Partial Nephrectomy Is Associated with Improved Overall Survival Compared to Radical Nephrectomy in Patients with Unanticipated Benign Renal Tumours

Christopher J. Weight, Gregory Lieser, Benjamin T. Larson, Tianming Gao, Brian R. Lane, Steven C. Campbell, Inderbir S. Gill, Andrew C. Novick, Amr F. Fergany

Glickman Urologic and Kidney Institute, Cleveland Clinic, Cleveland, Ohio, USA

Abstract

Background: Partial nephrectomy (PN) has been associated with improved overall survival (OS) in select cohorts with localised renal masses when compared to radical nephrectomy (RN). The driving forces behind these differences have been difficult to elucidate given the heterogeneity of previously compared cohorts.

Objective: Compare OS in a subset of patients with unanticipated benign renal masses to minimise the confounding effect of cancer.

Design, setting, and participants: We retrospectively evaluated 2608 consecutive clinical T1 enhancing renal masses that were treated with extirpative surgery at our institution between 1999 and 2006. Of these, 499 tumours (19%) were found to be benign on final pathology. Preoperative data and renal functional data were used to generate a propensity model that was then plugged into a multivariate model of survival. Median follow-up for the entire cohort was 50 mo (interquartile range [IQR]: 32–73).

Intervention: All patients underwent PN or RN.

Measurements: We measured OS and cardiac-specific survival.

Results and limitations: Five-year OS estimates for the PN (n = 388) and RN (n = 111) cohorts were 95% (95% confidence interval [CI], 93–98) versus 83% (95% CI, 74–90), respectively (P < 0.0001). On multivariate analysis, controlling for both comorbidity and age, RN was associated with a 2.5-fold increased risk of death compared to PN (hazard ratio [HR]: 2.5; 95% CI, 1.3–5.1). Postoperative estimated glomerular filtration rate (eGFR) was also an independent predictor of OS and cardiac-specific survival (HR: 0.97; 95% CI, 0.95–0.99 and HR: 0.96; 95% CI, 0.93–0.99, respectively). The retrospective nature of this analysis limits the strength of the conclusions.

Conclusions: PN was associated with better OS when compared to RN in patients with unanticipated benign tumours. This observed survival advantage appears partly to be the result of better preservation of eGFR, but other kidney functions or unmeasured factors may also play a role. These data indicate that PN should be aggressively pursued in any patient where PN is technically feasible.
1. Introduction

A good deal of research has attempted to compare survival in patients undergoing extirpative surgery for localised renal masses treated by either partial nephrectomy (PN) or radical nephrectomy (RN) [1–8]. These comparisons have been challenging to interpret because of small numbers, nonrandomisation, and selection bias. Although some have found PN to be associated with better overall survival (OS) and have hypothesised that this result is because of better preservation of renal function, the strength of these claims has been limited by the lack of renal function outcomes in the models and the preponderance of larger, more aggressive tumours found on final pathology in the RN cohort [1,3,6,9]. We therefore set out to study the effect of surgery type on cardiac-specific survival and OS in a cohort of patients who underwent surgery for enhancing renal masses suspected of being malignant but on final pathology were benign. By focusing on the unanticipated benign renal tumours, we have removed the confounding effect of cancer-specific death from our analysis and can better understand whether PN—and its attendant preservation of renal function—contributes to a survival benefit compared to RN.

2. Methods

2.1. Patient data and follow-up

From 1999 to 2006, 2608 patients with an enhancing cT1 renal mass underwent surgery. Though certain imaging and patient characteristics heighten our suspicion of a benign renal tumour, we have tended to regard enhancing renal masses as likely malignant and proceed with extirpation in most cases. Of these patients, 499 (19%) were found to have unanticipated benign tumours, including all patients either treated by RN (n = 111) or PN (n = 388). Perioperative and pathologic data were obtained from our internal review board–approved institutional kidney cancer patient registry. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study equation (GFR in ml/min per 1.73 m2 = 186 × serum creatinine [sCr] − 1.154 × age − 0.203 × (0.742 if female) × (1.210 if black).

