Predictors of disease recurrence in high-risk non-metastatic renal cell carcinoma patient's post-surgical resection: A single-center, retrospective study

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KEY MESSAGES

- 44% of T3-staged RCC patients at a single center experienced disease recurrence.
- Prognostic models should be used to facilitate conversations about disease recurrence.
- Clinicians should continue to monitor high-risk patients beyond the recommended 5-year followup period.

ABSTRACT

Introduction: Approximately 20–40% of kidney cancer patients treated for localized disease experience post-surgical recurrence. Several prognostic models exist to help clinicians determine the risk of distant recurrence, but these models vary in criteria and endpoints. We aimed to examine the recurrence rate and clinicopathologic factors as predictors of recurrence in high-risk renal cell carcinoma (RCC) patients.

Methods: We conducted a single-center, retrospective chart review of T3 RCC patients who underwent a nephrectomy between January 2000 and December 2015. Patients registered in clinical trials for adjuvant therapy and those with fewer than three years of followup were

excluded. Kaplan-Meier survival analysis and univariate and multivariate Cox regression were performed to identify the rate and predictors of disease recurrence.
Results: Eighty-eight pT3 RCC patients were included, and 39 patients had recurrence with a median of 23.5 months (range 1.6–127.5). Nine patients had disease recurrence beyond 58 months. Kaplan-Meier log-rank tests identified patients with negative surgical margins and low Fuhrman nuclear grades had greater recurrence-free survival. Univariate Cox regression revealed positive surgical margins, high Fuhrman nuclear grade, and large tumor sizes were significant predictors. In the multivariate Cox regression model, high Fuhrman nuclear grade and positive surgical margins were significant predictors of recurrence.
Conclusions: Disease recurrence occurred in 44% of T3-staged patients. High Fuhrman nuclear grade and positive surgical margins were associated with time to recurrence. Physicians should use prognostic models to facilitate conversations about disease recurrence and continue to monitor high-risk patients beyond the recommended five-year followup period. We recommend monitoring pT3 resected patients for up to 10 years post-surgery.

INTRODUCTION

Kidney cancer cases continue to increase worldwide as 431,288 new cases were diagnosed in 2020, [1] accounting for 3% of all reported human cancers worldwide. [2] Renal cell carcinoma (RCC) is the most common form of kidney cancer, accounting for 90% of all cases. [3–5] Localized RCC is often managed through the surgical intervention of partial or radical nephrectomy. [5] Despite surgery being the most effective treatment option, post-surgical disease recurrence is observed in 20-40% of patients treated for localized disease. [6]

Identifying the risk for recurrence is valuable for counselling and scheduling follow-up surveillance for patients. [7] Multiple prognostic and risk stratification models and nomograms are available to help clinicians predict RCC post-surgical outcomes in non-metastatic patients. [8–15] The most commonly used models include the Kattan postoperative RCC predictive nomogram, [7] the UISS postoperative prognostic RCC model based on UCLA risk group stratification, [8] the Leibovich RCC model for the prediction of progression after radical nephrectomy for patients with clear cell RCC (ccRCC), [9] the Mayo D-SSIGN Model for postoperative cancer-specific survival following radical nephrectomy for ccRCC, [10] and the Karakiewicz RCC cancer-specific survival nomogram. [13] Additionally, a recent prognostic model was developed using the ASSURE randomized trial data to predict oncological outcomes for nonmetastatic high-risk RCC cases. [16] All of these models differ in the prognostic variables used to determine the risk of recurrence, which include pre-and post-operative factors such as histology, TNM staging, tumour size and grade, necrosis, and lymph node status, Fuhrman grade, ECOG score, and symptoms. [8–16] These models aim to predict that patients with primary ≥pT3 may be at an intermediate to high risk for post-surgical recurrence; however, as these models differ in criteria and endpoints, the rate of recurrence often varies based on the model used, [14] leading to variation in the literature.

