Does an unexpected presence of non-organ disease at final pathology undermine cancer control in clinically T1N0M0 renal cell carcinoma patients who underwent partial nephrectomy?

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Abstract

**Background:** A non-negligible proportion of individuals diagnosed with cT1 renal cell carcinoma (RCC) is upstaged to pT3a at final pathology. Few data on oncologic outcomes of these patients are available to determine whether partial nephrectomy (PN) might jeopardize cancer control.

**Objective:** To assess, within an international multi-institutional collaboration, whether PN might undermine cancer control relative to radical nephrectomy (RN) in RCC patients with unexpected pT3a disease.

**Design, Setting, and Participants:** International multi-institutional collaboration including patients with cT1abN0M0-pT3a RCC.

**Intervention:** PN or RN.

**Outcome Measurements and Statistical Analysis:** Kaplan-Meier analyses, before and after propensity-score matching, evaluated differences in metastatic progression (MP) and cancer-specific mortality (CSM) rates during follow-up. Univariable and multivariable Cox regression analyses assessed predictors of MP and CSM.

**Results and limitations:** Overall, 309 RCC cT1abN0M0 RCC patients [cT1aN0M0 (n=107, 34.6%), cT1bN0M0 (n=202, 65.4%)] harboured pT3a disease at final pathology. Patients were treated with either PN (n=71, 23%) or RN (n=238, 77%). MP at 1, 2 and 5 years was detected in 9.1, 13.3 and 24.1%, respectively. CSM at 1, 2 and 5 years was observed in 3.5, 10.7 and 18.4%, respectively. After matching, no difference in terms of MP or CSM was observed between PN and RN cohorts (both p>0.3). At multivariable analysis, type of surgery (PN vs. RN) was neither an independent predictor of MP (p=0.3) nor of CSM (p=0.4). Limitations include the retrospective design.
Conclusions: In patients with unexpected pT3a RCC at final pathology, PN does not appear to jeopardize cancer control with regard to MP and CSM.

Patients summary: Cancer control is similar between patients treated with the removal of the entire kidney or only with a partial nephrectomy, even if the final histological examination demonstrates a tumor which is surprisingly non-confined within the kidney.
Introduction

The majority of patients currently diagnosed with renal cell carcinoma (RCC) harbour small, organ-confined disease[1]. In this setting, international urological guidelines recommend different management options, ranging from surveillance to nephron-sparing surgery, such as partial nephrectomy (PN) [2-4]. In small renal masses, PN reduces the risk of cardiovascular morbidity[5] and is associated with better functional outcomes[6-10], compared to radical nephrectomy (RN), without compromising cancer control[11]. That being said, a non-negligible proportion of individuals treated with PN shows invasion of perirenal, sinus fat tissue or involvement of the inner renal blood vessels at final pathology and thus are upstaged to stage pT3a[12-14]. The clinical impact of such upstaging is debated. Additionally, few small studies formally evaluated the impact of the surgical approach (PN vs. RN) on oncologic outcomes among patients with cT1 disease who experienced upstaging to pT3a and refer to extremely limited patient cohorts[12-14].

To overcome this gap, we relied on the largest multi-institutional cohort of clinical T1abN0M0 RCC patients treated with PN or RN that harboured an unexpected pT3a disease at final pathology. We hypothesized that PN does not compromise cancer control in this subset of patients relative to RN.
Methods

Study population

In the current retrospective analysis, we relied on a multi-institutional database of surgically treated RCC individuals that comprises 10 European tertiary care centers. Specifically, the study cohort consisted of individuals diagnosed with RCC and treated with either RN or PN between 1988 and 2015. All individuals were preoperatively staged as cT1N0M0 and were staged as pT3a at final pathology. Individuals with bilateral kidney cancer, as well as individuals with monolateral multifocal tumors were not considered.

