A comparison of long term renal functional outcomes following partial nephrectomy and radiofrequency ablation

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Introduction: *To compare long term glomerular filtration rate (GFR) outcomes of partial nephrectomy and radiofrequency ablation performed for renal malignancy.*
Materials and methods: *Renal function of 347 patients undergoing radiofrequency ablation (n = 142) or partial nephrectomy (n = 205) for renal malignancy between 1994 and 2011 were compared from a retrospective database at a single tertiary care center. Minimum 1 year of follow up was required, resulting in a mean follow up of 48.2 (SD +/- 28.2) months. Renal function was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The primary study outcome was progression of Chronic Kidney Disease (CKD) stage, calculated using the Kaplan-Meier life table method. Multivariate analysis was also conducted to determine the level of association between GFR decline and treatment modality.*
Results: *The 5 year freedom from CKD stage progression for radiofrequency ablation and partial nephrectomy was 85.4% (95% CI 76.8%-91.1%) versus 82.1% (95% CI 73.7%-88.1%) (p = 0.06). A longer follow up interval was associated with greater GFR decline, although hypertension, diabetes, age, and tumor size were not.*
Conclusion: *Radiofrequency ablation provides similar long term renal function preservation benefit as partial nephrectomy.*

Key Words: radiofrequency ablation, partial nephrectomy, renal function, glomerular filtration rate, long term

Introduction

Prior to the late 1990's, nephron-sparing surgery was largely reserved for patients with renal insufficiency, solitary kidneys, or bilateral tumors.[1] With mounting evidence that radical nephrectomy (RN) results in greater glomerular filtration rate (GFR) decline than partial nephrectomy,[2-8] practitioners have since adopted a more aggressive approach to nephron-sparing surgery. Approximately 45% of surgeries performed for cT1a kidney cancers are now partial nephrectomies (PN).[9] The principle driving force behind this change in practice is the correlation between decreasing GFR and the increased risk of death and cardiovascular events.[10,11]

Radiofrequency ablation (RFA) is an alternative less morbid treatment to PN for small renal masses. The relative impact of RFA compared to PN on long term renal function remains controversial. Small series of RFA suggest preservation of renal function[12-16] but these series are limited by small patient numbers and limited follow up. Large PN series demonstrate that postoperative GFR is affected by several variables such as ischemia time, proportion of parenchyma resected, and patient demographics, which complicates our understanding of the extent to which PN causes GFR decline.[17,18] Unfortunately there are no randomized studies, and few cohort studies, that directly compare GFR outcomes after tumor ablation and PN. One 3-armed small cohort study of patients with two kidneys and limited follow up undergoing RN, PN or RFA showed no difference in GFR outcomes between PN and RFA.[4] In contrast, another cohort study of patients with solitary kidneys found a greater GFR decline following PN versus RFA after 1 year of follow up.[19] We present the largest series evaluating

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long term renal functional outcomes following partial nephrectomy and radiofrequency ablation.

Materials and methods

From our Institutional Review Board (IRB)-approved retrospective database, patients 18 years of age or older were identified who underwent RFA or PN between February 1999 and February 2011 for renal neoplasms. Patients lacking preoperative creatinine data and those lost to follow up or with less than 1 year of follow up were excluded. Those undergoing multiple renal surgeries or renal surgery in a solitary kidney were also excluded, yielding 347 patients for inclusion.

The individualized treatment approach was based on the underlying renal disease, renal mass size and location, patient comorbidity, and preferences of the treating surgeon and patient. PN was performed primarily for non-central masses, while RFA was utilized primarily in patients who weren't ideal surgical candidates. RFA was first performed in 2000. Our techniques for laparoscopic and percutaneous RFA have been previously published.[20]

Statistical analysis

GFR was calculated from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to take into account gender and race and improve the accuracy of renal function estimates. All data were analyzed using STATA version 10.0. We report descriptive data for all variables of interest. We assumed the Central Limit Theorem applied for all non-normally distributed data and thus report only parametric analyses.