Following partial nephrectomy (PN) or radical nephrectomy (RN), recurrence rates remain high at 7%, 26%, and 39% for T1, T2, and T3 stage disease, respectively. [17] Utilizing predictive models to accurately assess the risk for RCC recurrence at any stage is useful. This can help identify patients who may benefit from adjuvant therapy in a clinical trial as well as close monitoring to improve oncologic outcomes. [18,19] However, for pathological (p) T3 disease, the available evidence concerning predictors of distant recurrence is divergent in the literature. [20,21] To further examine recurrence rate and clinicopathological factors as predictors of distant recurrence in patients with pT3 RCC, we evaluated patients who had PN or RN between 2000 and 2015 at our academic tertiary care center.

METHODS

Patient selection

After obtaining approval from the Hamilton Integrated Research Ethics Board (Project #12654) we performed a retrospective electronic chart review of all PN and RN cases completed between January 1, 2000 to December 31, 2015 at our centre. The date range was chosen to allow evaluation of recurrence for up to at least 5 years post-nephrectomy. Patients were eligible for inclusion if they had a pT3 non-metastatic RCC (nmRCC) tumour removed during the study period and were ≥18 years of age at the time of surgery. This included patients with pT1a cases that were upstaged to pT3a. Patients were excluded if they were part of a registered clinical trial for adjuvant therapy, received preoperative chemotherapy, underwent any ablative therapy, were followed up for fewer than three years at our center, had positive lymph node involvement or bilateral renal masses, had unavailable pathologic data, age <18, patients with non-RCC histology, or had a previous history of invasive kidney cancer. Follow-up data were collected until June 30, 2022.

Variables and outcome measures

Baseline variables were extracted including age, birth-assigned sex, and date of surgery, while postoperative parameters included type of surgery (PN or RN), RCC histology, tumour size and stage, Fuhrman nuclear grade, number of lymph nodes resected, surgical margin status (positive or negative), the status of recurrence (yes/no), recurrence date, months until the first recurrence, and metastatic disease sites. The variables ‘type of surgery’, ‘RCC histology’, ‘surgical margin status’, ‘tumour stage’, and ‘the status of recurrence’ were operationalized as categorical variables in this study. The Fuhrman nuclear grade variable was treated as an ordinal variable in the study. The variable was categorized according to the grade assigned in the pathology report. A grade of 4 was designated as the most severe. Additionally, tumour size, number of lymph nodes resected and months until the first recurrence were captured as continuous variables.

The primary outcome measure was time to progression, with progression defined as local recurrence in either kidney or regional or distant metastases. The secondary outcome was to identify prognostic variables for recurrence.

Statistical analysis
Baseline and postoperative characteristics were evaluated using descriptive statistics: means ± standard deviations (SDs) for continuous variables with normal distribution and medians with interquartile range (IQR) for continuous variables with non-normal distribution means; numbers (%) for categorical data; Univariate and multivariate binary logistic regression models were used to evaluate prognostic factors for recurrence. Given the low sample size of patients with disease recurrence (n=39), only three independent variables were used for multivariate analysis. [22] A multivariate analysis was conducted with the three significant variables from the univariate analysis. Kaplan-Meier analysis was used to estimate the survival probabilities and the log-rank test was used to determine the significance of recurrence-free survival (RFS) based on prognostic variables. Hazard ratios (HRs) were evaluated using the Cox proportional hazards model. Statistical significance was set at $p<0.05$ and all statistical tests were conducted using IBM SPSS Statistics v.28 (Armonk, NY).

RESULTS

Patients
We identified 273 cases with a computerized search that were classified as pT3 or higher at our institution. A total of 88 patients who underwent PN or RN at our center between January 1, 2000, to December 31, 2015, met the inclusion criteria. The demographic and clinicopathological characteristics of all patients are summarized in Table 1. Of the 88 patients, 74 (84.1%) had ccRCC histology, 4 (4.5%) had chromophobe RCC (ChRCC), 3 (3.4%) had papillary RCC type 2 (pRCC) and 7 (8%) were unclassified pRCC or an unclassified RCC (with or without sarcomatoid change). RCC recurrence was found in 39 (44.3%) patients, of which 29 (74.4%) were male, 28 (71.8%) underwent laparoscopic RN, 34 (87.2%) had clear cell renal cell carcinoma (ccRCC) histology, 26 (66.7%) had T3a disease, and the mean age was 62.9 (±11.59). Six (15.4%) of the patients that experienced recurrence had positive surgical margins. The median time to recurrence was 23.5 months (range 1.6-127.5; IQR 5.9, 58.2), with 9 patients experiencing recurrence past the 58-month post-operative mark. A total of 13 patients had metastasis at one site, while 26 had multiple metastatic sites. Metastases were observed in the lung, abdomen (e.g., liver, pancreas, duodenum), bone, brain, and thyroid. Out of the total of 39 patients, two experienced localized recurrence in the renal bed or fossa, whereas the remaining 37 patients had distant recurrence.

