Partial Nephrectomy Does Not Compromise Survival in Patients With Pathologic Upstaging to pT2/pT3 or High-grade Renal Tumors Compared With Radical Nephrectomy

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OBJECTIVE To compare survival in patients with clinical T1b renal tumors that are pathologically upstaged, or high-grade tumors, treated by either partial nephrectomy (PN) or radical nephrectomy (RN). The American Urological Association Guidelines recently advocated increasing use of PN in all patients with cT1 renal masses, but urologists are often hesitant to perform PN for larger more aggressive appearing cT1 renal tumors for fear of pathologic upstaging and a perceived compromise in cancer control.

METHODS From a single institutional kidney cancer registry, 2511 consecutive patients with presumed cT1 renal cell cancer underwent extirpative surgery; 1981 (79%) were found to have renal cell cancer (RCC) and 213 (10.7%) were upstaged on final pathology. In addition, 95 (5%) were found to have grade 4 cancer. Cancer-specific survival (CS) and overall survival (OS) were compared between the groups.

RESULTS In the upstaged cohort, patients treated by PN (n = 96, 45%) had comparable OS and CS when studied stage for stage with those treated by RN (n = 117, 55%). Multivariate cox-proportional hazards analysis of OS in the upstaged subset demonstrated that only age, grade, and Charlson score predicted OS, whereas PN vs RN and stage did not. PN did not compromise survival in patients with grade 4 RCC compared with RN.

CONCLUSIONS PN does not appear to compromise the chance for cancer cure in patients with cT1 tumors that are upstaged pathologically to pT2 or pT3 or high-grade renal masses when compared with RN. These concerns should not deter a surgeon from attempting PN when otherwise technically feasible. UROLOGY 77: 1142–1147, 2011. © 2011 Elsevier Inc.

Partial nephrectomy (PN) remains underused in the United States[1] and Canada,[2] despite accumulating data outlining the deleterious effects of chronic kidney disease (CKD) among patients with renal tumors.[3-5] The American Urological Association Guidelines defined PN as a reference standard for patients with cT1a tumors (PN), presuming that the patient is a good surgical candidate and has reasonable life expectancy. In addition, PN should also be considered a standard of care for patients with cT1b tumors, along with radical nephrectomy (RN) even with a normal contralateral kidney.[6] Data from multiple institutions have demonstrated that PN offers equal cancer-specific survival (CS).[4,5,7-10] In addition, the excess renal loss associated with RN was associated with a 17% increased risk of death from any cause and a 25% increased risk of death from a cardiovascular cause.[4] Even though recently published data demonstrate that at high-volume institutions, cT1a tumors are treated by PN about 90% of the time,[11] population-based data in the United States demonstrate PN rates only around 40% for tumors <4 cm.[12] Although trends over recent years in North America generally leaned toward increased use of PN, in Canada there was a sharp drop in the number of tumors treated with PN after the introduction of laparoscopic radical nephrectomy,[2] suggesting that choice of RN over PN is more a product of surgeon preference rather than patient or tumor characteristics.[13]

However, despite an overall trend toward increased use of PN observed in patients with renal masses ≤4 cm, in patients with cT1b tumors, widespread use of PN has been

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Table 1. Perioperative characteristics of patients with cT1 renal masses upstaged to pT2/pT3 on final pathology or to high-grade cancer

