Should patients with low risk renal cell carcinoma be followed differently after nephron-sparing surgery versus radical nephrectomy?

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Complete List of Authors:	Abu-Ghanem, Yasmin; Chaim Sheba Medical Center Powles, Thomas ; Barts Cancer Institute Capitanio, Umberto; IRCCS Ospedale San Raffaele Beisland, Christian; Haukeland University Hospital, Department of Urology Järvinen, Petrus; HYKS sairaanhoitopiiri Stewart, Grant; University of Cambridge, Department of Surgery Gudmundsson, Eirikur; Landspitali haskolasjukrahus, Urology Lam, Thomas; Aberdeen Royal Infirmary, Department of Urology Marconi, Lorenzo; Hospital and University Centre of Coimbra Fernandez-Pello, Sergio; Hospital de Cabueñes, Urology Nisen, Harry; Helsinki University Central Hospital, Abdominal Center, Urology Meijer, Richard; The Netherlands Cancer Institute - Antoni van Leewenhoek Hospital, Urology Volpe, Alessandro; Hospital Maggiore della Carità Ljungberg, Börje; Umeå University, Department of Surgical and Preoperative Sciences, Urology & Andrology Klatte, Tobias; Medical University of Vienna, Department of Urology Bensalah, Karim; Dept. of Urology Dabestani, saeed; Lund University Department of Clinical Sciences Malmo Bex, Axel; Netherlands Cancer Institute, Urology
Keywords:	Radical nephrectomy, partial nephrectomy, renal cell carcinoma, follow up, RECUR, survival, guidelines
Abstract:	Objective: To investigate whether pT1-renal cell carcinoma (RCC) should be followed differently after partial (PN) or radical nephrectomy (RN) based on a retrospective analysis of a multi-centre database (RECUR). Subjects: Retrospective study of 3380 patients treated for nonmetastatic RCC between January-2006 and December-2011 across 15 centres from 10 countries, as part of the RECUR-database project. For patients with pT1 clear-cell RCC (ccRCC), patterns of recurrence were compared between RN and PN according to recurrence site. Univariate and multivariate models were used to evaluate the association between surgical approaches and recurrence-free survival (RFS) and cancer-specific mortality (CSM).

	Results: From the database 1995 patients were identified as low-risk patients (pT1,pN0,pNx), of whom 1055 (52.9%) underwent PN. On multivariate analysis, features associated with worse RFS included tumour size (HR1.32, 95%CI 1.14-1.39,p<0.001), nuclear grade (HR 2.31, 95% CI 1.73-3.08, p<0.001), tumour necrosis (HR 1.5, 95%CI 1.03-2.3, p=0.037), vascular invasion (HR: 2.4 95%CI 1.3-4.4, p=0.005) and positive surgical margins (HR 4.4, 95%CI 2.3-8.5, p<0.001). Kaplan-Meier analysis of CSM revealed that the survival of patients with recurrence after PN was significantly better than those recurring after RN (p=0.02). While the above-mentioned risk factors were associated with prognosis, the type of surgery alone was not an independent prognostic variable for RFS nor CSM. Limitations include the retrospective nature of the study. Conclusion: Our results showed that follow-up protocols should not rely solely on stage and type of primary surgery. An optimized regimen should also include validated risk factors rather than the type of surgery alone, to select the best imaging modality and to avoid unnecessary imaging. A follow-up of more than three years should be considered in patients with pT1 tumours after RN. A novel follow-up strategy is proposed.

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*These authors contributed equally to the work

(1) Specialist Centre for Kidney Cancer, Royal Free London NHS Foundation Trust, UCL Division of Surgical and Interventional Science, London, UK.
(2) Barts Cancer Institute, Queen Mary University of London, London, UK.
(3) Division of Experimental Oncology, Urological Research Institute (URI), IRCCS Ospedale San Raffaele, Milan, Italy
(4) Department of Urology, Haukeland University Hospital, Bergen, Norway and Department of Clinical Medicine, University of Bergen, Bergen, Norway.
(5) Abdominal Center, Urology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland.
(6) Department of Surgery, University of Cambridge, Cambridge, UK.
(7) Department of Urology, Landspitali University Hospital, Reykjavik, Iceland.
(8) Academic Urology Unit, University of Aberdeen, Aberdeen, UK.
(9) Department of Urology, Coimbra University Hospital, Coimbra, Portugal.
(10) Department of Urology, Cabueñes University Hospital, Gijón, Spain.
(11) Department of Oncological Urology, University Medical Centre Utrecht, Utrecht, The Netherlands.
(12) Department of Urology, University of Eastern Piedmont, Maggiore della Carità Hospital, Novara, Italy.
(13) Department of Surgical and Perioperative Sciences, Umeå University, Umeå, Sweden.
(14) Department of Urology, Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust, Bournemouth, UK.
(15) Department of Urology, University Hospital of Rennes, Rennes, France.
(16) Dept. of Translational Medicine, Division of Urological Cancers, Central Hospital Kristianstad, Lund University, Lund, Sweden.
(17) Department of Urology, Netherlands Cancer Institute, Amsterdam, The Netherlands;

Corresponding author: Axel Bex, MD, PhD
Specialist Centre for Kidney Cancer, Royal Free London NHS Foundation Trust, UCL Division of Surgical and Interventional Science, Pond Street London NW3 2QG, UK. a.bex@ucl.ac.uk

Editor-in-Chief: BJU International

Prof. Freddie Hamdy

Dear Prof. Hamdy,

Thank you for consideration of our manuscript entitled " Should patients with low-risk renal cell carcinoma be followed differently after nephron-sparing surgery versus radical nephrectomy?" for publication in 'BJU International'.

We are grateful for the BJU International reviewers for pointing out several elements that needed clarification and correction; the changes and additions that we made using the reviewer's comments as guidelines are added in the text.

Referee: 1

Comments to the authors
The authors present an interesting and well written analysis of treatment and disease factors that influence RCC patient outcomes after radical and partial nephrectomy. The major strength of this analysis is its large multi-institution database, which affords generalizability and significant power to detect modest effect sizes. A major proposal by these authors is that post-nephrectomy surveillance should be altered from current national guidelines based on these findings. However, I struggle with interpreting the evidence in a way that provides substantial evidence for their proposed algorithm as outlined in Figure 5. Furthermore, a lot of their analysis focuses on outcomes stratified by PN or RN nephrectomy yet the authors themselves note that these associations are likely driven significantly by patient selection factors that cannot be easily adjusted. Thus trivializing in large part Fig 1-3. Finally, for a manuscript that seeks to define FU strategies after nephrectomy there is nothing mentioned about follow up strategies in these patients.

We thank the reviewer for his comments. Although we agree that differences in outcomes between PN and RN are likely to be driven by patient selection factors (i.e. indication bias, which is inherent in retrospective studies), our study findings support our main conclusion which is that planning follow-up schedules based on tumour stage and type of surgery alone as recommended by current AUA guidelines is sub-optimal, because there is significant variation in outcomes within each stage and surgical type. We have also attempted to adjust for known confounders and performed appropriate analyses, which mitigates the risk of indication bias somewhat although it is not eliminated. This has been acknowledged as a limitation. Secondly, in terms of specifying the different follow-up strategies within all centres involved in the RECUR study, identifying differences between different follow-up strategies was not the aim of the study, and indeed the study was not designed to investigate this issue. Regardless of specific strategies, essential information regarding the timing and nature of clinical and imaging follow-up were available for all included patients, and allowed comprehensive data analysis.

Major Point:
As the major point of this article as outlined by its title is to assess the follow up imaging protocols it may be helpful for the authors to describe the follow up procedures conducted in this patient dataset and their influence on outcomes. Given the range of institutions represented in this dataset I'm sure one

could find examples of different FU strategies and compare their outcomes which would be a much more direct approach to addressing their thesis.
A part of the author's rationale for this manuscript is an assertation that there are different FU routines supported by AUA and NCCN guidelines based on nephrectomy type. As far as I can tell in ver1.2021 NCCN kidney cancer guidelines there doesn't seem to be a distinction in FU guidelines after partial vs radical nephrectomy. Furthermore, AUA guidelines for "Follow-up for clinically localized Renal Neoplasms" (published in 2013) appear to be very similar regardless of whether patients receive partial vs radical nephrectomy, honestly one could do the same follow up schedule in a patient who received RN vs PN and follow AUA guidelines.