Evaluation of prognostic factors for disease recurrence

Univariate and multivariate logistic regression models were computed to identify prognostic factors for disease recurrence (Table 2). The univariate logistic regression analysis found positive surgical margins (OR 8.73, 95% CI: 1-75.9, p = 0.05) and a high Fuhrman nuclear grade (OR 2.41, 95% CI: 1.22-4.74, p = 0.011), and large tumor sizes (OR 1.14, 95% CI: 1-1.3, p = 0.047) were significant predictors of disease recurrence.

The multivariate analysis identified a high Fuhrman nuclear grade (OR 2.18, 95% CI: 1.04, 4.54, p = 0.038) as a significant predictor for disease recurrence when adjusted.

Recurrence-free survival (RFS)

Kaplan-Meier analyses showed patients with negative surgical margins and low Fuhrman nuclear grades had greater RFS (Figure 1a and Figure 1b). Kaplan-Meier analyses revealed no significant association between RFS and prognostic factors including birth-assigned sex (p = 0.115), pT staging (p = 0.232), surgical approach (p=0.276), or pathological subtype (p=0.343).

Subsequently, univariate Cox regression revealed a high Fuhrman nuclear grade (HR 2.27, 95% CI 1.40, 3.68, $p < 0.001$) positive surgical margins (HR 4.60, 95% CI 1.89, 11.23, $p < 0.001$), and large tumour sizes (HR 1.09, 95% CI 1.00, 1.19, p = 0.004) were associated with worse RFS (Table 3). Multivariate analysis found high Fuhrman nuclear grade (HR 2.12, 95% CI 1.30, 3.47, p = 0.003) positive surgical margins (HR 4.23, 95% CI 1.71, 10.46, p = 0.002) were significant factors for disease recurrence.

DISCUSSION

The rate and predictors of disease recurrence post-surgical resection in T3 RCC patients is not well defined in the literature. Our study examined recurrence rate and clinical-pathological predictors associated with disease recurrence in 88 patients with pT3 RCC. Our results demonstrated that positive surgical margins and high Fuhrman nuclear grade significantly impact the time to recurrence for patients with T3 stage disease.

Similar to our findings, other studies have reported high Fuhrman nuclear grade to be associated with recurrence for patients with T3 stage disease. [16,23–25]. Recently, a prognostic model for predicting disease recurrence for high-risk localized RCC was developed using the ASSURE clinical trial data. The model identified six factors (vascular invasion, histology, tumour size, grade and necrosis, nodal disease) which significantly impact disease recurrence. [16] In comparison to our findings, positive surgical margins were not a significant predictor in this analysis. This predictor could be surgeon specific or due to the inclusion of patients with T1b or T2 staging. Correa et al. developed this prognostic model to help clinicians provide an accurate risk assessment for patients as previous models were created using retrospective data. [16] Although, the generalizability of this prognostic model might be challenging, especially for this population. Clinical trials for adjuvant therapy often have strict inclusion and exclusion criteria, which may not be representative of the true patient population. [26] Additionally, patients that do meet the inclusion criteria for these trials may not be interested in partaking.

Given this, prognostic models such as the ASSURE trial tool should be used as a decision-aid tool. Clinicians can use this tool to determine the individualized risk of recurrence and facilitate conversations about surveillance and potential clinical trials or treatments with patients.