Choice of extirpative surgery was left to surgeon and patient preference after consideration of tumour size, radiographic appearance, overall patient health, life expectancy, and surgeon comfort. Comorbidity was evaluated using the Charlson-Romano Comorbidity Index or the Age-adjusted Charlson Comorbidity 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. Cardiac-related deaths included deaths attributable to ischemic heart disease, congestive heart disease, ischemic stroke, and peripheral vascular disease (International Classification of Disease, 9th Edition [ICD-9] codes 398, 402, 410–1, 414, 428, 433–4, 436, and 440; ICD, 10th Edition [ICD-10] codes I10–3, I20–I25, I46, I48, I50–1, I63–4, I69–71, and I73). Renal failure deaths were those deaths in which renal failure, renal insufficiency, or nephritic syndrome played a role in the patient’s death as determined by the physician pronouncing the patient dead and including the codes (N03, N17–19).

2.2. Statistics

Because these groups were not randomised, we used a propensity score model, including only preoperative clinical parameters to control for selection bias. The propensity to undergo PN was calculated using a multivariable logistic regression model and the following predictive variables: age, tumour size, surgery type (laparoscopic vs open), solitary kidney status, and Charlson Comorbidity Index. Each patient was then assigned a propensity score based on these preoperative characteristics. The patients were stratified into similar risk quintiles based on propensity scores and compared according to treatment group within each quintile in order to calculate a hazard ratio (HR) of OS.

A Cox multivariate hazard analysis of OS was performed using both renal function outcomes and propensity scores to attempt to control for both pre- and postoperative predictors of survival. Cardiac-specific survival analysis was limited by only 14 events, allowing only univariate analysis.

Proportions were analysed by $\chi^2$ or Fisher exact test as indicated. The Wilcoxon/Kruskal-Wallis test was used to compare nonparametric continuous data, and the Student $t$ test was used if the data were parametric. The Kaplan-Meier analysis was used to evaluate OS, along with the log-rank test. A random coefficient mixed-effect model was used to fit the observed decrease in eGFR after surgery as demonstrated previously [10]. All patients had at least one pre- and postoperative sCr measurement. The drop in eGFR was calculated by first modelling all preoperative sCr values, generating a line, and projecting it toward the day of surgery. All postoperative sCr values starting 3 wk after surgery were also modelled. This model demonstrated that the entire decline in renal function associated with surgery occurred within the first 3 wk. After this postoperative steady state was reached, no statistically significant decline in renal function was noted (data not shown). Therefore, the drop in eGFR associated with extirpative surgery could then be calculated by taking the difference between the preoperative eGFR obtained by extrapolating a line forward to the day of surgery (based on preoperative measurements) and the postoperative eGFR, obtained by extrapolating a line backward to the day of surgery.

HRs and their 95% confidence intervals (CI) were reported. A two-sided $p$ value $\leq 0.05$ was considered statistically significant. All analyses for this study were performed using SAS (SAS Institute, Cary, NC, USA) or JMP 8.0 (SAS Institute, Cary, NC, USA) statistical software.

3. Results

As expected in a nonrandomised cohort, there were significant differences between the groups (Table 1), with those selected for RN more likely to be older, have higher comorbidity scores, have larger tumours, and be treated by laparoscopic surgery. Those with solitary kidneys were much more likely to be treated by PN. Each of these variables significantly predicted the propensity score.

Renal preservation was optimised in the PN cohort, with the majority of patients treated by PN maintaining an eGFR above 60 (65%), compared with only 30% of the RN cohort ($p < 0.0001$). The average drop in eGFR was more than twice as great in the RN cohort (22.3 vs 10.1 ml/min per 1.73 m2; $p < 0.0001$).

Median follow-up for the entire cohort was 50 mo (interquartile range [IQR]: 32–73), and there were 40 deaths from any cause. On univariate analysis, using both the log-rank analysis (Fig. 1) and the Cox proportional hazards model (Table 2), RN was significantly associated with an increased risk of death from any cause (HR: 3.6; 95% CI,
When stratified according to propensity score class and combined into a multivariate Cox proportional hazards model, patients with unanticipated benign renal tumours treated by RN were still 2.5 times more likely to die from any cause than those treated by PN. Postoperative eGFR was also an independent predictor of OS (Fig. 2) and accounted for some but not all of the survival advantage associated with PN (HR: 0.97 per unit loss of eGFR; 95% CI, 0.95–0.99).