Upstaged Cohort (n = 213) Patient Characteristics Mean (IQR) or n (%)	Radical (N = 117)	Partial (N = 96)	*P* Value
Age	67 (58–76)	63 (56–71)	.02
Male gender, n (%)	75 (64)	73 (76)	.07
Pre-op tumor size (cm)	6 (5.0–6.7)	4 (2.6–5.2)	<.0001
Side of tumor			.7
Right	58 (50%)	50 (52%)	
Left	59 (50%)	46 (48%)	
Charlson group			.0001
0-1	69 (64%)	80 (87%)	
≥2	39 (36%)	12 (13%)	
Furman nuclear grade 4	23 (20%)	6 (7%)	.0004
pTstage group			.15
2	23 (20%)	12 (13%)	
3	94 (80%)	84 (87%)	
Median follow-up in mo (IQR)	50 (34-74)	61 (39-83)	.2
High-grade Cohort (n = 95) **Patient Characteristics** **Mean (IQR) or n (%)**	**Radical (N = 43)**	**Partial (N = 52)**	***P* Value**
Age	65 (56–69)	60 (50–71)	.1
Male gender, n (%)	26 (60%)	30 (58%)	.8
Pre-op tumor size (cm)	5.8 (5.0–6.6)	3.5 (2.9–4.7)	<.0001
Side of tumor			
right	22 (51%)	27 (52%)	.8
left	21 (49%)	25 (48%)	
Charlson group			.2
0-1	69 (51%)	33 (65%)	
≥2	19 (48%)	18 (35%)	
pTstage group			<.0001
1	20 (47%)	46 (88%)	
2	2 (5%)	2 (4%)	
3	21 (48%)	4 (8%)	
Median follow-up in mo (IQR)	41 (9-59)	56 (39-79)	.0006

particularly slow despite the fact that larger institutions now report treating 50–60% of all cT1 tumors with PN.[4,11] Larger tumors are more likely to be understaged by computed tomography imaging and one reason urologists may be hesitant to attempt PN in patients with these larger, more aggressive appearing tumors is the perception that RN may offer a more favorable oncological outcome to PN. In an attempt to address this issue, we compared overall survival (OS) and CS in a subset of patients with tumors ≤7 cm who were eventually upstaged to pT2/pT3 or had high-grade histology on final pathology.

MATERIAL AND METHODS

From 1999 to 2006, 2511 patients with an enhancing cT1 renal mass underwent extirpative surgery, 73% by PN (n = 1834) and 27% by RN (n = 677). Of these, 1981 (79%) were found to be malignant tumors, including 213 (10.7%) patients who were found to have stage pT2 or higher and 95 (5%) who were found to have Furhman nuclear grade 4 tumors on final pathology. Perioperative and pathologic data were obtained from our institutional review board–approved, institutional kidney cancer patient registry.

Choice of extirpative surgery was left to surgeon and patient preference, after consideration of tumor size, radiographic appearance, overall patient health, life expectancy, and surgeon comfort. Comorbidity was evaluated using the Charlson-Romano Index or the Age-Adjusted Charlson Index as indicated. For each patient, vital status was obtained using the Social Security death index and cause of death information was determined by reviewing the patient's medical records and information obtained from the National Death Index. Patients without a social security number were excluded from the analysis.

The Kaplan-Meier analysis was used to evaluate OS, with the log-rank test. Proportions were analyzed by chi-square or Fisher's exact test as indicated. Wilcoxon/Kruskal-Wallis was used to compare nonparametric continuous data, and Student's *t*-test was used if the data were parametric. Because the patients were not randomized, a Cox multivariate hazard analysis of OS was performed. Survival was modeled stage for stage, to limit selection bias. Hazard ratios (HR) and their 95% confidence intervals (CI) were reported. A two-sided *P* value of <.05 was considered statistically significant. All analyses for this study were performed with JMP 8.0 (SAS Institute, Cary, NC) statistical software.

RESULTS

There were significant differences between the RN and PN groups as might be expected in a nonrandomized