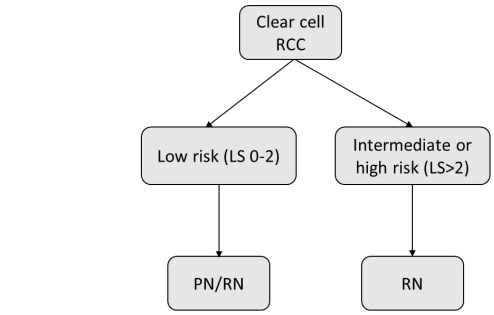
First, regarding the NCCN guidelines, the previous guidelines (2018) included a different follow up protocol for PN and RN. A recommendation that has recently been changed to include all nephrectomies, as the reviewer mentioned, therefore the referral to these guidelines was modified accordingly. Nevertheless, the NCCN, like the AUA stratifies a follow up regimen that is based solely on tumor stage which, as we tried to show, is inaccurate and insufficient. Moreover, we believe that the updated NCCN guidelines further emphasize the importance of the comparison between PN and RN outcomes in this manuscript. Patients who undergo these procedures are different, the pathology is different and hence the oncological outcomes. Therefore, we believe that pulling patients together based on stage alone is again, incorrect. In regard to the AUA, it is true that the differences seem minor, however, as mentioned in the text, the proposed frequency and length of abdominal imaging is different whereas the chest imaging seems uniform, regardless to the patterns of recurrence. We acknowledge the limitation of a retrospective study and hope that our ability to demonstrate the variability associated with stage alone may lead to a better "tailored" follow up approach. The text has been changed and revised accordingly.

The authors make interesting points regarding the patterns of recurrence in RN vs PN. However, it would be helpful if some simple statistical tests were used to test whether these differences with statistically significant. For example, authors state that more contralateral kidney recurrences occur in patients who received PN vs RN. This could be easily tested using a Fisher Exact or Chi-squared test.

Thank you for your comment. We agree that such analysis may enhance the manuscript and hence we have added a table (Table 3).

I find the proposed FU algorithm concerning (Fig. 5). There doesn't seem to be much analyses specifically directed towards non-clear cell RCC histologies yet there are recommendations presented here. Of particular concern is that for non-clear cell histologies pT1N0/X treated with RN, no abdominal imaging is recommended after 6 months FU. There are plenty of aggressive RCC histologies that frequently metastasize in the abdomen. Also why is there a grey box around 4 to >5yr for non-clear cell pT1,N0,Nx.

We thank the reviewer for this comment and agree. Since the analysis of "low risk" patients was performed based on LS for ccRCC patients only, the proposed FU algorithm will focus on this subset



Follow up	PN/RN	RN
6mo	Abd CT$^{\alpha}$	Abd CT$^{\alpha}$ Chest CT
1y	Abd CT$^{\alpha}$ Chest CT$^{\alpha}$	Abd CT$^{\alpha}$ Chest CT
2y	Abd CT/Us$^{\alpha}$	Abd CT$^{\alpha}$ Chest CT$^{\alpha}$
3y	Abd CT$^{\alpha}$ Chest CT $^{\alpha}$	Abd CT$^{\alpha}$ Chest CT$^{\alpha}$
4y	Abd CT/US$^{\alpha}$	Abd CT$^{\alpha}$ Chest CT$^{\alpha}$
5y	Abd CT$^{\alpha}$ Chest CT$^{\alpha}$	
>5y	If clinically indicated	CT every 2y

of patients only, and we have removed any reference to non-ccRCC patients.

Minor Point: in all the figures 1-3 the at-risk table labels the groups as RN and PN, while the image key labels the groups RN and NSS. Consider keeping the labels the same.
Thank you for the comments. Figures were changed accordingly.

There are several grammatical mistakes that should be corrected.
Thank you for the comments. The manuscript has been reviewed and corrected.

Referee: 2

Comments to the authors
Interesting work with a lot of patients. Who are the 15 institutions that contributed to the data? They should either be reflected in the author list or in the acknowledgement.

Thank you for your comment. It was our intention to reflect all institutes in author list. Following your comment, we in fact realized that one of them was missing. We have added the author and his affiliation following his approval of the manuscript.

The authors conclude that : A follow-up of more than three years should be considered in patients with pT1 tumours after RN.
They also state that the type of surgery alone was not an independent prognostic variable for RFS nor CSM. So I don't see this conclusion supported by the findings.
According to the results a longer FU should be recommended independent of type of surgery.

Thank you for comment. We agree that the discrepancy between PN vs RN in terms of late recurrence may have been due other confounding factors, since type of surgery was not an independent prognostic variable, although they were in univariate analysis. However, we believe that lack of independence does not negate the findings that RN has a higher risk of late recurrence, especially since this conclusion was based on controlling for stage. The reason for this loss of independence may be due to small sample bias.

UISS should be discussed.

Thank you for your comment. However, in the current study, we chose to focus on LS since it is one of the most widely used risk stratification tools in Europe and was the risk score selected for data collection in the RECUR registry. We avoided using other models in order to simplify our conclusion regarding the need for additional variables (other than tumor stage) when deciding on follow-up protocol. In addition, we believe that none of the models, whether Leibovich, UISS or SSIGN, has been shown to be superior to the other in head-to-head comparison and a systematic review of these models yielded similar accuracy (area under the curve, AUC) for the models.

Fig 4: I don't see any data or discussion for this figure. What should it tell us? Is there a correlation or not. Needs further explanation or should be omitted as histology is not mentioned to be influential. But I would wish for some data/comment/explanation about this (also in the tables)
We do make reference to Figure 4 on Pages 9 and 10.

Fig: 5: Recommendation for 6 moths scanning does not seem to be supported by data and needs to be omitted or justified otherwise.
This recommendation is based on the EAU guidelines (as marked in the figure) (see EAU Guidelines, RCC Table 8.1: Proposed surveillance schedule following treatment for RCC, taking into account patient risk profile and treatment efficacy (based on expert opinion [LE: 4]). We agree that the level of evidence is low, but this applies to all guidelines and we did not want to omit recommendations by the EAU RCC guideline panel and which are in the public domain.

Fig 1S: typo: contries
Thank you, typo was corrected.

Referee: 3

Comments to the authors
This is a retrospective multi centre assessing factor impacting recurrence after renal cancer surgery and aims to asses best method of follow up.
The main issue is variability in pathology/radiology and follow up assessment across the centres and this is further hampered by small number of events which is expected given the nature of cases. Subsequent extensive analysis of such small events along with inherit differences in factors influencing decision regarding PN vs RN all have an impact on the observed results.

Ultimately no new information is provided.

Essentially aggressive biology is likely to predict poor income and perhaps also likely dictate surgical treatment RN vs PN. the decision re Pn vs RN is impacted by expertise of the centre and complexity of the tumour (RENAL score for eg) which is not accounted for by the authors.

We agree with the reviewer's comments regarding the inherent biases in this retrospective cohort. We also acknowledge the limitation of a retrospective study and the lack of defined complexity.

Nevertheless, we disagree that no new information is provided. The objective of the current study was to examine the present follow-up protocols in an attempt to offer a "preferred" follow up regimen. As mentioned in the study, the current AUA and NCCN guidelines base the risk of recurrence, and hence the follow-up protocol, on stage alone. As the reviewer mentioned, there are multiple factors that may affect the complexity of the surgery and prognosis. In our study we showed that simply referring to 'T1' is not enough to define the tumor as "low risk" and by that potentially may risk missed recurrences. We agree that the key factor is tumor biology. However, in the current tools that we have this is poorly reflected and therefore we urge clinicians to take all factors, including necrosis/ grade into consideration and to not base the follow up protocol on stage or type of surgery alone.

Referee: 4

Comments to the authors
Authors presents a large multiinstitutional series with >5 year median follow-up in patients who underwent renal surgery.
Importantly n is large (~3,000), median follow up is long, and pattern of recurrence is documented.
Manuscript is concise and well-written.
Important contribution that has a value-added over current literature, especially since it highlights the reality that not only the guidelines themselves but also definitions within the guidelines such as AUA, NCCN, and EAU differ.

We thank the referee for these comments and feedback.

Referee: 5

Comments to the authors
This is an interesting study attempting to address the proper follow up strategies for patients with low risk RCC who underwent radical vs partial nephrectomy. While it is reasonable to use commonly used abbreviations, there are a lot of not-so-commonly used abbreviations which should be replaced with full terms to make the manuscript more readable.