Clinical and pathological evaluation

TNM stages were assigned according to the 2009 American Joint Committee on Cancer/Union Internationale Contre le Cancer classification (AJCC/UICC)[2]. Cases before the introduction of the most recent classification scheme were reclassified. Clinical tumor size was based on preoperative imaging and defined as the greatest tumor diameter in centimetres. Stage cT1 was defined in accordance to the 2009 TNM classification for RCC: tumor of 7 cm or less in the greatest dimension, limited to the kidney and without radiographic signs of extension to the perinephric tissue or the major veins[2]. Surgery was performed within 3 months from clinical staging. All specimens were evaluated by experienced uro-pathologist at each single treating institution. Patients were evaluated at 3 months after surgery and, subsequently, with individualized follow-up schedules that in any case comprised of at least two annual visits.

Outcomes
Co-primary outcomes were metastatic progression (MP) and cancer specific mortality (CSM). MP was defined as retroperitoneal nodal recurrence or systemic recurrence (skeletal and/or visceral relapse) at imaging during follow-up. Patients who died from RCC were defined as having CSM. CSM was defined by the attending urologist or oncologist who followed the patient and/or by death certificates.

**Statistical analyses**

Initially, descriptive statistics were used to categorize the baseline characteristics among patients treated with either PN or RN. Frequencies and proportions were reported for categorical variables. Mean, medians and interquartile ranges were reported for continuously coded variables. Mann-Whitney U test and Chi square test tested the statistical significance of differences in medians and proportions, respectively.

Secondly, the effect of treatment type (PN vs. RN) on MP and CSM was assessed in the overall cohort. Actuarial survival rates at various time points after PN vs. RN were calculated.

Thirdly, to account for possible differences between the two groups that might be related to differences in the surgical approach, propensity-score matching was performed. Specifically, propensity scores were computed by a logistic regression model that evaluated the odds of receiving PN vs. RN according to clinical tumor size, age and year of surgery. The nearest-neighbour method, with a caliper width of 0.2 of the standard deviation of the logit and a 1-to-1 matching ratio, was used. After matching, Kaplan-Meier plots were used to graphically depict the observed survival rates between the matched cohorts. Differences in the rates of MP and CSM were tested with the log-rank test.
Finally, to test the hypothesis that treatment type (PN vs. RN) may affect the risk of MP and CSM after surgery, multivariate Cox regression analyses were performed in the unmatched cohort by adjusting for all clinical and pathological covariates.

All statistical tests were two-sided with a level of significance set at $p<0.05$. Analyses were performed using SPSS version 20 (IBM Corp., Somers, NY, USA) for statistical computing and R software environment for graphics (version 3.3.0; http://www.r-project.org/).
Results

Overall, among 3,863 patients with a clinically-defined diagnosis of T1abN0M0 RCC, 309 (8%) harboured pT3a disease at final pathology \([cT1aN0M0 \text{ (n=107, 34.6%)}, cT1bN0M0 \text{ (n=202, 65.4%)}]\). Patients were treated with either PN \((n=71, 23\%)\) or RN \((n=238, 77\%)\). Relative to RN, PN cases were treated more recently \((p<0.001, \text{Table 1})\), have smaller diseases \((\text{median tumor size: 3.0 vs 5.5 cm, p<0.001})\) and lower percentage of high Fuhrman grade \((G3-4: 29.6 \text{ vs. } 47.1\%)\). PN was performed with open vs. laparoscopic vs. robotic approach in 72.9\% vs. 2.8\% vs. 24.3\%, respectively. RN was performed with open vs. laparoscopic vs. robotic approach in 60.7\% vs. 36.5\% vs. 2.8\%, respectively. No differences were recorded between the two groups as regards patients’ age and presence of necrosis or sarcomatoid features \(\text{Table 1}\). pT3a was defined for the presence of only perirenal fat invasion in 82.1\% vs. 43.6\% in PN vs. RN patients, respectively \((p<0.001)\) \(\text{Table 1}\). Only 6 patients \(1.9\%)\) demonstrated positive surgical margins at final pathology \((0.8 \text{ vs. } 5.6\% \text{ in RN vs. PN, respectively, p=0.01})\).