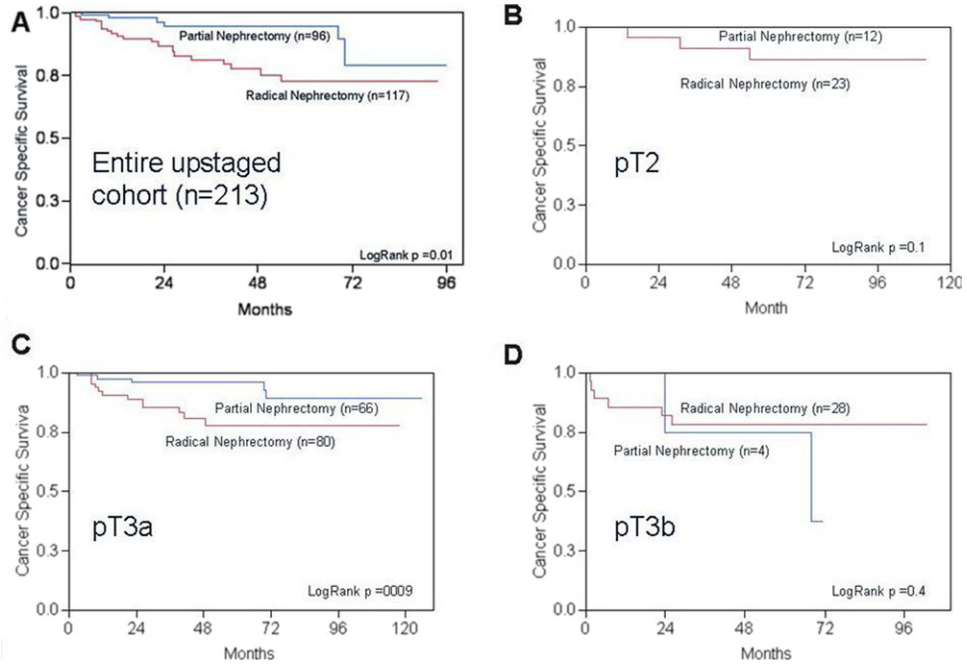

Figure 1. Kaplan-Meier analysis comparing CS for patients treated with either RN or PN for the entire upstaged cohort **(A)**, pathologic stage T2 **(B)**, pathologic stage T3a **(C)**, and pathologic stage T3b **(D)**.

cohort (Table 1). Median follow-up for the upstaged cohort was 53 months (IQR, 37-76), and for the high-grade cohort it was 49 months (IQR, 26-72).

Cancer-Specific Survival

In the entire malignant cohort of 1981 cT1 patients, there were 100 deaths as a result of cancer. Multivariate analysis of CS demonstrated that Furhman grade and pathologic stage predicted CS, but age, tumor size, and type of nephrectomy did not. There were 95 patients (5%) who were found to have high-grade (Furhman grade 4) cancer on final pathology; 5-year CS for these patients was 63% (95% CI, 50-75). In the upstaged cohort (n = 213), 5-year CS was 82% (95% CI, 76-89). The 24 and 28 cancer-specific deaths in these smaller cohorts, respectively, preclude multivariate analysis, but Kaplan-Meier analysis demonstrated that PN offers at least equivalent cancer control compared with RN in both the high-grade cohort, 5-year CS 88% (95% CI, 73-99) vs 37 (95% CI, 17-58) (log-rank P <.001), and the upstaged cohort 5-year CS 94% (95% CI, 89-99) vs 73 (95% CI, 62-84) (log-rank P = .01), respectively. Stratifying stage for stage demonstrates that PN performs equally well in cancer control compared with RN (Fig. 1).

Overall Survival

Kaplan-Meier analysis of OS demonstrated that PN was at least equivalent to RN in both upstaged tumors and high-grade tumors (Fig. 2). During follow-up, 43 patients in the high-grade cohort and 72 in the upstaged cohort died of any cause. Multivariate analysis was performed, including Charlson comorbidity index, pathologic stage, age, grade, and type of nephrectomy; only age, high-grade cancer, and comorbidity score predicted OS (Table 2), whereas nephrectomy type did not.

