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Long-term recurrence after robot-assisted partial nephrectomy for clinical T1 renal cell carcinoma: clinicopathological insights from over 1,000 patients

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Abstract

Background

We explored the preoperative and postoperative factors associated with recurrence-free survival (RFS) after robot-assisted partial nephrectomy (RAPN) during long-term follow-up.

Methods

We retrospectively evaluated patients who underwent RAPN for clinical T1 renal cell carcinoma (RCC) between 2013 and 2020. Sequential multivariate Cox models were constructed. Model 1 included preoperative factors alone, and Model 2 included postoperative pathological features. As a post-hoc exploratory analysis, RFS was evaluated based on the cumulative number of factors associated with RFS.

Results

Of the 1,008 patients analyzed, 67 developed recurrence during a median follow-up of 82.2 months. In Model 1, male sex (hazard ratio [HR] 2.57, 95% confidence interval [CI] 1.27–5.22) and tumor size ≥ 40 mm (HR 4.67, 95% CI 2.85–7.66) were associated with shorter RFS. In Model 2, the association between male sex and RFS was attenuated (HR 1.89, 95% CI 0.92–3.86), while tumor size ≥ 40 mm (HR 2.67, 95% CI 1.56–4.56) and lymphovascular invasion (HR 4.94, 95% CI 2.87–8.52) were associated with shorter RFS. Post hoc analysis showed 5-year RFS rates of 98.3%, 93.4%, and 76.1% for patients with zero, one, and two factors, respectively. In the clear cell RCC subgroup, higher Fuhrman grade was also associated with shorter RFS (HR 2.44, 95% CI 1.42–4.19).

Conclusions

Sequential modeling suggested that the association between male sex and RFS could be explained by postoperative pathological features. Stratification based on the cumulative number of associated factors showed stepwise differences in the 5-year RFS. These findings may inform individualized surveillance after RAPN.

1. Introduction

Partial nephrectomy (PN) is the standard treatment for localized renal cell carcinoma (RCC) and provides excellent oncological control while preserving renal function. Robot-assisted partial nephrectomy (RAPN) has become the preferred surgical approach for small renal masses owing to its favorable perioperative and functional outcomes compared to open or laparoscopic techniques. [1–4]

Although the oncological outcomes of PN are generally favorable, [5] disease recurrence remains a critical clinical concern. Previous studies have identified several prognostic factors associated with recurrence after nephron-sparing surgery, including tumor size, pathological upstaging, tumor grade, positive surgical margins, and lymphovascular invasion (LVI). [6, 7] However, many contemporary RAPN series are limited by relatively small sample sizes, low event rates, and insufficient follow-up periods. Consequently, the long-term recurrence dynamics and sustained prognostic relevance of these factors in contemporary RAPN cohorts remain unclear.

The identification of recurrence risk is essential both at the preoperative counseling stage and upon final pathological evaluation, as it enables risk-adapted surveillance strategies. Therefore, using data from over 1,000 patients at a single high-volume center, we aimed to investigate the long-term oncological outcomes after RAPN with extended follow-up. Moreover, we sequentially evaluated the association between preoperative clinical parameters, postoperative pathological findings, and long-term recurrence-free survival (RFS).

2. Methods

2.1. Patient population

We retrospectively evaluated all the patients with T1a or T1b RCC who underwent RAPN at our institution between January 2013 and December 2020. Patients with incomplete clinical data, those who were lost to follow-up within 12 months after surgery, and those with hereditary RCC syndromes or translocation-associated RCC were excluded.

2.2. Data collection

Preoperative variables recorded included sex, age, body mass index (BMI), Eastern Cooperative Oncology Group Performance Status (ECOG PS) score, and serum C-reactive protein (CRP) levels. The operative and postoperative pathological variables included tumor size, surgical approach, histopathology, Fuhrman grade, tumor focality, pathological T stage, surgical margin status, and LVI. RCC staging was performed according to the Union for International Cancer Control (UICC) TNM classification, 8th edition, [8] and anatomical tumor complexity was assessed using the R.E.N.A.L. (Radius, Exophytic/endophytic, Nearness of the collecting system, Anterior/posterior, and Location relative to the polar line) nephrometry score. [9]

Postoperatively, all patients underwent surveillance every 3–6 months, including routine blood tests and computed tomography (CT) of the chest and abdominal computed tomography.