The Pearson product moment correlation coefficient was used to determine the level of association between GFR change (preoperative GFR minus GFR at last follow up) and surgery type, hypertension (HTN), diabetes mellitus (DM), age, months of follow up and tumor size. In a multivariate linear regression model, HTN, DM, age, tumor size and months follow up were statistically controlled by forcing these four variables into the regression model first. These independent variables were determined based on their deemed biological relevance.

Survival analysis was performed using the Kaplan-Meier life table method. An 'event' was defined

TABLE 1. **Patient characteristics**

	RFA (n = 142)	**PN (n = 205)**	**p value**
Age at surgery (mean, SD)	61.3, 13.2	54.3, 12.7	< 0.001
Gender (M/F)	79/63	113/92	0.93
Race (#, %)			0.26
White	109, 76.8	143, 69.8	
Black	17, 12.0	29, 14.1	
Hispanic	7, 4.9	10, 4.9	
Other	9, 6.3	15, 7.3	
Unknown	0, 0	4, 2.0	
Asian	0, 0	4, 2.0	
DM (#, %)	26, 18.3	37, 18.0	0.97
HTN (#,%)	60, 42.2	104, 50.7	0.11
Tumor size (mean, SD)	2.31, 0.78	3.1, 2.8	0.001
GFR preop (mean, SD)	75.0, 22.5	80.7, 21.8	0.02
Preop GFR < 60 (#, %):	38, 26.8	31, 15.1	0.38
Preop CKD stage (n, %)			
I-II: GFR > 60	104 (73.2%)	175 (85.4%)	0.41
III: GFR 30-59	32 (22.5%)	27 (13.2%)	0.99
IV: GFR 15-29	1 (0.7%)	4 (2.0%)	0.92
V: GFR < 15	0 (0%)	0 (0%)	-
Follow up, months (mean, SD)	56.72, 30.3	42.2, 25.2	< 0.001

CKD staging (GFR, mL/min per 1.73m^2): I: > = 90, II: 60-89, III: 30-59, IV: 15-29, V: < 15; RFA = radiofrequency ablation; PN = partial nephrectomy; DM = diabetes mellitus; HTN = hypertension; GFR = glomerular filtration rate as progression of Chronic Kidney Disease (CKD) stage, as defined by the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation[21] from the preoperative GFR to the time of last follow up. The CKD stages are defined in the legend of Table 1. Progression from stage I to stage II (i.e, GFR > 90 to GFR 60-90) was not considered an event for the purposes of this analysis, thus GFR was required to fall at least below 60 before meeting the criteria for an 'event'. Survival curves for PN and RFA cohorts were compared using the log rank test, with calculation of actuarial 5 year freedoms from CKD stage progression.

Results

Participants were similar with regard to gender, race, and presence/absence of hypertension and diabetes. The RFA cohort had significantly older patients subjected to longer follow up and a lower mean preoperative GFR. RFA treated patients also had a smaller mean tumor size, Table 1.

Within the PN cohort, warm ischemia times were available for 63.4% (130/205) of patients. The mean WIT was 33.8 +/- 13.6. Median WIT was 34 minutes with a range of 0-80 minutes. Of the 205 tumors, final pathology showed clear cell (62%), papillary (12.2%), chromophobe (5.9%), unclassified RCC (5.4%), oncocytoma (7.8%), angiomyolipoma (2.4%), cystic nephroma (2%), benign inflammatory lesions (1.5%) and 'other' (1%). Margins were positive in 17 cases.

On univariate and multivariate analysis, only follow up time was significantly associated with GFR change ($p = 0.02$) while treatment approach, HTN, DM, age and tumor size were not ($p > 0.05$), Tables 2 and 3.

The five year freedom from CKD stage progression for radiofrequency ablation and partial nephrectomy was 85.4% (95% CI 76.8%-91.1%) versus 82.1% (95% CI 73.7%-88.1%) ($p = 0.06$). The survival curves are shown in Figure 1.