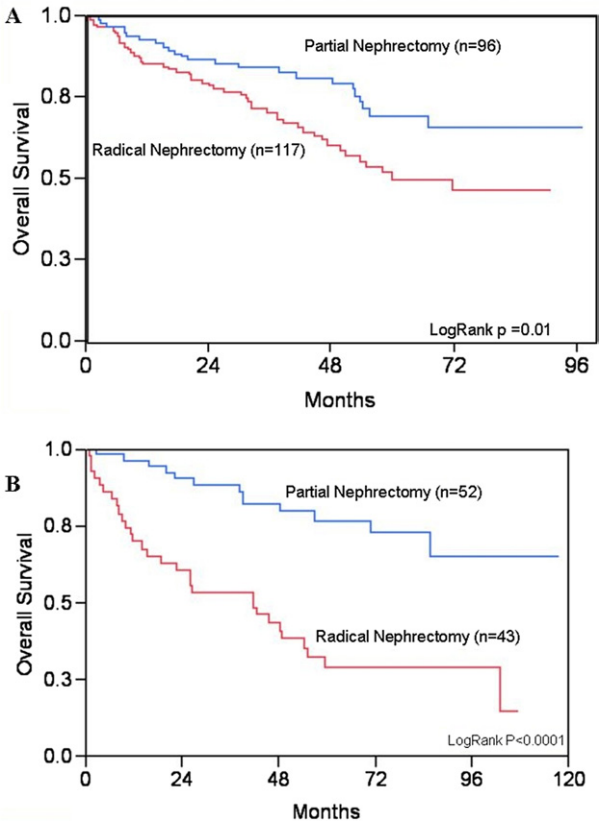

Figure 2. Kaplan-Meier analysis of OS in patients who were upstaged **(A)** or had high-grade tumors **(B)** on final pathology treated with either PN or RN.

Table 2. Multivariate analysis of OS in patients with cT1 masses pathologically upgraded to pT2/pT3, N = 213

	Hazard Ratio	95% CI Lower	95% CI Upper	*P* Value
Charlson score (≥2 vs 0-1)	1.79	1.02	3.13	.04
Pathologic T stage (3 vs 2)	1.23	0.31	4.21	.8
PN vs RN	0.99	0.54	1.76	.9
Age per year	1.05	1.02	1.08	.0003
Grade (4 vs 1-3 vs)	4.0	2.21	7.78	<.0001

COMMENT

RN for the treatment of localized kidney tumors continues to be the mainstay treatment for patients with T1b renal masses,[1,14] despite a growing body of literature that chronicles the deleterious effects of nephrectomy-induced CKD in this population.[3-5,15,16] Radical extirpative surgery has long been the mainstay for oncological surgeons in many disciplines, including urology. With stage migration,[17,18] nearly every newly diagnosed localized kidney tumor is being treated surgically, and cancer control when the tumor is confined to the kidney is well above 90%.[4] Despite these excellent oncological results, we observe puzzling data that demonstrate that OS for patients with kidney masses has not improved.[19] One possible reason for this disconnect between increasing treatment without improving survival could be the morbidity of the treatment. There is an increasing awareness of the morbidity and mortality associated with CKD in the general medical patient,[20] and this has led the urological community to reevaluate the paradigm of RN for localized kidney tumors. Indeed, now there are studies from several centers outlining the improved renal function associated with PN[3,21] and a subsequent association with improved OS.[4,5,16]

These data have contributed to a rising use of PN in the United States and Canada, particularly in the small renal masses <4 cm in size, but there has been relative resistance to use PN in larger renal masses >4 cm.[12,14] Many surgeons remain concerned that these larger tumors are more aggressive, and thus likely to be upstaged or have a high Furhman grade, and therefore would be better treated by RN. Although our data found significant percentages of upstaged and high-grade tumors, the data do not indicate that these patients are better served by RN. In this cohort of 1981 cT1 tumors, 759 were cT1b (38%). Of this subset of patients with larger tumors, 148 tumors (20%) were upstaged to pT2 or higher and 55 tumors (7%) were found to be grade 4. Therefore, although the concern of upstaging and higher-grade tumors is reasonable, the argument that RN offers any oncological advantage over PN is not supported by our data. In no analysis did PN compromise CS or OS, even on multivariate analysis (Table 2, Figs. 1 and 2). With emerging data confirming both the theoretical and measured benefits of preserving as much renal function as possible, the question of whether to perform a PN should largely revolve around the technical feasibility and whether the patient's comorbidities may preclude the attendant benefits of renal preservation.

