. N (%)	82/12 (87.2/12.8)	2176/354 (86.0/14.0)	0.853	3.6%	82/12 (87.2/12.8)	81/13 (86.2/13.8)	1.000	3.1%
Sex: female/male. N (%)	24/70 (25.5/74.5)	743/1787 (29.4/70.6)	0.492	8.6%	24/70 (25.5/74.5)	21/73 (22.3/77.7)	0.732	7.5%
Histology: ccRCC/nccRCC. N (%)	83/11 (88.3/11.7)	2277/253 (90.0/10.0)	0.716	5.5%	83/11 (88.3/11.7)	83/11 (88.3/11.7)	1.000	<0.1%
Grade: I or II/III or IV	34/60 (36.2/63.8)	965/1565 (38.1/61.9)	0.781	4.1%	34/60 (36.2/63.8)	32/62 (34.0/66.0)	0.879	4.5%
Size, cm. Mean (SD)	9.2 (1.82)	9.8 (2.02)	0.004	31.9%	9.19 (1.82)	9.46 (1.74)	0.292	15.4%
SD, standard deviation; SMD, standardized mean difference; PN, partial nephrectomy; RN, radical nephrectomy; ccRCC = clear cell renal cell carcinoma; nccRCC = non-clear cell carcinoma.								

TABLE 2. Survival outcomes in patients with pT3a renal cell carcinoma						
	All-cause mortality*		RCC-caused mortality**		Other-caused mortality**	
	HR (95%CI) ¶	P	sHR (95%CI) ¶	P	sHR (95%CI) ¶	P
Unmatched data						
All cohort						
Surgery (RN vs. PN)	1.57 (1.25–1.97)	<0.01	1.63 (1.17–2.28)	0.004	1.41 (1.02–1.94)	0.036
Cohort of T3a ≤4 cm						
Surgery (RN vs. PN)	1.65 (1.09–2.51)	0.019	1.42 (0.66–3.05)	0.370	1.78 (1.05–3.00)	0.032
Cohort of 4 cm < T3a ≤7 cm						
Surgery (RN vs. PN)	1.53 (1.06–2.22)	0.022	1.51 (0.91–2.51)	0.110	1.46 (0.86–2.46)	0.160
Cohort of T3a >7 cm						
Surgery (RN vs. PN)	1.12 (0.71–1.78)	0.616	1.28 (0.73–2.25)	0.400	0.74 (0.34–1.59)	0.440
Matched data						
All cohort						
Surgery (RN vs. PN)	1.52 (1.15–2.00)	0.003	1.97 (1.34–2.89)	0.001	1.14 (0.77–1.69)	0.520
Cohort of T3a ≤4 cm						
Surgery (RN vs. PN)	1.77 (1.14–2.74)	0.010	1.57 (0.74–3.36)	0.240	1.50 (0.89–2.54)	0.130
Cohort of 4 cm <T3a ≤7 cm						
Surgery (RN vs. PN)	1.46 (0.91–2.33)	0.117	1.52 (0.79–2.89)	0.210	1.35 (0.68–2.66)	0.400
Cohort of T3a >7 cm						
Surgery (RN vs. PN)	1.65 (0.89–3.08)	0.115	1.69 (0.78–3.63)	0.180	1.08 (0.39–3.00)	0.890
HR, hazard ratio; sHR, sub-distribution hazard ratio; CI, confidence interval. model;						
*Cox proportional hazards regression						
**Fine and Gray competing risks proportional hazards regression model.						
¶, Surgery type was adjusted for the year at diagnosis, age at diagnosis, ethnicity, sex, histology, grade, and tumor size (per 1 cm).						