### Table 1 – Perioperative characteristics of the 499 patients with unanticipated benign tumors stratified according to treatment type

<table>
<thead>
<tr>
<th></th>
<th>Radical (n = 111)</th>
<th>Partial (n = 388)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics: mean (IQR) or no. (percentage)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr (range)</td>
<td>68 (57–76)</td>
<td>62 (53–71)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Male gender, no. (%)</td>
<td>59 (57)</td>
<td>209 (56)</td>
<td>0.96</td>
</tr>
<tr>
<td>Preoperative tumour size, cm (range)</td>
<td>4 (3.0–5.2)</td>
<td>2.7 (2.0–3.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Preoperative eGFR, ml/min per 1.73 m² (range)</td>
<td>75.0 (59–91.3)</td>
<td>78.3 (64.8–91.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>Average decrease in eGFR at 95% CI, no. (range)</td>
<td>22.3 (19.4–25.2)</td>
<td>10.1 (8.6–11.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Charlson Group, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>67 (78)</td>
<td>284 (81)</td>
<td>0.5</td>
</tr>
<tr>
<td>&gt;2</td>
<td>19 (22)</td>
<td>65 (19)</td>
<td></td>
</tr>
<tr>
<td>Preoperative coronary artery disease, no. (%)</td>
<td>17 (22)</td>
<td>45 (13)</td>
<td>0.06</td>
</tr>
<tr>
<td>Solitary kidney, no. (%)</td>
<td>2 (2)</td>
<td>30 (8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Laparoscopic, no. (%)</td>
<td>74 (67)</td>
<td>172 (44)</td>
<td></td>
</tr>
<tr>
<td>Pathology, no. (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiomyolipoma</td>
<td>18 (16)</td>
<td>89 (23)</td>
<td>0.4</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>61 (55)</td>
<td>199 (51)</td>
<td></td>
</tr>
<tr>
<td>Benign cyst/multiocular cysts</td>
<td>1 (1)</td>
<td>6 (2)</td>
<td></td>
</tr>
<tr>
<td>Other benign lesions (eg, adenoma, inflammatory mass, hematoma)</td>
<td>31 (28)</td>
<td>94 (24)</td>
<td></td>
</tr>
<tr>
<td>Median follow-up, mo (IQR)</td>
<td>52.1 (36–76)</td>
<td>49.6 (32–73)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

IQR = interquartile range; eGFR = estimated glomerular filtration rate; CI = confidence interval.

### Table 2 – Unstratified univariate and stratified multivariate Cox proportional hazards analysis of overall survival, stratified according to propensity score class

<table>
<thead>
<tr>
<th>Stratifier</th>
<th>Factor</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No propensity Score adjustment</td>
<td>RN vs PN</td>
<td>3.6</td>
<td>1.9–6.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Postoperative GFR</td>
<td>0.96</td>
<td>0.95–0.98</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propensity score class</td>
<td>RN vs PN</td>
<td>2.5</td>
<td>1.1–5.3</td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td>Postoperative GFR</td>
<td>0.97</td>
<td>0.95–0.99</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval; RN = radical nephrectomy; PN = partial nephrectomy; GFR = glomerular filtration rate; eGFR = estimated glomerular filtration rate.

* For each unit of eGFR loss, there was a 3% decrease in survival.

Fig. 1 – Kaplan-Meier analysis of overall survival in 499 patients with unanticipated benign renal tumours stratified according to treatment type. OS = overall survival; PN = partial nephrectomy; RN = radical nephrectomy.

Fig. 2 – Kaplan-Meier analysis of overall survival stratified according to postoperative estimated glomerular filtration rate. OS = overall survival; eGFR = estimated glomerular filtration rate.

1.9–6.7).
Sixteen cardiac-related deaths occurred in this cohort. The risk of cardiovascular death was significantly higher for those with decreasing postoperative renal function (HR: 0.96 per unit loss of eGFR; 95% CI, 0.93–0.99; Fig. 3).