After a mean follow-up of 52 months \((55 \text{ months for RN patients vs. } 43 \text{ months for PN counterparts})\), local recurrence was recorded in 6 cases \(2.8\%)\) vs. 2 cases \(2.9\%)\) in RN vs. PN cases, respectively. MP at 1, 2 and 5 years was observed in 9.1, 13.3 and 24.1\%, respectively \((\text{Figure 1A})\). CSM at 1, 2 and 5 years was observed in 3.5, 10.7 and 18.4\%, respectively \((\text{Figure 2A})\). After matching, no difference in terms of MP or CSM was observed between PN and RN counterparts \((\text{both p>0.3})\) \((\text{Figures 1B-2B})\).

In the multivariable analyses predicting MP, clinical tumor size \(\text{HR 1.4; 95\%CI 1.0-1.8; p=0.02})\) and sarcomatoid features \(\text{HR: 4.3; 95\%CI: 1.1-16.3; p=0.003})\) were independent predictors. In the multivariable analyses predicting CSM, age at surgery...
(HR: 1.1; 95%CI: 1.0-1.1; p=0.005) and clinical tumor size (HR 1.4; 95%CI 1.1-1.9; p=0.03) were independent predictors. Type of surgery (PN vs. RN) was neither an independent predictor of MP nor of CSM (p=0.3 and p=0.4, respectively; Table 2).
Discussion

International guidelines recommend that RCC patients with organ confined tumors should undergo PN whenever technically feasible, which allows adequate cancer control and the preservation of functional parenchyma [2-4]. Based on these recommendations benefits regarding the general health of the patients during the follow-up period have been well established [5][6-10][11].

Though, preoperative assessment of clinical stage may sometimes underestimate the actual tumor burden leading to a pathological upstaging with potential detrimental effect on patient’s prognosis related to pathological tumor stage [16]. Roughly 10-20\% of patients with clinically organ defined disease staged cT1N0M0 show an unexpected non-organ confined disease at final pathology (pT3a) due to the presence of microscopic invasion of the renal vein and/or of the perirenal/sinus fat [14,17,18]. CT scan has demonstrated a sensitivity of 59–88\% and specificity of 71–93\% in predicting the presence of pathological T3 disease[19]. Moreover, if such an upstaging occurs in patients who underwent PN, it has been advocated that cancer control could be jeopardized relative to RN [12-14,20].

Many reports have already assessed potential predictors of unfavourable characteristics at final pathology in patients treated with PN [18,20][21]. For instance, Gorin and colleagues evaluated the early oncological endpoint of recurrence-free survival in patients with RCC up-staged from cT1 to pT3a but only in the specific setting of robotic PN [13]. Only 41 patients (4.8\%) were up-staged to pT3a. The 24-month recurrence-free survival estimates for cT1-pT3a tumors were 99.2\% and 91.8\%, respectively (p=0.003) [13]. Factors associated with tumor up-staging included high tumor complexity (nephrometry score), increasing preoperative tumor diameter and hilar location [13]. Similarly, Ball et al. investigated the predictors
associated with adverse pathology, defined as pathologically high grade and/or pT3a disease, among 771 cT1 RCC cases [18]. Male gender, tumor size larger than 4 cm and high tumor complexity score resulted independent predictors of adverse pathology following PN [18]. These studies and others focused on upstaging only; however, very little data comparing cancer control of PN and RN in upstaged patients is available. Nayak et al. assessed the risk of progression in The Canadian Kidney Cancer Information System including 1,448 clinically defined T1 RCC[14]. Overall, 134 patients had disease upstaging to pT3a (PN vs. RN, n=66 vs. n=68). After a median follow-up of 23 months, the 3-year recurrence free survival (RFS) was 76% in upstaged patients compared with 93% in those not upstaged (p<0.001) [14]. Unfortunately, multivariable analyses comparing the effect of PN vs. RN in the subgroup of patients with upstaging were not achievable, due to a limited sample size [14]. Jeldres and colleagues performed a multi-institutional matched comparison between PN (n=30) and RN (n=63) demonstrating no significant cancer-specific survival differences after PN for pT3a lesions (HR: 2.5, p=0.9) [22]. Due to the small cohort size, a sub-analysis of cT1N0M0 patients could not be undertaken [22].