Our data are limited by the fact that they are retrospective and come from a nonrandomized cohort. Table 1 demonstrates that those treated by RN had larger, more aggressive tumors, and although we tried to control for confounding factors, the relatively little number of events preclude adequate multivariate comparison, particularly for CS. However, these data should provide practitioners with reassurance that they are not compromising CS by offering PN in these larger tumors. In addition, these data are supported by multiple studies from several other institutions which find that a complete tumor resection by PN offers equal cancer control when compared with RN.[10]

CONCLUSIONS

PN does not appear to compromise the oncological outcomes in patients with cT1 tumors that are upstaged pathologically to pT2 or pT3 or high-grade renal masses when compared with RN. Therefore, these concerns should not deter a surgeon from attempting PN when otherwise technically feasible.

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References

1. Miller DC, Hollingsworth JM, Hafez KS, et al. Partial nephrectomy for small renal masses: an emerging quality of care concern? *J Urol.* 2006;175:853-857; [Discussion: 858].
2. Abouassaly R, Alibhai SM, Tomlinson G, et al. Unintended consequences of laparoscopic surgery on partial nephrectomy for kidney cancer. *J Urol.* 2010;183:467-472.
3. Huang WC, Levey AS, Serio AM, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol.* 2006;7:735-740.
4. Weight CJ, Larson BT, Fergany AF, et al. Nephrectomy induced chronic renal insufficiency is associated with increased risk of cardiovascular death and death from any cause in patients with localized cT1b renal masses. *J Urol.* 2010;183:1317-1323.
5. Weight CJ, Larson BT, Gao T, et al. Elective Partial nephrectomy in patients with Clinical T1b Renal Tumors is associated with Improved Overall Survival. *Urology.* 2010;76(**3**):631-637.
6. Campbell SC, Belldegrun A, Blute ML, et al. AUA Guideline for Management of the Clinical Stage 1 Renal Mass, American Urologic Association Annual Meeting. Chicago, IL: Education and Research, Inc.; 2009.
7. Leibovich BC, Blute ML, Cheville JC, et al. Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. *J Urol.* 2004;171:1066-1070.
8. Fergany AF, Hafez KS, Novick AC. Long-term results of nephron sparing surgery for localized renal cell carcinoma: 10-year follow up. *J Urol.* 2000;163:442-445.
9. Thompson RH, Siddiqui S, Lohse CM, et al. Partial versus radical nephrectomy for 4 to 7 cm renal cortical tumors. *J Urol.* 2009;182:2601-2606.

10. Patard JJ, Shvarts O, Lam JS, et al. Safety and efficacy of partial nephrectomy for all T1 tumors based on an international multicenter experience. *J Urol.* 2004;171:2181-2185, [Quiz: 435].
11. Thompson RH, Kaag M, Vickers A, et al. Contemporary use of partial nephrectomy at a tertiary care center in the United States. *J Urol.* 2009;181:993-997.
12. Dulabon LM, Lowrance WT, Russo P, et al. Trends in renal tumor surgery delivery within the United States. *Cancer.* 2010;116:2316-2321.
13. Miller DC, Saigal CS, Banerjee M, et al. Diffusion of surgical innovation among patients with kidney cancer. *Cancer.* 2008;112:1708-1717.
14. Baillargeon-Gagne S, Jeldres C, Lughezzani G, et al. A comparative population-based analysis of the rate of partial vs radical nephrectomy for clinically localized renal cell carcinoma. *BJU Int.* 2010;105:359-364.
15. Huang WC, Elkin EB, Levey AS, et al. Partial nephrectomy versus radical nephrectomy in patients with small renal tumors—is there a difference in mortality and cardiovascular outcomes? *J Urol.* 2009;181:55-61; [Discussion: 62].
16. Thompson RH, Boorjian SA, Lohse CM, et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. *J Urol.* 2008;179:468-471; [Discussion: 472-473].
17. Hollingsworth JM, Miller DC, Daignault S. Rising incidence of small renal masses: a need to reassess treatment effect. *J Natl Cancer Inst.* 2006;98:1331-1334.
18. Nguyen MM, Gill IS, Ellison LM. The evolving presentation of renal carcinoma in the United States: trends from the Surveillance, Epidemiology, and End results program. *J Urol.* 2006;176:2397-2400; [Discussion: 400].
19. Chow WH, Devesa SS, Warren JL, et al. Rising incidence of renal cell cancer in the United States. *JAMA.* 1999;281:1628-1631.
20. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004;351:1296-1305.
21. Lau WK, Blute ML, Weaver AL, et al. Matched comparison of radical nephrectomy vs nephron-sparing surgery in patients with unilateral renal cell carcinoma and a normal contralateral kidney. *Mayo Clin Proc.* 2000;75:1236-1242.