TABLE 3. Overview of the current literature regarding partial nephrectomy and radical nephrectomy in patients with pT3a renal cell carcinoma

Study	Cohort (PN/RN)	Tumor size, cm (PN/RN)	Follow-up, months	Results
Ramaswamy et al. ²	44/22	3.8*†	50 range (1–122)†	No patients had a recurrence or RCC-specific mortality in PN and RN cohorts
Weight et al. ⁵	66/80	–	53 (3–72) †	PN exhibited a better DSS than RN in Kaplan–Meier analyses (data not shown).
Andrade et al. ⁶	70/70	–	–	<p>1. 2.9% and 1.4% of patients had local recurrence after robotic-assisted PN and RN (P = 1.0);</p> <p>2. 8.6% and 5.7% of patients had distant metastasis after robotic-assisted PN and RN (P = 0.74);</p> <p>3. Robotic-assisted PN vs. RN: 3-year OS, DSS, and RFS was 90% vs. 84%, 94% vs. 95%, and 95% vs. 100%, respectively (all P values were non-significant).</p>
Oh et al. ⁷ ¶	45/298	3.50 (1.55)/7.99 (3.68) *	43*	<p>1. For all cohort of pT3a RCC, 2.2%, 0%, and 4.4% vs. 18.5%, 12.8%, and 31.5% of patients with all- and RCC-caused mortality, and recurrence at a median of 44 and 43 months for PN and RN, respectively;</p> <p>2. For pT3a <4 cm RCC, 3.3%, 0%, and 3.3% vs. 9.1%, 6.1%, and 12.1% of patients with all- and RCC-caused mortality, and recurrence at a median of 35 and 30.5 months for PN and RN months, respectively;</p> <p>3. For pT3a 4–7 cm RCC, 0%, 0%, and 6.7% vs. 11.8%, 5.5%, and 19.7% of patients with all- and RCC-caused mortality, and recurrence at a median of 15 and 25.5 months for PN and RN, respectively.</p>
Lee et al. ⁸	57/158	5.0 (3.7–6.2) †	–	<p>1. Patients upstaged from clinical stage T1 to pathologic stage T3a RCC showed shorter survival outcomes than those without upstaging;</p> <p>2. No significant differences in RFS, OS, and DSS between PN and RN</p>
Shah et al. ⁹	49/91	–	37†	<p>1. Larger tumor size was associated with a higher risk of pT3a upstaging (4.4% vs. 24.4% upstaged from clinical-stage T1a vs. clinical stage T1b);</p> <p>2. PSM increased the risk of recurrence, recurrence was observed in 44 (31%) of pT3a patients during a median follow-up of 38 months; median time to recurrence was 18 months;</p> <p>3. Shorter RFS was observed after PN compared with RN because PSM was observed only for PN.</p>
Mouracade et al. ¹⁰	113/-	4.2 (3.0–5.2)	35 (22–52)	<p>1. pT3a RCC were highly complex tumors;</p> <p>2. 5.3% and 13.5% of patients with pT3a RCC had local recurrence (median: 13 [IQR: 10–18] months) and metastasis (median: 15 [IQR: 13–29] months);</p>