Clinical guidelines currently recommend that patients with T3 stage non-metastatic disease are followed for surveillance (routine imaging, blood work) for up to 5 years post-surgical resection. However, routine follow-up beyond five years is at the discretion of the treating physician. [4,27,28] Our results revealed median survival time for patients with T3-stage non-metastatic disease was 23.5 months. Though, 10% (n=9) of our sample experienced disease recurrence past 58 months of surgical resection. These findings highlight important implications for physicians providing follow-up care for post-surgical resection. Physicians can identify whether the patient is eligible for any adjuvant therapy clinical trials. A survey by KCCure identified that RCC patients are interested in and willing to use adjuvant therapy to achieve recurrence-free survival and overall survival. [29] Alternatively, physicians should continue to monitor patients with T3 stage disease beyond 60 months or provide strong recommendations for primary care providers to continue routine imaging beyond the 5-year mark.

Our study has some limitations. Our institution is a tertiary care centre, where patients may receive surgery and continue follow-up with their community urologist or primary care physician. Given this, we had to exclude many patients as we were unable to obtain at least three years of follow-up data. Additionally, our institution actively participates as a site for large clinical trials in adjuvant therapy. To ensure patients receive optimal care, a significant number of T3 stage patients are enrolled in these trials, causing them to be excluded from this retrospective analysis. The pT3 cohort is defined by the pathologic stage and the authors are aware of the work by Bonsib and Taneja et al. [30,31] An internal analysis at our institution of 912 clear cell renal cell carcinoma (accessioned 2013-2020) suggests some inconsistency in the pathology call at the pT2x-pT3 interface and a relatively high call rate of pT2x.[32] Preliminary data from a national kidney cancer collaboration (Canadian Kidney Cancer Information System) suggests this quality issue is present in a majority of participating (Canadian) institutions and requires further research to be fully understood and addressed. Due to this, our sample size remains quite low. Lastly, we may have omitted some critical predictors in disease recurrences, such as necrosis or vascular invasion.

CONCLUSIONS

Disease recurrence was found in 44.3% of patients in our sample, with a median recurrence-free survival of 23.5 months. High Fuhrman nuclear grade and positive surgical margins were clinicopathological predictors associated with time to recurrence. Physicians should continue to monitor patients with pT3 stage disease beyond the five-year mark. We recommend monitoring T3 resected patients up to 10 years post-surgery.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209-49. https://doi.org/10.3322/caac.21660
2. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin* 2016;66:271-89. https://doi.org/10.3322/caac.21349
3. Hotte SJ, Kapoor A, Basappa NS, et al. Management of advanced kidney cancer: Kidney cancer research network of Canada (KCRNC) consensus update 2019. *Can Urol Assoc J* 2019;13:343-54. https://doi.org/10.5489/cuaj.6256
4. Ljungberg B, Albiges L, Abu-Ghanem Y, et al. European association of urology guidelines on renal cell carcinoma: The 2019 update. *Eur Urol* 2019;75:799-810. https://doi.org/10.1016/j.eururo.2019.02.011
5. Sharma T, Tajzler C, Kapoor A. Is there a role for adjuvant therapy after surgery in "high risk for recurrence" kidney cancer? An update on current concepts. *Curr Oncol* 2018;25:e444-53. https://doi.org/10.3747/co.25.3865
6. Janzen NK, Kim HL, Figlin RA, et al. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. *Urol Clin North Am* 2003;30:843-52. https://doi.org/10.1016/S0094-0143(03)00056-9
7. Blackmur JP, Gaba F, Fernando D, et al. Leibovich score is the optimal clinico-pathological system associated with recurrence of non-metastatic clear cell renal cell carcinoma. *Urol Oncol* 2021;39:438.e11-438.e21. https://doi.org/10.1016/j.urolonc.2021.04.007
8. Kattan MW, Reuter V, Motzer RJ, et al. A postoperative prognostic nomogram for renal cell carcinoma. *J Urol* 2001;166:63-7. https://doi.org/10.1016/S0022-5347(05)66077-6
9. Zisman A, Pantuck AJ, Dorey F, et al. Improved prognostication of renal cell carcinoma using an integrated staging system. *JCO* 2001;19:1649-57. https://doi.org/10.1200/JCO.2001.19.6.1649
10. Leibovich BC, Blute ML, Cheville JC, et al. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma. *Cancer* 2003;97:1663-71. https://doi.org/10.1002/cncr.11234
11. Frank I, Blute ML, Cheville JC, et al. An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: The SSIGN score. *J Urol* 2002;168:2395-400. https://doi.org/10.1016/S0022-5347(05)64153-5
12. Sorbellini M, Kattan MW, Snyder ME, et al. A postoperative prognostic nomogram predicting recurrence for patients with conventional clear cell renal cell carcinoma. *J Urol* 2005;173:48-51. https://doi.org/10.1097/01.ju.0000148261.19532.2c
13. Speed JM, Trinh Q-D, Choueiri TK, et al. Recurrence in localized renal cell carcinoma: A systematic review of contemporary data. *Curr Urol Rep* 2017;18:15. https://doi.org/10.1007/s11934-017-0661-3
14. Karakiewicz PI, Briganti A, Chun FK-H, et al. Multi-institutional validation of a new renal cancer-specific survival nomogram. *J Clin Oncol* 2007;25:1316-22. https://doi.org/10.1200/JCO.2006.06.1218