Sub-analyses of cT1 patients are rarely reported in literature, and exclusively in small cohorts of patients. Oh et al. carried out a retrospective comparison of PN vs. RN for pT3a M0 RCC patients who had undergone surgery at five institutions in Korea (2000-2010) [12]. There was a subgroup analysis of 63 cT1a patient upgraded to pT3a patients with similar the recurrence-free survival rates between PN and RN cases [12].

To the best of our knowledge, the present study evaluated the largest patient cohort available to date for the current topic. We are unaware of previous reports based on larger patient samples, as well as no previous analysis that relied on
propensity-score matched cohorts. Several questions might be raised by the current study. First, although future investigations are needed to draw a definitive conclusion, it might be asked whether the use of frozen sections during PN is needed in patients with clinical low risk, organ confined and small renal masses, when similar oncologic outcomes might be expected regardless of the surgical procedure. Second, it might be hypothesized that completion nephrectomy might not necessary in patients with unexpected non-organ confined disease at final pathology. Third, it appears that the surgical procedure should not be contemplated when assessing the most adequate follow-up schedule after surgery. Unfortunately, all those hypotheses can be formally validated only in prospective settings which are nowadays unapproachable.

Our study is not devoid of limitations. First, the retrospective nature of the current study must be considered. In consequence, it is conceivable that unmeasured variables that pertained to patient characteristics might have affected the results. Second, we observed the RN group represented individuals with larger and possibly more complex tumors, for which surgical challenges might have influenced the decision to perform RN instead of PN. Additionally, PN patients were more represented in the later years of the current study. However, year of surgery was included in our multivariable analyses to adjust for potential biases related to different lengths of follow-up. Third, the lack of central review for imaging and pathology specimen evaluation must be considered, as well. Specifically, the ability to correctly perform an adequate clinical staging depends on the imaging technique (computed tomography vs. magnetic resonance imaging), as well as the experience of the radiologist and the protocols in effect at each single institution.
Conclusions

Utilising a large multi-institutional cohort of cT1N0M0 RCC patients, this study aimed to define whether PN might undermine cancer control when an unanticipated pT3a is finally found at final pathology. In this specific scenario, despite the presence of an unexpected non-organ confined disease, PN does not seem to jeopardize cancer control.
Acknowledgements
None

Conflict of interest
None
Table 1: Clinical and pathological characteristics of 309 patients treated with NSS or RN for a clinically defined cT1abN0M0 RCC and a pathologically unexpected pT3a disease. Data were further stratified according to treatment type (PN vs. RN).