Thank you for this comment. The manuscript was revised and edited and some of the abbreviations were omitted.

Comments:
1. This study include a large number of patients but given the retrospective nature of this database, the analysis is subject to bias. Given this large number of patients, it may be helpful to include a matched propensity score analysis comparing the endpoints in patients who had RN vs PN and this may help validate the current observations, rendering the conclusions more robust.

We thank the reviewed for these valid points. Propensity-score matching is a means of accounting and adjusting for known baseline confounders. We have performed multivariable regression analysis including important baseline confounders, which similarly accounts and adjusts for confounders. The main advantage of multivariable regression in our cohort is that it does not lead to a significant reduction in sample size, thereby potentially reducing event rates and exaggerating small sample size bias.

2. The curves of Figures 1-3 are not properly labeled. What is NSS (red curve)?

Thank you for this comment. We refer to Nephron sparing surgery. A comment was added to the figure legends.

3. The algorithm in figure looks sound. There seems to be something missing in the column under LS >2 (5 y).

Thank you for your comment. Since a CT is recommended every 2 years, a comment was added ("every 2 years") to the subsequent line.

Additional comments from reviewers about ethics:

Referee: 1

Ethics: This paper appears to be from a database that was already published. It would benefit from a specific statement regarding IRB approval.

Thank you for this point. All participating centers had indeed appropriate IRB approval as was previously mentioned in the earlier RECUR publications. The manuscript has been revised accordingly.

Referee: 2

Ethics: No ethics concerns

Referee: 3

Ethics: no issues

Referee: 4

Ethics: no issues

Referee: 5

Ethics: The author may want to explain the RECUR process in terms of how the ethical and privacy issues were addressed.

We have added the following line to the manuscript: all participating centres had appropriate institutional review board approval. Also, all data were anonymized and no patient-identifiable features were included in the database.

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*These authors contributed equally to the work

(1) Specialist Centre for Kidney Cancer, Royal Free London NHS Foundation Trust, UCL Division of Surgical and Interventional Science, London, UK.
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(3) Division of Experimental Oncology, Urological Research Institute (URI), IRCCS Ospedale San Raffaele, Milan, Italy
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(5) Abdominal Center, Urology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland.
(6) Department of Surgery, University of Cambridge, Cambridge, UK.
(7) Department of Urology, Landspitali University Hospital, Reykjavik, Iceland.
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(13) Department of Surgical and Perioperative Sciences, Umeå University, Umeå, Sweden.
(14) Department of Urology, Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust, Bournemouth, UK.
(15) Department of Urology, University Hospital of Rennes, Rennes, France.
(16) Dept. of Translational Medicine, Division of Urological Cancers, Central Hospital Kristianstad, Lund University, Lund, Sweden.
(17) Department of Urology, Netherlands Cancer Institute, Amsterdam, The Netherlands;

Corresponding author: Axel Bex, MD, PhD
Specialist Centre for Kidney Cancer, Royal Free London NHS Foundation Trust, UCL Division of Surgical and Interventional Science, Pond Street London NW3 2QG, UK. a.bex@ucl.ac.uk

Abstract:

Objective: To investigate whether pT1-renal cell carcinoma (RCC) should be followed differently after partial (PN) or radical nephrectomy (RN) based on a retrospective analysis of a multi-centre database (RECUR).

Subjects: Retrospective study of 3380 patients treated for nonmetastatic RCC between January-2006 and December-2011 across 15 centres from 10 countries, as part of the RECUR-database project. For patients with pT1 clear-cell RCC (ccRCC), patterns of recurrence were compared between RN and PN according to recurrence site. Univariate and multivariate models were used to evaluate the association between surgical approaches and recurrence-free survival (RFS) and cancer-specific mortality (CSM).

Results: From the database 1995 patients were identified as low-risk patients (pT1,pN0,pNx), of whom 1055 (52.9%) underwent PN. On multivariate analysis, features associated with worse RFS included tumour size (HR1.32, 95%CI 1.14-1.39,p<0.001), nuclear grade (HR 2.31, 95% CI 1.73-3.08, p<0.001), tumour necrosis (HR 1.5, 95%CI 1.03-2.3, p=0.037), vascular invasion (HR: 2.4 95%CI 1.3-4.4, p=0.005) and positive surgical margins (HR 4.4, 95%CI 2.3-8.5, p<0.001). Kaplan-Meier analysis of CSM revealed that the survival of patients with recurrence after PN was significantly better than those recurring after RN (p=0.02). While the above-mentioned risk factors were associated with prognosis, the type of surgery alone was not an independent prognostic variable for RFS nor CSM. Limitations include the retrospective nature of the study.

Conclusion: Our results showed that follow-up protocols should not rely solely on stage and type of primary surgery. An optimized regimen should also include validated risk factors rather than the type of surgery alone, to select the best imaging modality and to avoid unnecessary

imaging. A follow-up of more than three years should be considered in patients with pT1 tumours after RN. A novel follow-up strategy is proposed.

Keywords: Radical nephrectomy; partial nephrectomy; renal cell carcinoma; follow up; RECUR; survival; guidelines

Introduction:

Renal cell carcinoma (RCC) is the most common primary malignancy of the kidney, representing 2-3% of all adult cancers[1,2]. To date, surgical resection is the standard of treatment for localised tumour by either radical (RN) or partial nephrectomy (PN), depending mainly on tumour size, stage and anatomical location[3,4]. Regardless of the surgical approach, local and distant recurrence after nephrectomy for kidney cancer is not uncommon. Following surgical resection, the recurrence rates may reach up to 20%-40% following nephrectomy, up to 45 years after surgery[5–7]. Thus, surveillance and long-term follow-up for recurrent disease is recommended in those who have undergone curative resection.

Nevertheless, despite the increasing availability of treatment modalities offering improved survival in recurrent cases, there is still a discrepancy between existing surveillance protocols regarding the duration or the nature of follow-up in patients undergoing partial or radical resection. While the American Urological Association (AUA) renal cancer guidelines and the National Comprehensive Cancer Network (NCCN) guidelines[8,9] consider all pT1 tumours as low-risk for adverse oncological outcomes, the European Urology Association RCC guidelines (EAU)[2] relies on risk stratification. Moreover, the AUA guidelines offer more abdominal imaging during follow-up for PN compared to RN for this tumour stage, whereas the frequency of abdominal imaging in the EAU guidelines is not depending on the type of primary treatment.

Nevertheless, the type of surgery is influenced by more than the tumour stage only. While PN is the recommended treatment of choice for patients with T1 renal tumours, RN is advocated in some patients, mainly when PN is unsuitable, primarily due to tumour-related or patient-related reasons (unfavourable tumour location, significant co-comorbidities, or surgeon preference). Consequently, stage alone does not necessarily reflect the risk for recurrence. Given these discrepancies, we sought to characterize the risk factors and the patterns of recurrence following nephrectomy for pT1 renal cancer, which is defined as low risk by the AUA and NCCN

guidelines, and to evaluate the patterns of recurrence after both partial and radical nephrectomies, in order to investigate the impact of surgical approach on surveillance strategies, relying on a large multi-institutional consortium focusing on follow-up after surgery (i.e. the euRopEan association of urology renal cell carcinoma guidelines panel Collaborative multicenter consortium for the studies of follow-up and recurrence patterns in Radically treated renal cell carcinoma patients [RECUR]).

Patients and methods:

This retrospective analysis included data from 3380 patients who underwent a RN or PN for RCC between January-2006 to December-2011. All data were retrieved from the RECUR database, collected from 15 centres (all with appropriate institutional approval) in 10 European countries as described previously [10]. All participating centres had appropriate institutional review board approval. Also, all data were anonymized and no patient-identifiable features were included in the database. Clinicopathologic variables recorded included: year of surgery, age, gender, tumour stage, grade, size, RCC tumour subtype, Leibovich risk-score and individual number of risk points. Patients with ccRCC were stratified into low, intermediate, and high risk of recurrence groups according to Leibovich score (LS). Operative variables included the type of operation and surgical approach. Pathological variables included: surgical margin status, vascular invasion, tumour necrosis and presence of sarcomatoid differentiation. Patients with malignant tumours other than RCC and patients with metastatic disease upon diagnosis were excluded from this analysis. The primary outcomes assessed were disease recurrence (local ipsilateral recurrence, contralateral recurrence, or distant metastasis) and cancer-specific mortality (CSM). Local recurrence was defined as new tumour formation in the lumbar-fossa, remaining renal vein or inferior vena cava after radical nephrectomy and in the residual kidney after partial nephrectomy. Recurrence variables included the time of recurrence, type of recurrence (isolated local recurrence, solitary distant metastatic, oligometastatic (three or fewer lesions at a single site), or disseminated disease (dissemination to two or more sites)), presence of symptoms and imaging modality to detect recurrence. CSM was calculated from the date of diagnosis until either death due to RCC or date of the last follow-up. Recurrence-free survival (RFS) was calculated from the time of surgery until recurrence of tumour, death or date of the last follow-up. Time-to-recurrence (TTR) was calculated from the subtraction of Date of recurrence Event (DoE)–Date of Surgery (DoS) in months.