15. Kapoor A, Gharajeh A, Sheikh A, et al. Adjuvant and neoadjuvant small-molecule targeted therapy in high-risk renal cell carcinoma. *Curr Oncol* 2009;16:S60-6. https://doi.org/10.3747/co.v16i0.415
16. Correa AF, Jegede O, Haas NB, et al. Predicting renal cancer recurrence: Defining limitations of existing prognostic models with prospective trial-based validation. *J Clin Oncol* 2019;37:2062-71. https://doi.org/10.1200/JCO.19.00107
17. Chin AI, Lam JS, Figlin RA, et al. Surveillance strategies for renal cell carcinoma patients following nephrectomy. *Rev Urol* 2006;8:1-7.
18. Patel HD, Puligandla M, Shuch BM, et al. The future of perioperative therapy in advanced renal cell carcinoma: how can we PROSPER? *Future Oncol* 2019;15:1683-95. https://doi.org/10.2217/fon-2018-0951
19. Klatte T, Rossi SH, Stewart GD. Prognostic factors and prognostic models for renal cell carcinoma: a literature review. *World J Urol* 2018;36:1943-52. https://doi.org/10.1007/s00345-018-2309-4
20. Shimizu T, Miyake M, Hori S, et al. Clinical significance of tumor size, pathological invasion sites including urinary collecting system and clinically detected renal vein thrombus as predictors for recurrence in pT3a localized renal cell carcinoma. *Diagnostics (Basel)* 2020;10:154. https://doi.org/10.3390/diagnostics10030154
21. Leopold Z, Srivastava A, Singer EA. Predictors of recurrence for T3a RCC: A recurring conundrum. *Diagnostics (Basel)* 2020;10:983. https://doi.org/10.3390/diagnostics10110983
22. Bujang MA, Sa'at N, Sidik TMITAB, et al. Sample size guidelines for logistic regression from observational studies with large population: emphasis on the accuracy between statistics and parameters based on real life clinical data. *Malays J Med Sci* 2018;25:122-30. https://doi.org/10.21315/mjms2018.25.4.12
23. Chang T-W, Cheng W-M, Fan Y-H, et al. Predictive factors for disease recurrence in patients with locally advanced renal cell carcinoma treated with curative surgery. *J Chin Med Assoc* 2021;Latest Articles. https://doi.org/10.1097/JCMA.0000000000000501
24. Hakam N, Abou Heidar N, Khabsa J, et al. Does a positive surgical margin after nephron sparing surgery affect oncological outcome in renal cell carcinoma?: A systematic review and meta-analysis. *Urology* 2021;156:e30-9. https://doi.org/10.1016/j.urology.2021.04.058
25. Shah PH, Moreira DM, Okhunov Z, et al. Positive surgical margins increase risk of recurrence after partial nephrectomy for high risk renal tumors. *J Urol* 2016;196:327-334. https://doi.org/10.1016/j.juro.2016.02.075
26. Stuart EA, Bradshaw CP, Leaf PJ. Assessing the generalizability of randomized trial results to target populations. *Prev Sci* 2015;16:475-85. https://doi.org/10.1007/s11121-014-0513-z
27. Campbell SC, Uzzo RG, Karam JA, et al. Renal mass and localized renal cancer: Evaluation, management, and follow-up: AUA Guideline: Part II. *J Urol* 2021;206:209-18. https://doi.org/10.1097/JU.0000000000001912
28. Kassouf W, Monteiro LL, Drachenberg DE, et al. Canadian Urological Association guideline for followup of patients after treatment of non-metastatic renal cell carcinoma. *Can Urol Assoc J* 2018;12:231-8. https://doi.org/10.5489/cuaj.5462