4. Discussion

Previous analyses of the role that postoperative renal insufficiency may play in the OS of patients with renal mass have been somewhat clouded by the nonrandomisation of patients and the heterogeneous pathologic stage of tumours [1–9,11]. Nearly every report to date that attempts to control for this, there remains some uncertainty that statistical models can adequately eliminate these obvious confounding factors. Therefore, we set out to study a subset of patients who had clinical T1 enhancing renal masses on preoperative imaging but benign tumours on final pathology. Even today, the absence of cancer on biopsy is invariably an uncertain finding until the general medical patient [14]. We believe that patients with kidney tumours are not captured in our multivariate propensity analysis that favoured survival for those in the PN cohort or that some function of the kidney beyond filtration may be contribut-
ing to a survival advantage in these patients. Although this study was not designed to look at this issue in particular, we note that erythropoesis and vitamin D regulation are also markedly different in large part on the kidney, and it merits discussion and study to determine whether perturbations in these systems may have deleterious effects.

We were also surprised to find that this cohort of patients commonly died from some additional malignant tumour. It is known that sometimes renal cell cancer is associated with benign renal tumours such as oncocytoma [18], but 38% of these patients died from tumours from various organ systems (Table 3), and it is unclear whether this was merely a spurious observation or whether benign renal tumours may be part of a larger syndrome.

In this cohort of patients with benign tumours, cardiovascular death was the most common cause of death. When treating a patient with a cT1 renal mass, even if the mass turns out to be malignant, it is important to remember that most patients will die of some other cause [19], many of which appear to be worsened by renal insufficiency. This finding appears to be especially true of those patients with benign renal masses. The increased risk of death associated with RN in this cohort was much higher than that observed in our previously published malignant cohorts (HR: 2.5 vs 1.25) [8].

Obviously, the ideal scenario would be to not operate at all for a benign tumour, but unfortunately, the identification of benign histology is invariably an uncertain finding until final pathology. Even today, the absence of cancer on biopsy cannot always guarantee that malignant pathology in the
same lesion was merely not missed on biopsy. It is recognised that in certain cohorts with renal lesions, the chance of the tumour being benign is significant. These patients include those with fat density on computed tomography (CT) scan (−20 Hounsfield units), those with Bosniak 2F and 3 lesions [20], and younger women with solid tumours [21]. In these cases, every effort should be made to perform a PN [22]. It seems prudent, given the excellent cancer-specific outcomes noted with PN, always to attempt a PN in patients where it is technically feasible, because a significant portion (20%) of enhancing renal masses will harbour no malignancy. We note that most clinical T1 tumours are “technically amenable” to PN, and 1904 of 2608 (73%) of this cohort were treated by PN.

This study is limited by its retrospective nature and the fact that the cohorts were not randomised. There were obvious selection differences between the cohorts, and although we attempted to control for these differences, it remains possible that selection bias may explain some of the survival differences. We note, however, that a randomised trial of benign renal tumours would be impossible, given the fact that the diagnosis is not confirmed until after surgery.

5. Conclusions

The better renal preservation associated with PN was associated with better cardiac-specific survival and OS when compared to RN in patients who were found to have unanticipated benign tumours. In light of the observations that a substantial proportion of patients with unanticipated benign renal tumours stand to benefit markedly from PN and the excellent cancer control PN has demonstrated in patients with malignant tumours, taken collectively, these data argue that a patient with a cT1 renal tumour appears to be best served by PN whenever technically feasible.

Author contributions: Amr F. Fergany had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Weight, Fergany, Novick, Lane, Gill.

Acquisition of data: Weight, Lieser, Larson, Lane, Gill, Novick.

Analysis and interpretation of data: Weight, Gao, Lane, Campbell, Fergany.

Drafting of the manuscript: Weight, Lane, Campbell, Fergany.

Critical revision of the manuscript for important intellectual content: Weight, Lieser, Larson, Gao, Lane, Campbell, Gill, Fergany.

Statistical analysis: Gao, Weight.

Obtaining funding: None.

Administrative, technical, or material support: None.

Supervision: Fergany.

Other (specific): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Acknowledgement statement: The authors acknowledge Wei Liao, Mary Federico, and Kay Tucker for their assistance with database management.

References