Patients with: metastatic disease upon diagnosis, hereditary disease increasing the risk of developing RCC (such as Von Hippel-Lindau, Birt-Hogg-Dubé syndrome and Hereditary Papillary Renal Cell Carcinoma), death during or shortly after hospitalisation. Patients with essential data missing (Date of Surgery, LS, UICC, event (recurrence), last follow-up/survival data) were excluded from the analysis (Figure 1S).

To investigate whether pT1 RCC should be followed differently after PN or RN, recurrence patterns were analysed for patients with pT1a-pT1b disease according to AUA and NCCN guidelines. Survival was estimated as the time from nephrectomy to event using the Kaplan-Meier method and compared between cohorts with the log-rank test. Separate analyses for CSM were also performed for patients with recurrence, measured from the onset of recurrence to either death or date of last follow-up, for the entire cohort and sub-groups. Variables that were statistically significant by univariate analysis were included in a multivariate analysis using the Cox-proportional hazards model.

Separate sub-group analyses were performed on patients with low-risk disease, stratifying patients into type of surgery (PN and RN) to evaluate risk factors associated with disease recurrence and CSM, and a separate analysis of patterns of recurrence. To evaluate if stratification by Leibovich low-risk group (Leibovich score 0-2) is superior to pT1, patients were further analysed based on risk groups. To avoid potential bias in the Leibovich-risk based analysis, we included only patients with clear cell RCC, *and* a calculated Leibovich score. All analyses were performed using Statistical Package for Social Sciences (SPSS, Version 25.0, Chicago, IL, USA). A p-value<0.05 was considered statistically significant.

Results:

1. Main analysis involving the entire cohort

A total of 3085 patients out of a total of 3380 in the database (i.e. 91.3%) were eligible for inclusion, of which 1969 (63.8%) patients underwent RN and 1116 (36.2%) underwent PN. Patient characteristics are displayed in Table 1, stratified according to surgical treatments. For the entire cohort, disease recurrence was detected in 544 (17.6%) patients, during a median post-operative follow-up of 59.8 months (IQR 36.7-79.1). Overall, most patients (69.4%) recurred during the first 3 years of follow-up, 18.6% recurred after 3-5 years, and the remaining 12% recurred after more than 5 years after surgery. Figure 1a shows the Kaplan-Meier curve for RFS stratified according to the type of surgery for the entire cohort. For RFS, PN had significantly better outcomes than RN (HR 6.18, 95%CI4.1-9.3), (Table 1S). Figure 1b shows the Kaplan-Meier curve for CSM stratified according to the type of surgery for the entire cohort. PN had significantly better outcomes than RN (HR 6.2, 95%CI(4.1-9.3), (Table S1). On multivariable analysis, the type of surgery was not associated with RFS nor CSM (Table S2). Kaplan-Meier analysis of CSM for patients with recurrence measured from the time of recurrence revealed that the survival time of patients following PN was significantly longer than patients who had undergone RN (p=0.01, Figure 1c).

2. Sub-group analyses

i. **pT1, N0, Nx disease as defined by AUA guidelines**

A total of 1995 patients with pT1N0M0 disease were identified, of which 1055 (52.9%) underwent PN and 940 (47.1%) underwent RN. Patient characteristics for this subgroup are displayed in Table 2. Most of the findings mirrored those of the main cohort's, except that sarcomatoid differentiation was no longer significantly different between both groups (p=0.052) although numerically, RN had a higher proportion of patients with sarcomatoid differentiation.

There were significantly more patients undergoing RN than PN for pT1b disease, adverse pathological characteristics including higher nuclear grade (p<0.001) and tumour necrosis (p<0.001), which remained significant despite controlling for tumour stage. On univariate-analysis, features associated with shorter RFS included: type of surgery (PN vs. RN), (p=0.04), size, grade, necrosis, vascular invasion and PSM (all p<0.001), (Table S3). The variables that remained significant on multivariate analysis included tumour size (HR:1.3, 95%CI(1.14-1.39), p<0.001), nuclear grade (HR:2.3, 95%CI(1.7-3.08),p<0.001), tumour necrosis (HR:1.5, 95%CI(1.03-2.3),p=0.037), vascular invasion (HR:2.4 95%CI(1.3-4.4), p=0.005) and PSM, (HR: 4.4, 95%CI(2.3-8.5),p<0.001), but not type of surgery (Table 4). Figure 2a shows the Kaplan-Meier curves for RFS stratified according to the type of surgery for patients with low-risk disease. Regarding the detection of recurrences, overall, 68.5% of the recurrences were asymptomatic and hence were detected incidentally during regular follow-up, whereas 29.1% were symptomatic upon diagnosis.

For CSM, the overall 5-year CSM for low-risk patients was 97%. On univariate analysis, CSM was associated with the type of surgery (0.003), tumour size, grade, and vascular invasion (all p<0.001). On multivariate analysis, CSM remained associated with tumour size (HR:1.36, 95%CI(1.1-1.68), p=0.004), tumour grade (HR:2.7 95%CI(1.73-4.2),p<0.001), and vascular invasion (HR:4.1, 95%CI(1.7-9.7),p=0.002), but not type of surgery. Figure 2b shows the Kaplan-Meier curves for CSM stratified according to the type of surgery. Kaplan-Meier analysis of CSM showed that patients with recurrence who had undergone PN had significantly better cancer-specific survival than patients with recurrence who had undergone RN (p=0.02, Figure 3a).

ii. Recurrence patterns based on the type of surgery for patients with low-risk disease

Further subgroup analysis was performed on patients with pT1,N0,Nx to determine recurrence patterns for each type of surgery.

a. RN

Among the 940 patients with low-risk disease treated with RN, 87 (9.3%) recurred at a median of 38.4 (IQR:15.6-60.1) months following surgery. Upon diagnosis, 26.1% of these patients had a solitary lesion, whereas 40.9% were diagnosed with disseminated disease. Observed RFS rates were 89% at 5 years. The two most common sites of recurrence were lung in 36 patients (42.4%), and bone in 20 (23.5%). The mean time to thoracic recurrence and specifically lung recurrence was 41.9±28 and 40.5±28.6 months, respectively. Lung metastasis was diagnosed after *more* than 3 years in 52.8% of patients (Figure 4a). *Solitary* lung metastasis was observed in 14 patients, 8 of those (57.1%) recurred after more than 3 years. The median TTR was 40.5 months (IQR:22-61). On univariate analysis, RFS was associated with tumour size, grade, tumour necrosis, vascular invasion (all p<0.001), (Table S4). On the multivariable Cox model, RFS remained associated with tumour size (HR:1.45, 95% CI(1.22-1.72),p<0.001), grade (HR:2.26, 95%CI(1.56-3.3),p<0.001), necrosis (HR:1.78, 95%CI(1.06-2.98),p=0.029) and vascular invasion (HR:3.89, 95%CI(1.97-7.6),p<0.001), (Table S5). Surgical margin status was not included in the analysis due to the small number of patients in this subgroup (3 of 940).

b. PN

Among the 1055 patients with low-risk disease treated with PN, 71 (6.7%) recurred at a median of 31.8 (IQR: 14.3-53.4) months following surgery. Upon diagnosis of recurrence, 42.9% of the patients had a solitary lesion, whereas 14.3% were diagnosed with disseminated disease. In contrast to RN, the most common site of recurrence was local recurrence in 22 patients (34.4%) followed by contralateral kidney in 21 (32.8%) of patients. The mean time for the detection of local recurrence and contralateral kidney metastasis was 38.4±27.4 and 49.3±27.4 months, respectively. Eleven of the 22 (50%) recurred after more than 3 years, (Figure 4b). Single-site local recurrence was observed in 18 of 22 patients, 9 (50%) recurred after more than 3 years, 4 after more than 5 years following surgery. Lung recurrence was observed in 13 patients

(20.6%), 2 of the 13 had simultaneous local recurrence and 11 of those (85%) recurred in the first 3 years of follow-up. Isolated lung recurrence was observed in 6 patients, all of which recurred in the first 3 years. Observed RFS rates at 5 years were 93%. On univariate analysis, RFS was associated with tumour grade (p<0.001) and PSM (p<0.001). On the multivariable Cox model, RFS remained associated with tumour grade (HR:2.82, 95%CI(1.86-4.28),p<0.001) and PSM (HR:4, 95% CI(2.12-7.6),p<0.001). On multivariate analysis, RFS was associated with nuclear grade (HR: 2.3, 95% CI(1.49-3.7),p=0.001), and PSM (HR: 3.85, 95%CI(2.04-7.24, p<0.001), (Table S5). Comparison of the patterns of recurrence between the two groups is presented in Table 3.