29. Battle D, Jonasch E, Hammers HJ, et al. Patients perspectives on adjuvant therapy in renal cell carcinoma. *JCO* 2018;36:644. https://doi.org/10.1200/JCO.2018.36.6_suppl.644
30. Bonsib SM. T2 clear cell renal cell carcinoma is a rare entity: a study of 120 clear cell renal cell carcinomas. *J Urol* 2005;174:1199-202. https://doi.org/10.1097/01.ju.0000173631.01329.1f
31. Taneja K, Arora S, Rogers CG, et al. Pathological staging of renal cell carcinoma: a review of 300 consecutive cases with emphasis on retrograde venous invasion. *Histopathology* 2018;73:681-91. https://doi.org/10.1111/his.13672
32. Bonert M, Nikzad N, El-Shinnawy I, et al. Tumor stage by size and pathologist in clear cell renal cell carcinoma from synoptic reports: Estimating rates by tumor size and a case for mandated reviews USCAP 2022 abstracts: Quality and patient Safety. *Mod Pathol* 2022;35:1473-522. https://doi.org/10.1038/s41379-022-01050-6

FIGURES AND TABLES

Figure 1A. Kaplan-Meier survival curve for Fuhrman nuclear grade.

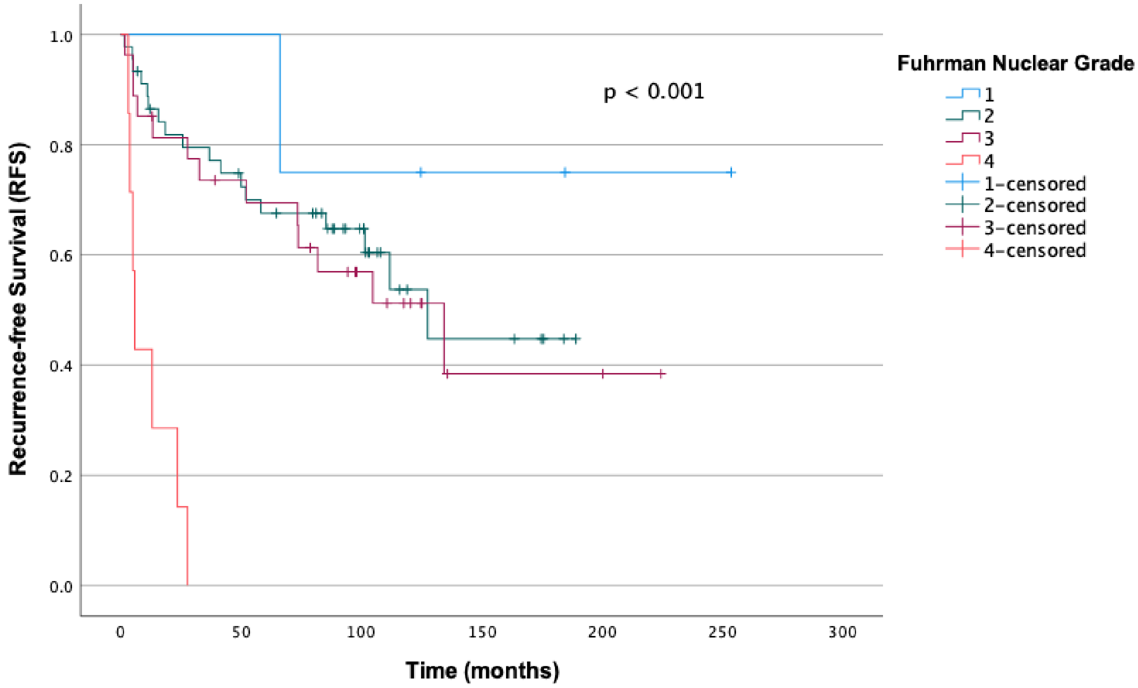

Figure 1B. Kaplan-Meier survival curve for tumour margin.