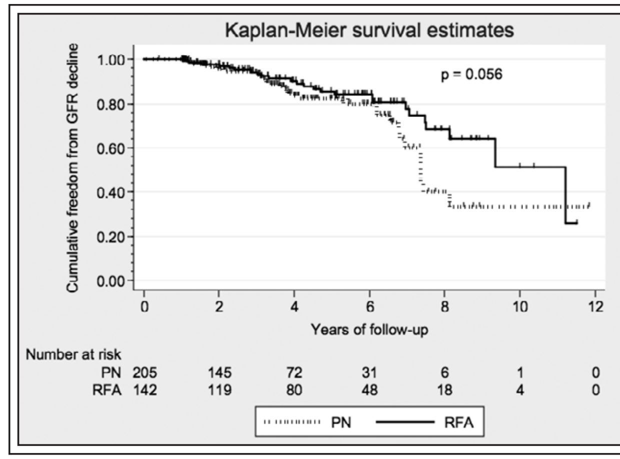

Figure 1. Kaplan-Meier survival curve.

Discussion

To conduct the survival analysis, an 'event' was defined as progression of CKD stage because of the progressive burden of disease between stages. A GFR less than 60 mL/min/m^2 (stage III) represents loss of 50% or greater of the normal kidney function of an adult. At this stage patients are at higher risk for complications secondary to renal insufficiency including anemia, malnutrition, bone disease, neuropathy, decreased quality of life.[21] Furthermore, GFR < 60 mL/min/m^2 is associated with increased risk of progression to end-stage renal disease, cardiovascular disease, and premature death.[18] At stage IV (GFR 15-29 mL/min/m^2), the National Kidney Foundation recommends involvement of a nephrologist and preparation for

TABLE 2. **Univariate analyses**

Variable	**Correlation coefficient, (95% CI)**	**p value**
RFA (PN reference)	-0.04, [-3.3, 3.2]	0.98
HTN	-0.47, [-3.7, 2.7]	0.78
DM	-3.86, [-8.0, 0.28]	0.07
Age	0.10, [-0.02, 0.22]	0.10
Months of follow up	-0.07, [-0.13, -0.01]	0.017
Tumor size	-0.59, [-1.3, 0.14]	0.11

RFA = radiofrequency ablation; PN = partial nephrectomy; HTN = hypertension; DM = diabetes mellitus

TABLE 3. **Multivariate linear regression**

Independent variables	**Unstandardized ß (95% CI)**	**p value**
RFA (PN reference)	-0.98, [-4.5, 2.6]	0.581
HTN	-1.6, [-5.0, 1.8]	0.366
DM	-3.5, [-7.7, 0.78]	0.109
Age	0.12, [-0.01, 0.25]	0.069
Months follow up	-0.08, [-0.14, -0.02]	0.010
Tumor size	-0.63, [-1.4, 0.11]	0.095

RFA = radiofrequency ablation; PN = partial nephrectomy; HTN = hypertension; DM = diabetes mellitus kidney replacement therapy. At stage V (GFR < 15 mL/min/m^2), patients are in kidney failure by definition, and usually suffer signs and symptoms of uremia.[21]

PN and RFA did not lead to significant differences in GFR decline. Not only was the rate of CKD stage progression similar, but when change in GFR was examined as a continuous variable with multivariate analysis, treatment approach did not affect GFR outcomes. Moreover, during the course of follow up, there were mean GFR declines of 7.97 mL/min/m^2 (+/- 15.3) for PN and 8.01 mL/min/m^2 (+/- 15.0) for RFA. The ability of both approaches to preserve GFR is reassuring given the high rates of preexisting renal insufficiency in this population. Indeed, even prior to treatment, 23.2% and 15.2% of the RFA and PN cohorts had CKD stage III renal insufficiency. In other studies, the prevalence of GFR < 60 mL/min/m^2 is as high as 26%-27% of patients with a renal mass,[3,4,17] likely due to common risk factors for both renal cancer and renal insufficiency, including smoking, obesity and hypertension.[11,22-25]