EDITORIAL COMMENT

"Compared to radical nephrectomy partial nephrectomy does not appear to compromise the chance for cancer cure in patients with clinical T1 tumors that are upstaged pathologically to pT2 or pT3." This is the conclusion of this interesting paper.

Many urologists continue to mistakenly believe that in a patient with larger tumors (T1b and T2), radical nephrectomy (RN) should be considered as the treatment of choice. Authors' data well underline that tumor size or grade should not deter a surgeon from attempting a partial nephrectomy (PN) when otherwise technically feasible. Nephron-sparing surgery (NSS) warrants complete local resection of a renal tumor while leaving the largest possible amount of normal functioning parenchyma in the involved kidney. Although in the past the use of partial nephrectomy has been limited to patients who would be rendered anephric after RN (ie, solitary functioning kidney, bilateral renal cell carcinoma [RCC], unilateral RCC with some compromise of the contralateral kidney) during the last decade, PN has been accepted as a safe and effective alternative in elective situations. Many studies have shown equivalent cancer control when comparing RN and PN in T1b tumors, thus suggesting that it may be safe to increase the indications of NSS from 4-7 cm.[1,2]

It is reasonable to expect in imperative indications a high rate of major complications that could be considered acceptable to prevent anephria in clearly informed patients, but currently, major complications could be considered rare in elective indications and experienced hands.[3]

Another important aspect to be considered is the incidence of benign lesions after renal surgery for *presumed* RCC. In addition to results in the present paper, approximately 20% of renal masses after radical surgery have been found to be benign tumors.[4]

For these reasons, the authors' conclusions give clinicians facilities to counsel patients recently diagnosed with small renal masses and decide the most appropriate treatment, to avoid unnecessary neprectomy.

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References

1. Leibovich BC, Blute ML, Cheville JC, et al. Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. *J Urol.* 2004;171:1066-1070.
2. Patard JJ, Shvarts O, Lam JS, et al. Safety and efficacy of partial nephrectomy for all T1 tumors based on an international multicenter experience. *J Urol.* 2004;171:2181-2185.
3. Pomara G, Campo G, Francesca F. Intraoperative and postoperative complications of nephron sparing surgery: prevention and possible treatments. *Arch Ital Urol Androl.* 2009;81(2):80-85.
4. Jeon HG, Lee SR, Kim KH, et al. Benign lesions after partial nephrectomy for presumed renal cell carcinoma in masses 4 cm or less: prevalence and predictors in Korean patients. *Urology.* 2010;76(3):574-579.

doi:10.1016/j.urology.2010.12.065
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REPLY

This paper has been presented with the goal of encouraging urologists that, even in the face of more locally advanced or high-grade disease, partial nephrectomy (PN) in select patients can provide oncological results comparable with radical nephrectomy (RN). As presented in the editorial comment, it appears that PN is oncologically equivalent to RN in renal tumors up to 7 cm in size, and recent studies suggest that this may even be extended to T2 tumors.[1,2] In the authors' opinion, size should not impact the decision to perform PN if the surgeon feels it is technically feasible with meaningful renal parenchyma spared.[3] Patient survival has been shown to be superior in patients undergoing PN vs RN,[4] presumably related to improved postoperative renal function, and should provide the major impetus for performing PN whenever possible. Unnecessary RN is still performed for a significant number of patients, particularly in the elderly, as well as in lower-volume centers. The rationale of a laparoscopic RN as a less invasive alternative to an open PN is attractive to both patients and surgeons, and perpetuates the practice of unnecessary RN for smaller tumors. Future progress will depend on increasing awareness of the risks of renal insufficiency, as well as increasing implementation of