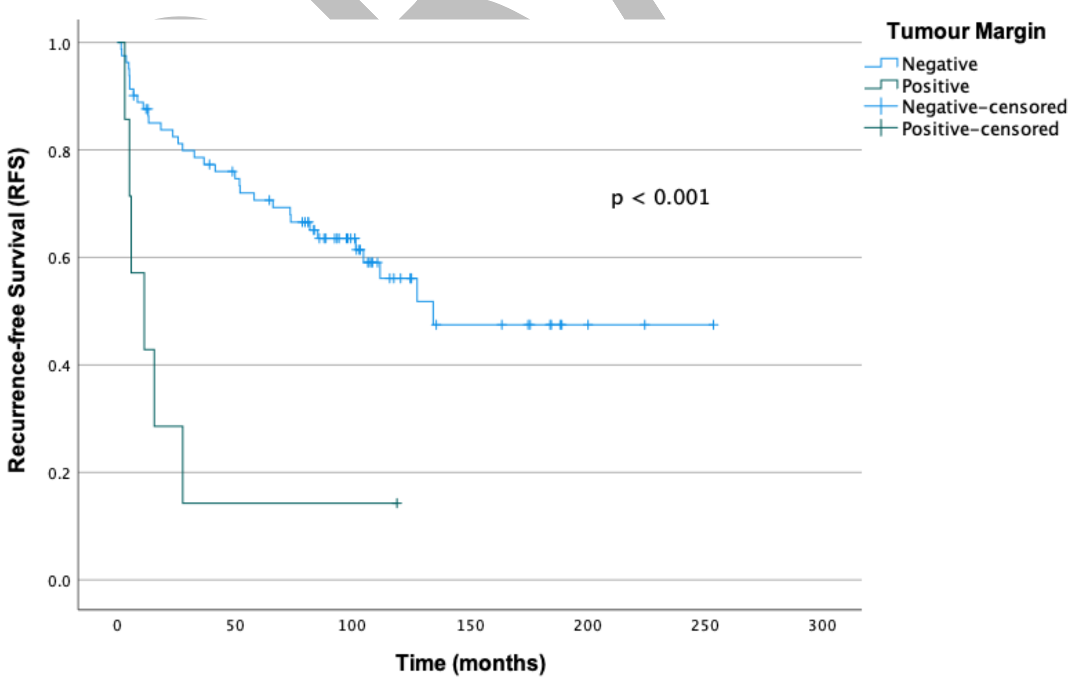

Table 1. Clinicopathological characteristics of patients			
Variables	**Overall (n=88)**	**Recurrence (n=39)**	**No recurrence (n=49)**
Median age, years	64 ± 12.3	64 ± 11.59	66± 13
Sex			
Male	59 (67%)	29 (74.4%)	30 (61.2%)
Female	29 (33%)	10 (25.6%)	19 (38.8%)
Surgical approach			
Open radical nephrectomy	20 (22.7%)	10 (25.6%)	10 (20.4%)
Laparoscopic radical nephrectomy	62 (70.5%)	28 (71.8%)	34 (69.4%)
Open partial nephrectomy	2 (2.3%)	0	2 (4.1%)
Laparoscopic partial nephrectomy	4 (4.5%)	1 (2.6%)	3 (6.1%)
Pathological subtype			
Clear-cell renal cell carcinoma	74 (84.1%)	34 (87.2%)	40 (81.6%)
Chromophobe renal cell carcinoma	4 (4.5%)	0	4 (8.2%)
Papillary renal cell carcinoma (type 2)	3 (3.4%)	2 (5.1%)	1 (2%)
Other (e.g., sarcomatoid, RCC unclassified, papillary RCC type not specified)	7 (8%)	3 (7.7%)	4 (8.2%)
pT classification			
T3a	66 (75%)	26 (66.7%)	40 (81.6%)
T3b	8 (9.1%)	6 (15.4%)	2 (4.1%)
T3c	1 (1.1%)	0	1 (2%)
T3 undefined	13 (14.8%)	7 (17.9%)	6 (12.2%)
Fuhrman nuclear grade			
1	4 (4.5%)	1 (2.6%)	3 (6.1%)
2	45 (51.1%)	18 (46.2%)	27 (55.1%)
3	27 (30.7%)	13 (33.3%)	14 (28.6%)
4	7 (8%)	7 (17.9%)	0
Not classified	5 (5.7%)	0	5 (10.2%)
Surgical margin			
Positive	7 (8%)	6 (15.4%)	1 (2%)
Negative	81 (92%)	33 (84.6%)	48 (98%)
Median largest tumor size (IQR)	7.1 (5, 9.5)	8 (6, 10)	7 (4, 9.5)
Mean number of lymph nodes resected	2.3±4.2	3.1±5.1	1.7±3.7