RFA and PN both have theoretical advantages and limitations regarding the preservation of renal function. PN generally requires a transient ischemic insult that may manifest as permanent nephron damage, particularly if ischemic times are prolonged beyond 20-30 minutes.[6] RFA, by comparison, does not require a period of global renal ischemia. However, complete thermal destruction of cancer cells by an ablation technology requires energy deposition that results in partial necrosis of normal parenchyma around the tumor.[26,27] PN permits precise excision of the tumor with minimal loss of normal parenchyma. Indeed, recent reports suggest that maximal preservation of renal parenchyma may have greater importance to long term renal function than ischemia time.[6,28] Based on these conflicting concepts, there is still no consensus regarding which treatment approach (PN versus RFA) optimizes renal function preservation. Our study, which was limited to patients with two kidneys undergoing a single procedure, found no difference in GFR despite large patient cohorts and long term follow up. Neither was there a difference in progression of CKD stage on survival analysis. Although differences in age and tumor size between cohorts may have been expected to affect the change in GFR, it did not alter our conclusions following multivariate analysis.

Our findings reinforce a previous smaller study that compared cohorts of patients with two kidneys undergoing RFA and PN. The 3 year freedom from GFR decline to below 60 mL/min/m^2 was 95.2% and 70.7% respectively. Although the RFA cohort appeared to maintain superior renal function, the difference was not statistically significant. In another retrospective study, Raman and colleagues did detect a GFR benefit in patients undergoing RFA compared to PN. Although a small study size (n = 89), a statistically significant difference in the percentage GFR decline after 1 year was noted between RFA and PN cohorts (10.4% versus 24.5%, p = 0.001). There was also new onset of GFR < 30 mL/min/m^2 in 7% versus 16.7% respectively (p = 0.005). Unfortunately, this retrospective cohort study was subject to several inequalities of patient selection, which limits the certainty of their conclusion. RFA patients were older (median 65.9 versus 59.6 years, p = 0.03) and had a lower median preoperative GFR (46.5 versus 55.9 mL/min/m^2). However, PN tumors were larger (3.9 cm versus 2.8 cm, p = 0.001) and likely required excision of greater nephron mass. Furthermore, patients in the PN cohort had longer follow up (median 30 months versus 18.1 months) exposing them to the potential of greater loss of function. Nevertheless, this study suggests that appropriately selected patients with solitary kidneys may benefit from RFA, although any purported GFR benefit in comparison to PN is of secondary importance to oncological control.

We acknowledge certain limitations of this retrospective study, including the inherent selection bias resulting from treatment group designation based on clinical and tumor characteristics. As expected, patients undergoing RFA were significantly older (61.3 years versus 54.3, p < 0.001). The preoperative GFR was also lower (75.0 versus 80.7 mL/min/m^2, p = 0.02), which may be a combination of more advanced age and higher likelihood of associated comorbidities that would steer treatment away from PN. They also had a longer mean follow up time than PN (56.7 months versus 42.2 months, p < 0.001) due to the extended follow up recommended for patients undergoing RFA. These differences may have rendered RFA patients at higher risk for GFR decline following treatment. On the other hand, RFA patients also had smaller tumors which may have resulted in less collateral damage of surrounding normal parenchyma during treatment. Finally, our study was limited to GFR comparison, an endpoint that does not consider oncologic control or overall survival outcomes.

Conclusions

Less than 20% of patients undergoing nephron-sparing therapies have chronic kidney stage progression with extended follow up. Both PN and RFA appear to effectively preserve renal function. While multiple factors, including tumor size, location, proximity to the renal hilum, surgeon experience, patient comorbidity and patient preference dictate the choice of PN or RFA for each patient, the findings in this manuscript provide assurance that similar renal function outcomes are possible with either approach. ☐

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