Sub-group analysis by Leibovich score 0-2

We performed additional analysis on risk grouping by Leibovich score (LS). A total of 2691 patients has clear cell RCC, *and* a calculated Leibovich score. Of those, 1555 patients (50.4%) had low-risk (i.e.LS 0-2) whilst 1136 (43.9%) had intermediate to high risk (LS of ≥3). Of the 1555 patients with low-risk, 641 (41.2%) and 914 (58.8%) patients underwent RN and PN, respectively. Patient characteristics and pathological tumour features were comparable between the two subgroups. The overall TTR and RFS were similar between the 2 groups. Regarding CSM, type of surgery was not associated with survival. Yet, CSM- analysis from the time of recurrence was significantly shorter in patients undergoing RN compared to PN (p=0.02, Figure 3b). Of the 553 patients in the RN group, 43 (7.8%) experienced disease recurrence at a median of 44.3 months (IQR:26.9-63.3). The most common site of recurrence was lung, in 18 patients (38.3%) at a mean time of 54.5±28.6 months. Of the 18 patients, 13 were diagnoses with lung metastasis after more than 3 years. Among the 914 patients undergoing PN, 61 (6.7%) recurred at a median of 34.95 (IQR:13.6-55.9) months following surgery. The most common site of recurrence was local recurrence in 33.9% of patients. Nine of the 19 (47.3%) local recurrence events were detected after more than 3 years after surgery.

Discussion:

In the current analysis, we examined whether the approach to surveillance after PN should be different compared to RN in the pT1 population as recommended by the AUA guidelines. According to the AUA, pT1 RCCs are considered low-risk and while imaging of the chest is recommended at low frequency, additional abdominal imaging is advised for patients after PN. Interestingly, the definition of low-risk disease varies among guidelines. While the surveillance protocol proposed by the EAU takes into account patients' risk profile assessed with one of the validated risk models [2,11], the NCCN and AUA guidelines recommend that patients should be stratified by TNM staging alone. Furthermore, the AUA also offers different patterns of surveillance according to the treatment received (RN, PN or ablation therapy) [9]. Looking exclusively at stage, at first glance, it appears sensible to combine the two surgical approaches. However, in the current analysis, we found that controlling for stage alone does not eliminate the innate differences between these two approaches, as patients undergoing RN still had higher nuclear grade and a higher rate of vascular invasion and necrotic tumors, all of which are not accounted for when patients are stratified solely by TNM staging and grouped collectively as pT1 (Table 2). These differences could probably explain the worse CSM observed in the analysis for RN patients after recurrence (Figure 3) as well as the worse RFS and TTR. This is remarkable because CSM from *treatment* to cancer-specific death does not show any difference, which may be explained by the overall low frequency of events in this group. Still, although the type of surgery affected both RFS and CSM on univariate analysis, it lost its prognostic significance on multivariate analysis.

Consequently, our data have conclusively shown that that the risk of recurrence and survival does not depend on stage and type of surgery alone, and that there are other independent prognostic variables which are more important. These findings are supported by our second analysis for patients with low LS. In this subgroup, the RN and PN patients were comparable,

meaning that if we choose to follow this definition of “low-risk" we could more reliably address the two approaches as one, given that the significant risk factors for survival are included in the core of the classification. The fact that the type of surgery was not an independent prognostic variable, but instead appeared to depend on established risk factors supports this assertion.

We found significant variations in the basic criteria between RN and PN that are known to affect prognosis in validated risk scores, such as the Leibovich risk model [12]. For example, in our analysis we showed that tumour size, grade, necrosis and vascular invasion were all significant risk factors for recurrence among T1 patients undergoing RN. In contrast, grade and PSM were risk factors in those who had PN. Hence, we could conclude that if we do prefer to choose staging as the primary criteria to distinguish between follow-up protocols, we should include the type of primary treatment, *as well as* the main prognostic factors for a more individualised and accurate follow-up.

In other words, we showed that by using the approach that depends solely on stage and type of surgery, we have too many biases that prevent us from tailoring the "best fit" protocol. For example, we cannot follow a patient with T1b, grade 3, with pathological necrosis that underwent PN due to CRF the same way we follow a T1a grade 1 tumor, just because they both underwent PN for T1/N0. Therefore, using a risk stratification tool allows us to follow the patients in a more accurate way. (Figure 5).

Nevertheless, in cases where we do not have validated risk classifications (pRCC for example) and hence have to rely on staging information alone, the type of surgery does indeed play a role since it reflects the complexity of the tumor and, as shown in our study, impacts on prognosis.

In the current study, we also found that the pattern of recurrence was different, as well as survival following recurrence. While lung, as expected, was the most common site of progression following RN, patients who underwent PN had significantly more local recurrences

as well as 'recurrence' to the contralateral kidney. Therefore, although the risk classification may be more accurate, and may not require separate follow-up based on the type of surgery alone to improve RFS, it may require such regimen to improve survival. We do, however, acknowledge the option that the differences in outcome could be attributed to other factors, for example, intra-parenchymal or hilar location as well as tumour complexity, all of which often necessitates RN, and may attribute to poorer prognosis [13,14].

Interestingly, while the higher frequency of local and contralateral recurrences following PN are addressed by more abdominal CT scans in the AUA guidelines, the higher frequency of thoracic metastases and development beyond three years after RN are not. This argues for follow-up recommendations that will include the relevant risk factors in combination with the primary treatment received, as well as the expected site of recurrence. For example, the risk of thoracic metastasis in the same Leibovich risk category, is more common after RN, suggesting that follow-up for these patients should be different. Moreover, RN and PN do not only differ in the rate of thoracic recurrence but in time of recurrence. In the current study, lung metastasis was diagnosed after more than three years after RN in 47% of patients (Figure 2), and isolated lung metastasis was observed in 16 patients, 7 of those (44%) recurred after more than three years. For PN, the rate of lung metastasis was significantly lower, and the majority recurred within the first three years. While more frequent follow-up imaging has not been shown to improve survival in RCC [10,15], these data suggest that patients with pT1 disease after RN should be followed longer than currently recommended, certainly beyond three years (Figure 5).

Limitations of this study include its retrospective design and the possible absence of data on potential factors that could have affected the choice between RN and PN in a low-risk population. Moreover, follow-up protocols at the hospitals involved in this study were not uniform. Also, the subgroup analysis of patterns of recurrences within the low-risk group of patients was restricted to a subset of the entire cohort (65%), in which the outcome only

affected 8% of this subset. Consequently, the findings are subject to small sample bias. Nevertheless, we believe there is enough evidence from the data to issue recommendations to tailor follow-up following surgery (Figure 5).

I. Conclusions:

Our data showed that the prediction factors provide independent prognostication regarding the estimation of RFS. Thus, current follow-up protocols should not rely solely on stage and treatment received as proposed by the AUA guidelines. An optimized regimen should include independent variables predicting recurrence based on the given treatment. Further, the type of follow-up after treatment should be based on the common sites of recurrence, in order to select the best imaging modality and to avoid unnecessary imaging. Finally, follow-up of the chest beyond three years should be considered in all patients who have undergone RN for pT1 tumours.