Table 2. Binary logistic regression to evaluate prognostic factors for recurrence

Variables	**Univariate analysis**		**Multivariate analysis**	
	Odds ratio (95% CI)	**p**	**Odds ratio (95% CI)**	**p**
Age	0.99 (0.96, 1.03)	0.813		
Sex				
Male	1.84 (0.73, 4.61)	0.195		
Female	Reference	Reference		
Pathological subtype				
Clear-cell renal cell carcinoma	1.53 (0.47, 5.00)	0.482		
Other (e.g., chromophobe, sarcomatoid, RCC unclassified, papillary renal cell carcinoma)	Reference	Reference		
Surgical approach				
Partial nephrectomy	Reference	Reference		
Radical nephrectomy	4.32 (0.48, 38.6)	0.191		
Largest tumor size	1.14 (1, 1.3)	0.047	1.1 (0.95, 1.26)	0.215
Number of lymph nodes resected	1.08 (0.97, 1.21)	0.150		
pT classification				
T3a and T3 undefined	Reference	Reference		
T3b and T3c	0.36 (0.084, 1.54)	0.168		
Fuhrman nuclear grade	2.41 (1.22, 4.74)	0.011	2.18 (1.04, 4.54)	0.038
Surgical margin				
Positive	8.73 (1.00, 75.9)	0.050	7.05 (0.77, 64.95)	0.085
Negative	Reference	Reference	Reference	Reference
Goodness of Fit - Hosmer and Lemeshow test			**X2, DF**	**p value**
			8.594, 8	0.378

Table 3. Cox Regression predicting recurrence-free survival				
Variables	**Univariate analysis**		**Multivariate analysis**	
	Hazard ratio (95% CI)	**p**	**Hazard ratio (95% CI)**	**p**
Age	0.99 (0.97, 1.02)	0.936		
Sex				
Male	1.77 (0.86, 3.65)	0.120		
Female	Reference	Reference		
Pathological subtype				
Clear-cell renal cell carcinoma	1.57 (0.61, 4.03)	0.347		
Other (e.g., chromophobe, sarcomatoid, RCC unclassified, papillary renal cell carcinoma)	Reference	Reference		
Surgical approach				
Partial nephrectomy	Reference	Reference		
Radical nephrectomy	1.05 (0.39, 20.9)	0.298		
Largest tumor size	1.09 (1.00, 1.19)	0.044	1.06 (0.97, 1.15)	0.240
Number of lymph nodes resected	1.03 (0.97, 1.09)	0.235		
pT classification				
T3a and T3 undefined	Reference	Reference		
T3b and T3c	1.69 (0.71, 4.05)	0.238		
Fuhrman nuclear grade	2.27 (1.40, 3.68)	< 0.001	2.12 (1.30, 3.47)	0.003
Surgical margin				
Positive	4.60 (1.89, 11.23)	< 0.001	4.23 (1.71, 10.46)	0.002
Negative	Reference	Reference	Reference	Reference

Goodness of fit			**X2, DF**	**p value**
			19.64, 3	<0.001