				<p>3. 1.6% and 2.3% of patients with pT1 RCC had local recurrence (median: 14 [IQR: 11–24] months) and metastasis (median: 27 [IQR: 16–41] months);</p> <p>4. The 2- and 5-year OS probabilities for pT3a and pT1 were 94.7 vs. 89% and 99.2 vs. 95.6%, respectively (log-rank P = 0.02).</p>
Nayak et al. 15	66/68	-	23†	<p>1. The 3-year RFS was 73% for PN vs. 77% for RN, P = 0.34;</p> <p>2. The PSM rate was higher among upstaged patients (9.7% compared with 4.3% in non-upstaged patients), P = 0.019;</p> <p>3. There was no difference in the PSM rate between cT1/pT3a and cT1/pT1 patients.</p>
Shvero et al. 17 †	48/86	4.0 (2.8–5.2)/7.0 (5–9.5)	55.2 for PN vs. 48.8 for RN	1. The surgery type was not associated with local recurrence (P = 0.978), metastatic progression (P = 0.972), DSS (P = 0.626), or OS (P = 0.974).
Capitanio et al. 18 ¶	71/238	3.0 (2.2–4.4)/5.5 (4.2–6.5)	55 for RN vs. 43 for PN*	<p>1. 2.9% vs. 2.8% of cases experienced local recurrence in PN vs. RN;</p> <p>2. PN cohort: 1-, 2-, and 5-year metastatic progression was 9.1%, 13.3%, and 24.1%, respectively;</p> <p>3. PN cohort: 1-, 2-, and 5-year CSM was 3.5%, 10.7%, and 18.4%, respectively;</p> <p>4. There were no differences in metastatic progression and CSM between PN and RN after propensity-score matching;</p> <p>5. The surgery type was not an independent predictor of metastatic progression or CSM.</p>
Peng et al. 19	18/18	5.27 (1.5)/5.03 (1.42)*	35.5 (10–86)†	<p>1. The 5-year DSS and RFS for PN and RN patients was 80.5% vs. 85.9%, respectively, (P = 0.305) and 76% vs. 80.8%, respectively, (P = 0.524);</p> <p>2. Cox multivariate regression analysis showed that the surgery type (RN vs. PN) was not associated significantly with DSS or RFS.</p>
Jeong et al. 16	37/54	–	48.5 (27.8)*†	PN and RN showed no significant difference in 2-year RFS (91.9% vs. 83.7%, respectively, P = 0.251)
Bertolo et al. 20	24/-	4.4 (1.75)*	30.1 (11.3–43.9)	1. 8.3% of patients had local recurrence and 4.2% of patients had metastasis; no patients died due to RCC during follow-up.
Russell et al. 21 ¶	95/-		38.2 (11.6–56.8)	<p>1. In pT3a, 3% and 18% of patients had local disease and metastasis, respectively, during a median follow-up of 32.6 (IQR 10.5–48.1) months) post-PN;</p> <p>2. In pT1, 3% and 6% of patients had local disease and metastasis, respectively, during the median follow-up of 34.1 (IQR 26.3–43.2) months post-PN;</p> <p>3. Recurrence prevalence was significantly higher in pT3a vs. pT1 disease (P < 0.01);</p> <p>4. Among those with pT3a disease and subsequent disease recurrence, 30% had PSM but it was not associated with local disease.</p>

RCC, renal cell carcinoma; PN, partial nephrectomy; RN, radical nephrectomy; OS, overall survival; DSS, disease-specific survival; CSM, cancer-specific mortality; RSF, recurrence-specific survival; PSM, positive surgical margin; IQR = interquartile range.

Tumor size and follow-up time are presented as the median (IQR).

The study design was a retrospective single-center study; tumors without lymph-node and distant metastasis (NOM0), and Kaplan–Meier and multivariate analysis were used for survival prediction.

†, data from two-institutions;

¶, data from multiple institutions;

*, data are the mean or mean (standard deviation);

‡, Only the detailed information of all cohorts of PN and RN.

Figures

Figure 1

Kaplan–Meier analysis of the overall survival between different types of surgery (partial nephrectomy [PN] and radical nephrectomy [RN]), in patients with T3a renal cell carcinoma stratified according to tumor size category. (A-D) Prior to propensity-score matching for the two types of surgery, and (E-H) after propensity-score matching for the two types of surgery.

Figure 2

Kaplan–Meier analyses of overall survival between different types of surgical procedure (partial nephrectomy [PN] and radical nephrectomy [RN]) in patients with T3a renal cell carcinoma stratified according to tumor size and invasion type. The dataset included patients for whom accurate information of invasion type was available (2010–2015 the Surveillance, Epidemiology, and End Results (SEER) database). The hazard ratio (HR) of all cause-mortality for surgery type (RN vs. PN) was adjusted for the year at diagnosis, age at diagnosis, ethnicity, sex, histology, grade, and tumor size (per 1 cm).

Figure 3

“Sketch map” of our study findings in surgical decision-making for pT3aN0M0 renal cell carcinoma (local advanced). Partial nephrectomy (PN) rather than radical nephrectomy (RN) should be recommended for small (≤ 4 cm) pT3aN0M0 renal cell carcinomas without invasion of sinus/perisinus fat

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Sfigures.doc](#)
- [Stables.docx](#)