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Table 1: Baseline characteristics of the entire cohort of RCC patients included in main analysis (n=3085)

		RN (n=1969)	PN (n=1116)	p value
Age		64±12	61.1±11.9	0.43
Gender	Male	1259 (63.9)	354 (31.7)	0.015
	Female	710 (36.1)	762 (68.3)	
Side	Left	953 (50.1)	472 (44.1)	0.09
	Right	933 (49.1)	552 (55.5)	
	Both	15 (0.8)	47 (4.4)	
Size (cm)		6.87±3.5	3.2±1.6	<0.001
Stage	T1a	385 (19,6)	842 (75.4)	<0.001
	T1b	555 (28.2)	213 (19.1)	
	T2a	250 (12.7)	18 (1.6)	
	T2b	122 (6.2)	4 (0.4)	
	T3a	517 (26.3)	36 (3.2)	
	T3b	107 (5,4)	1 (0.1)	
	T3c	13 (0.7)	1 (0.1)	
	T4	20 (1)	1 (0.1)	
Grade	1	104 (5.8)	145 (16)	<0.001
	2	965 (54.2)	628 (69.2)	
	3	557 (31.3)	126 (13.9)	
	4	154 (8.7)	8 (0.9)	
Sarcomatoid differentiation		69 (3.7)	4 (0.4)	<0.001
Tumor necrosis		796 (42,4)	216 (20.1)	<0.001
Vascular invasion		391 (21.5)	38 (3.9)	<0.001
PSM		32 (1.7)	80 (7.4)	<0.001
Risk Score	Low risk	698 (35.4)	966 (86.6)	<0.001
	Int risk	682 (34.6)	113 (10.1)	
	High risk	589 (29.9)	37 (3.3)	

Table 2: Baseline characteristics of patients with low-risk disease (i.e. pT1N0Nx RCC) included in sub-group analysis (n=1995)

		RN (n=1055)	PN (n=940)	P value
Age		63.7±12	61.1±11.9	0.41
Gender	Male	590 (62.8)	723 (68.5)	0.07
	Female	350 (37.2)	332 (31.5)	
Side	Left	445 (48.4)	444 (43.8)	0.08
	Right	469 (51)	525 (51.8)	
	Both	6 (0.7)	45 (4.4)	
Size (cm)		4.5±.15	3.05±1.3	p<0.001
Stage	T1a	385 (41)	842 (79.8)	p<0.001
	T1b	555 (59)	213 (20.2)	
Grade	1	74 (8.7)	142 (16.5)	p<0.001
	2	581 (68.1)	606 (70.4)	
	3	180 (21.1)	109 (12.7)	
	4	18 (2.1)	5 (0.5)	
Sarcomatoid differentiation		9 (1)	3 (0.3)	0.052
Tumor necrosis		246 (27.7)	193 (19)	p<0.001
Vascular invasion		46 (5.3)	31 (3.4)	0.04
PSM		3 (0.3)	76 (7.4)	p<0.001

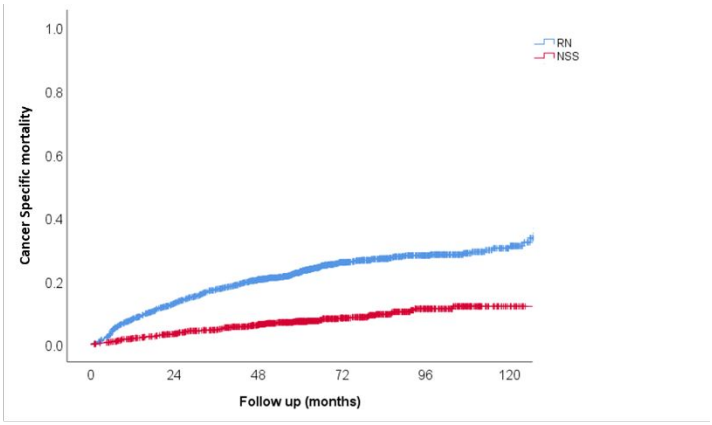
Table 3: Patterns of recurrence among low-risk disease (i.e. pT1N0Nx RCC) included in sub-group analysis (n=1995)

	RN (n=1055)	PN (n=940)	P value
Lung	36 (42.4%)	13 (20.3%)	0.005
Bone	20 (23.5%)	5 (7.8%)	0.01
Local recurrence	10 (11.8%)	22 (34.4%)	0.001
Contralateral kidney	8 (9.4%)	21 (32.8%)	<0.001
Liver	6 (7.1%)	0 (0%)	0.03

Table 4: Multivariate analysis of factors associated with tumor recurrence and Cancer-specific survival (CSS) in patients with pT1, N0, Nx RCC patients (n=1995)

Variable	Disease recurrence			CSS		
	HR	95% CI	P value	HR	95% CI	P value
Type of surgery (PN vs.RN)	1.27	0.80-2.01	0.303	1.02	0.47-2.2	0.963
Size (cm)	1.30	1.13-1.48	<0.001	1.36	1.10-1.6	0.004
Grade (high grade vs. low garde)	2.29	1.70-3.07	<0.001	2.72	1.73-4.2	<0.001
Tumor necrosis (yes vs. no)	1.54	1.02-2.31	0.037			
Vascular invasion (yes vs. no)	2.38	1.29-4.38	0.005	4.08	1.70-9.7	0.002
PSM (yes vs. no)	4.41	2.28-8.50	<0.001			

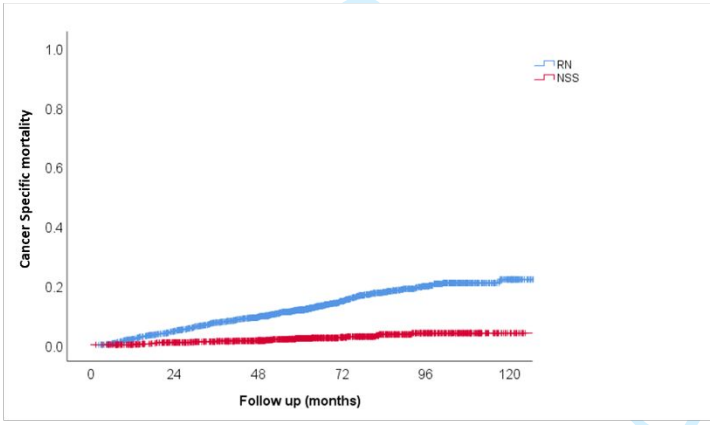
a



Patients at risk (n)

RN	1748	1573	1240	565	290	96
NSS	1057	991	809	367	161	30

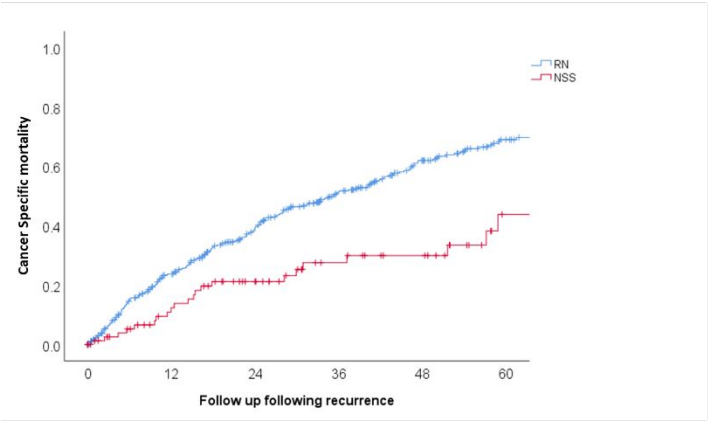
b



Patients at risk (n)