<table>
<thead>
<tr>
<th>Variable</th>
<th>PN (n=71, 23%)</th>
<th>RN (n=238, 77%)</th>
<th>p-value</th>
</tr>
</thead>
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<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>67 (60-76)</td>
<td>66 (58-74)</td>
<td>0.6</td>
</tr>
<tr>
<td>Year of surgery</td>
<td>2010 (2006-2012)</td>
<td>2006 (2001-2009)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>3.0 (2.2-4.4)</td>
<td>5.5 (4.2-6.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical T stage</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cT1aN0M0</td>
<td>53 (74.6%)</td>
<td>54 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>cT1bN0M0</td>
<td>18 (25.4%)</td>
<td>184 (77.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Pathological features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT3a subclassification</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PFI only</td>
<td>82.1%</td>
<td>43.6%</td>
<td></td>
</tr>
<tr>
<td>SFI only</td>
<td>14.9%</td>
<td>24.1%</td>
<td></td>
</tr>
<tr>
<td>PFI+SFI or PFI/SFI+RVI</td>
<td>3.0%</td>
<td>32.3%</td>
<td></td>
</tr>
<tr>
<td>Surgical margins</td>
<td>5.6%</td>
<td>0.8%</td>
<td>0.01</td>
</tr>
<tr>
<td>Fuhrman grade 3-4</td>
<td>29.6%</td>
<td>47.1%</td>
<td>0.009</td>
</tr>
<tr>
<td>Sarcomatoid features</td>
<td>1.5%</td>
<td>1.8%</td>
<td>0.8</td>
</tr>
<tr>
<td>Necrosis</td>
<td>26.1%</td>
<td>37.6%</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Legend: MP: Metastatic Progression; CSM: Cancer Specific Mortality; SFI: Sinus Fat Invasion; PFI: Perinephric Fat Invasion; RVI: Renal Vein Invasion; PN: Partial Nephrectomy; RN: Radical Nephrectomy
Table 2: Multivariable Cox regression analyses predicting MP and CSM. 95% confidence intervals are provided.

<table>
<thead>
<tr>
<th>Variables</th>
<th>MP</th>
<th></th>
<th>CSM</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>p</td>
<td>HR (95%CI)</td>
<td>p</td>
</tr>
<tr>
<td>Age</td>
<td>1.0 (1.0-1.1)</td>
<td>0.07</td>
<td>1.1 (1.0-1.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Year of surgery</td>
<td>1.0 (0.9-1.0)</td>
<td>0.6</td>
<td>1.0 (0.9-1.1)</td>
<td>0.5</td>
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<tr>
<td>Tumour size</td>
<td>1.4 (1.0-1.8)</td>
<td>0.02</td>
<td>1.4 (1.0-1.9)</td>
<td>0.03</td>
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<tr>
<td>Fuhrman grade 3-4</td>
<td>1.9 (0.9-3.8)</td>
<td>0.08</td>
<td>1.8 (0.8-4.2)</td>
<td>0.2</td>
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<tr>
<td>Sarcomatoid features</td>
<td>4.3 (1.1-16.3)</td>
<td>0.03</td>
<td>4.7 (0.8-25.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Necrosis</td>
<td>1.1 (0.6-2.3)</td>
<td>0.7</td>
<td>1.2 (0.5-2.7)</td>
<td>0.7</td>
</tr>
<tr>
<td>pT3a subclassification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFI only vs. PFI only</td>
<td>0.9 (0.3-2.3)</td>
<td>0.2</td>
<td>0.6 (0.2-2.0)</td>
<td>0.7</td>
</tr>
<tr>
<td>PFI+SFI or PFI/SFI+RVI vs. PFI only</td>
<td>1.7 (0.8-3.6)</td>
<td>0.9</td>
<td>0.9 (0.4-2.3)</td>
<td></td>
</tr>
<tr>
<td>Surgical margins</td>
<td>2.3 (0.3-18.4)</td>
<td>0.9</td>
<td>2.7 (0.4-15.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>Treatment type</td>
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<tr>
<td>PN vs. RN</td>
<td>0.5 (0.1-1.8)</td>
<td>0.3</td>
<td>0.6 (0.1-2.3)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Legend: MP: Metastatic Progression; CSM: Cancer Specific Mortality; SFI: Sinus Fat Invasion; PFI: Perinephric Fat Invasion; RVI: Renal Vein Invasion; PN: Partial Nephrectomy; RN: Radical Nephrectomy
Figure 1: Kaplan-Meier analyses depicting metastatic progression-free survival according to surgical treatment (partial vs. radical nephrectomy) a) before propensity-score matching and: b) after propensity-score matching.

Figure 2: Kaplan-Meier analyses depicting cancer-specific mortality-free survival according to surgical treatment (partial vs. radical nephrectomy) a) before propensity-score matching and: b) after propensity-score matching.
References