RN	1869	1738	1436	684	332	107
NSS	1078	1016	845	394	172	30

c

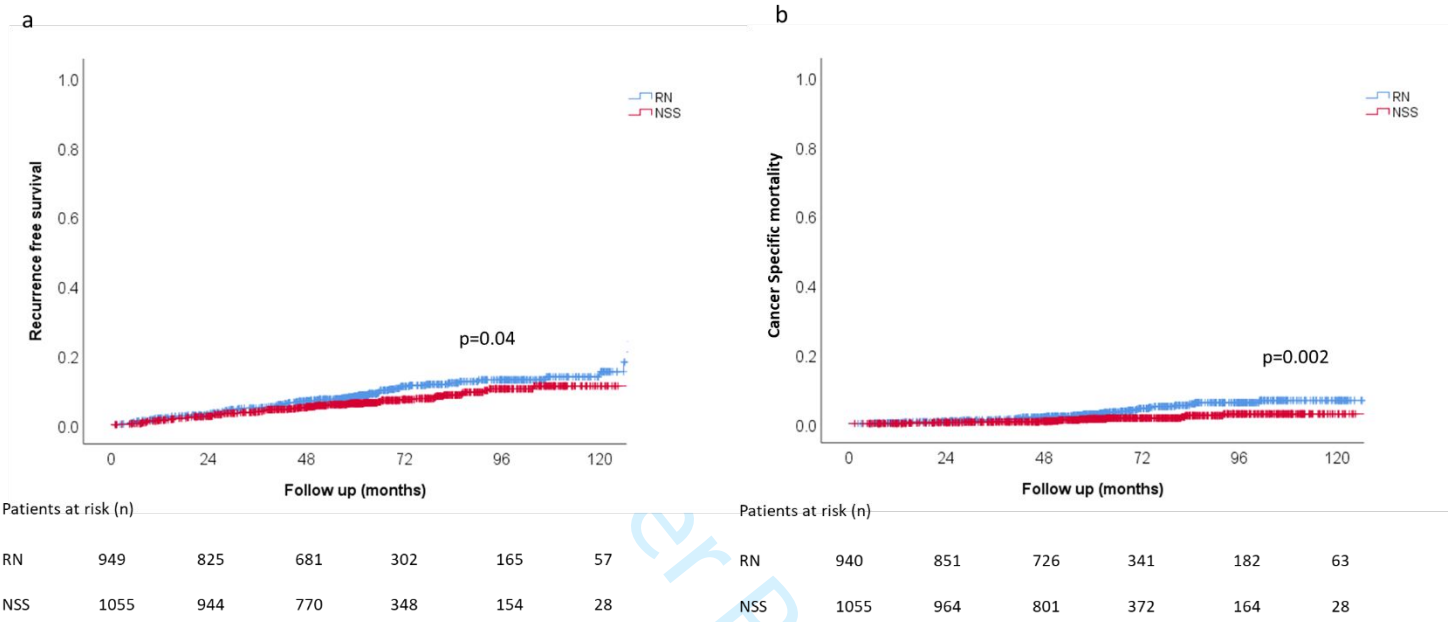


Patients at risk (n)

RN	460	316	222	147	88	46
NSS	85	60	44	30	24	9

Figure 1: Outcomes for entire cohort of RCC patients (n=3085) stratified according to type of surgery: (a) Recurrence-free survival; (b) Cancer-specific survival; and (c) Landmark analysis of CSM for patients with recurrence from the time of recurrence; RN- radical nephrectomy; NSS- nephron sparing surgery

Figure 2: Outcomes for patients with pT1, N0, Nx RCC patients (n=1995) stratified according to type of surgery: (a) Recurrence-free survival; and (b) Cancer-specific mortality; RN- radical nephrectomy; NSS- nephron sparing surgery



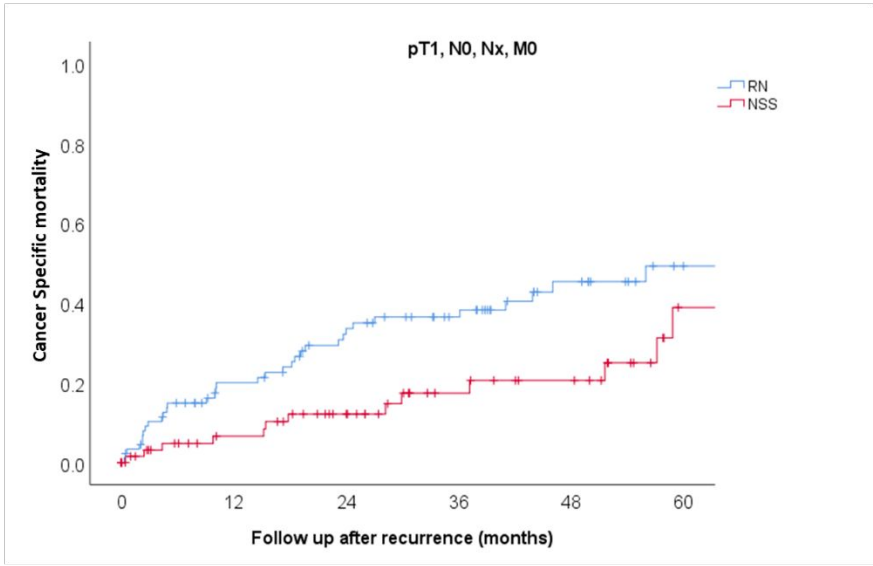
Patients at risk (n)

RN	949	825	681	302	165	57
NSS	1055	944	770	348	154	28

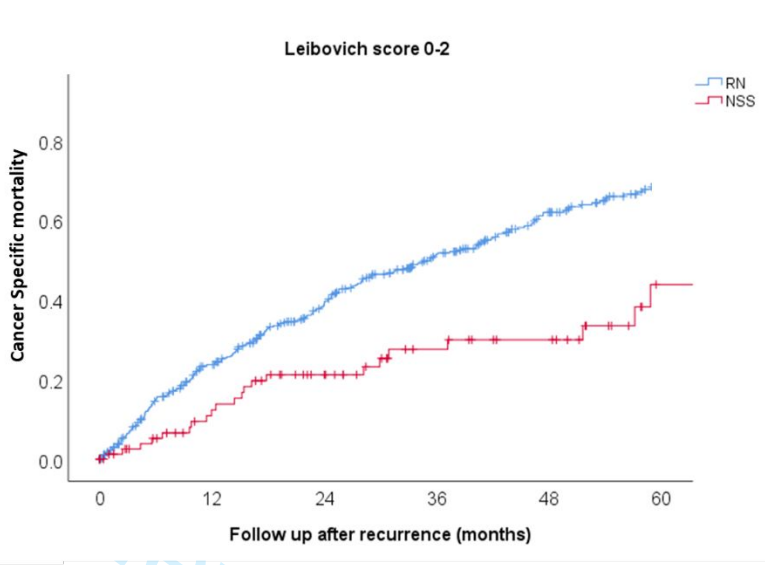
Patients at risk (n)

RN	940	851	726	341	182	63
NSS	1055	964	801	372	164	28

Figure 3: Landmark analysis of CSM from the time of recurrence stratified according to type of surgery for sub-group analysis of: (1) Patients with pT1, N0, Nx; and (2) Leibovich score 0-2 (n=1995 for both groups); RN- radical nephrectomy; NSS- nephron sparing surgery



Patients at risk (n)						
RN	89	62	47	36	21	8
NSS	70	51	39	26	21	7



Patients at risk (n)						
RN	49	30	23	17	11	6
NSS	61	45	35	23	18	6

Fig 4: Distribution of patients with (a) Lung metastasis following RN; and (b) Local recurrence following NSS, over time; RN- radical nephrectomy; NSS- nephron sparing surgery

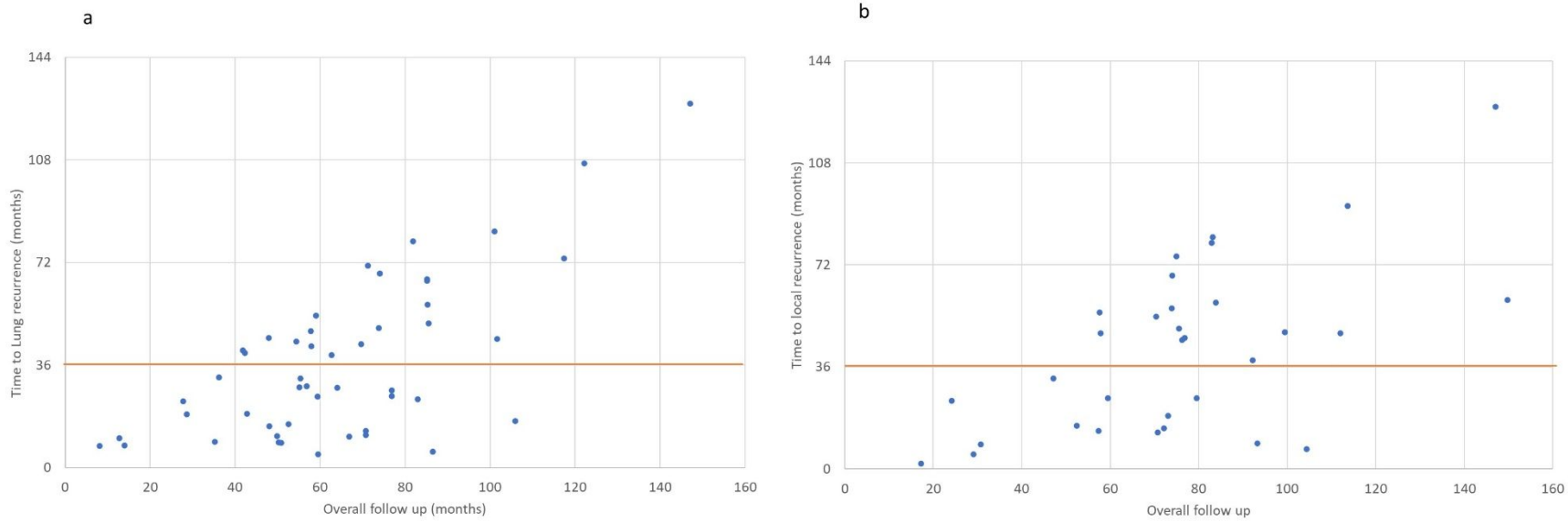
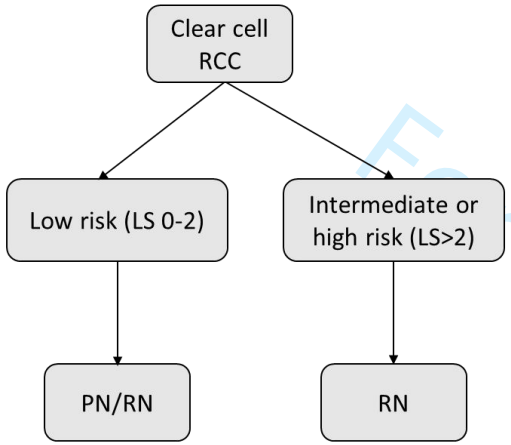


Figure 5: suggested follow-up algorithm in patients with RCC following nephrectomy



Follow up		
6mo	Abd CT$^{\alpha}$	Abd CT$^{\alpha}$ Chest CT
1y	Abd CT$^{\alpha}$ Chest CT$^{\alpha}$	Abd CT$^{\alpha}$ Chest CT
2y	Abd CT/Us$^{\alpha}$	Abd CT$^{\alpha}$ Chest CT$^{\alpha}$
3y	Abd CT$^{\alpha}$ Chest CT $^{\alpha}$	Abd CT$^{\alpha}$ Chest CT$^{\alpha}$
4y	Abd CT/US$^{\alpha}$	Abd CT$^{\alpha}$ Chest CT$^{\alpha}$
5y	Abd CT$^{\alpha}$ Chest CT$^{\alpha}$	
>5y	If clinically indicated	CT every 2y

$^{\alpha}$EAU guidelines; ^ AUA/NCCN guidelines; ‡ Current study; $^{\tau}$ CXR is an alternative to chest CT in circumstances where the latter is not feasible;

RCC- ranal cell carcimoma; EAU- European association of urology; AUA- American urology association; NCCN- National Comprehensive Cancer Network; CT- computed tomography; US- ultrasound; abd- abdomen; LS- Leibovich score

Table S1: Univariate analysis of factors associated with tumour recurrence and Cancer-specific mortality (CSM) in main cohort of RCC patients (n=3085)

Variable	Disease recurrence			CSM		
	HR	95% CI	P value	HR	95% CI	P value
Type of surgery (PN vs.RN)	3.3	2.6-4.2	<0.001	6.2	4.1-9.3	<0.001
Size (cm)	1.17	1.15-1.2	<0.001	1.19	1.16-1.2	<0.001
Tumor stage (<T2 vs. ≥T2)	1.65	1.6-1.7	<0.001	1.81	1.7-1.9	<0.001
Grade (high grade vs. low grade)	2.97	2.7-3.3	<0.001	3.46	2.97-4.03	<0.001
Tumor necrosis (yes vs. no)	3.5	2.9-4.2	<0.001	4.1	3.2-5.2	<0.001
Vascular invasion (yes vs. no)	4.45	3.7-5.4	<0.001	5.3	4.1-6.7	<0.001
PSM (yes vs. no)	3.17	2.3-4.3	<0.001	3.07	2.0-4.6	<0.001

*CMS- cancer specific mortality; PN-partial nephrectomy; RN-radical nephrectomy; PSM-positive surgical margins

Table 2S: Multivariate analysis of factors associated with tumour recurrence and Cancer-specific mortality (CSM) in main cohort of RCC patients (n=3085)

Variable	Disease recurrence			CSM		
	HR	95% CI	P value	HR	95% CI	P value
Type of surgery (PN vs.RN)	0.94	0.67-1.29	0.692	1.18	0.71-1.96	0.521
Size (cm)	1.065	1.03-1.09	<0.001	1.06	1.02-1.1	0.003
Tumor stage (<T2 vs. ≥T2)	1.31	1.22-1.41	<0.001	1.37	1.24-1.51	<0.001
Grade (high grade vs. low grade)	1.67	1.46-1.92	<0.001	1.97	1.63-2.36	<0.001
Tumor necrosis (yes vs. no)	1.77	1.43-2.19	<0.001	1.6	1.2-2.1	0.002
Vascular invasion (yes vs. no)	1.43	1.14-1.79	0.002	1.44	1.1-1.9	0.016
PSM (yes vs. no)	3.01	2.13-4.26	<0.001	2.3	1.4-3.6	<0.001

*CMS- cancer specific mortality; PN-partial nephrectomy; RN-radical nephrectomy; PSM-positive surgical margins

Table S3: Univariate analysis of factors associated with tumour recurrence and Cancer-specific mortality (CSM) in sub-group of pT1, N0, Nx RCC patients (n=1995)

Variable	Disease recurrence			CSM		
	HR	95% CI	P value	HR	95% CI	P value
Type of surgery (PN vs.RN)	0.74	0.53-0.98	0.04	0.4	0.22-0.73	0.003
Size (cm)	1.26	1.14-1.39	<0.001	1.41	1.2-1.67	<0.001
Grade (high grade vs. low grade)	2.52	1.96-3.24	<0.001	2.87	1.87-4.4	<0.001
Tumor necrosis (yes vs. no)	2.09	1.48-2.94	<0.001	1.8	0.96-3.4	0.066
Vascular invasion (yes vs. no)	3.42	1.96-5.96	<0.001	4.8	2.0-11.4	<0.001
PSM (yes vs. no)	3.54	2.1-5.95	<0.001	1.67	0.5-5.3	0.383

*CMS- cancer specific mortality; PN-partial nephrectomy; RN-radical nephrectomy; PSM-positive surgical margins

Table S4: Univariate analysis of factors associated with tumour recurrence in sub-group of pT1, N0, Nx RCC patients (n=1995) stratified according to type of surgery

Variable	RN (n=940)			PN (n=1055)		
	HR	95% CI	P value	HR	95% CI	P value
Size (cm)	1.38	1.2-1.6	<0.001	1.12	0.95-1.34	0.18
Grade (high grade vs. low grade)	2.41	1.72-3.37	<0.001	2.7	1.81-4.01	<0.001
Tumor necrosis (yes vs. no)	2.35	1.5-3.7	<0.001	1.69	0.98-2.89	0.058
Vascular invasion (yes vs. no)	4.17	2.19-7.9	<0.001	1.96	0.6-6.3	0.26
PSM (yes vs. no)				3.83	2.08-7.03	<0.001

*PN-partial nephrectomy; RN-radical nephrectomy; PSM-positive surgical margins

Table S5: Multivariate analysis of factors associated with tumour recurrence in sub-group of pT1, N0, Nx RCC patients (n=1995) stratified according to type of surgery

Variable	RN (n=940)			PN (n=1055)		
	HR	95% CI	P value	HR	95% CI	P value
Size (cm)	1.457	1.22-1.72	<0.001			
Grade (high grade vs. low grade)	2.264	1.26-3.28	<0.001	2.82	1.86-4.28	<0.001
Tumor necrosis (yes vs. no)	1.780	1.06-2.98	0.029			
Vascular invasion (yes vs. no)	3.889	1.97-7.6	<0.001			
PSM (yes vs. no)				4.0	2.12-7.58	<0.001

*PN-partial nephrectomy; RN-radical nephrectomy; PSM-positive surgical margins

Figure 1S: Flowchart demonstrating inclusion and exclusion criteria for the present study.