2.3. Ethical approval

The Internal Ethics Review Board of Tokyo Women's Medical University approved this study (ID: 382F), which was conducted in accordance with the guidelines of the Declaration of Helsinki. Owing to the retrospective observational nature of this study, the requirement for informed consent was waived.

2.4. Surgery

All RAPN procedures were performed by experienced board-certified urologists using the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA) at a single high-volume center. The choice of surgical approach (transperitoneal or retroperitoneal) was determined based on tumor location and size. Renal artery clamping under warm ischemia was performed in all the cases. [10]

2.5. Construction of Multivariable Models

To assess the association of preoperative clinical variables and postoperative pathological findings with RFS, we constructed two sequential multivariate Cox proportional hazard models according to the timing at which clinical information became available. Candidate variables were selected a priori based on clinical relevance and previous urological literature, [11-15] rather than stepwise variable selection from univariate analyses. Model 1 included clinical variables available preoperatively, including age, sex, serum CRP level, and tumor size. Model 2 included the following postoperative pathological variables: histological subtype, Fuhrman grade, pathological upstaging to pT3a, surgical margin status, and LVI. Notably, because the application of the Fuhrman grading system lacks robust validation in non-clear cell RCC variants, particularly chromophobe RCC, the Fuhrman grade was intentionally excluded from the primary multivariate analysis of the overall cohort to ensure pathological stringency. [16] Instead, to rigorously evaluate its prognostic value when clinically established, a predefined subgroup analysis was conducted exclusively within the clear cell RCC (ccRCC) cohort, incorporating Fuhrman grades into the fully adjusted Model 2.

2.6. Statistical analysis

Baseline characteristics were presented as medians (interquartile ranges [IQRs]) for continuous variables and numbers (%) for categorical variables.

RFS was defined as the interval between the date of surgery and the documented radiological or pathological cancer recurrence. Patients who survived without recurrence were censored on the date of last follow-up. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for factors associated with RFS. As a post hoc exploratory analysis, patients were grouped according to the number of factors associated with a shorter RFS in Model 2. Kaplan–Meier curves and 5-year RFS estimates were used to describe the cumulative recurrence risk across these groups. This grouping was intended to provide a descriptive illustration of the risk gradients.

All statistical analyses were performed using JMP, version 19 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $p < 0.05$. significant.

3. Results

3.1. Patient and tumor characteristics

The baseline demographic and clinicopathological characteristics of the study population are summarized in Table 1. In total, 1,008 patients who underwent RAPN were included in the final analysis (Figure 1). The median follow-up duration was 82.2 months (IQR, 61.3–99.7 months). The median age and BMI of the cohort were 59 years (IQR, 49–68 years) and 24 kg/m² (IQR: 22–27 kg/m²), respectively. The median primary tumor size was 30 mm (IQR: 21–41 mm). Preoperatively, 769 tumors (76.3%) were classified as cT1a and 239 (23.7%) were classified as cT1b. Pathological evaluation revealed upstaging to pT3a in 20 patients (2.0%), whereas pT1a and pT1b disease was confirmed in 813 (80.7%) and 175 (17.4%) patients, respectively. The predominant histological finding was ccRCC, which was observed in 810 patients (80.4%). In the ccRCC cohort, the pathological Fuhrman grades were grade 1 in 145 patients (17.9 %), grade 2 in 486 patients (60.0 %), grade 3 in 165 patients (20.4 %), and grade 4 in 14 patients (1.7 %). LVI was identified in 218 tumors (21.6%) and a positive surgical margin was reported in 15 patients (1.5%).

3.2. Recurrence patterns

During follow-up, seven patients died of non-cancer-related causes without evidence of recurrence, while cancer recurrence was documented in 67 patients (6.7%). The overall 3-year and 5-year RFS rates for the entire cohort were 96.4% and 94.5%, respectively, with a median time to recurrence of 35 months (IQR, 19–59 months). The anatomical distributions of the sites of first recurrence are shown in Table 2. The most frequent sites of initial recurrence were the operated kidney (local recurrence) and lungs, which occurred in 14 patients (20.1%). These were followed by lymph node and bone metastases, each occurring in nine patients (13.4%). Synchronous multiple-organ recurrence was observed in nine patients (13.4%). Adrenal gland and skin metastases were less common, occurring in four (6.0%) and three patients (4.5%), respectively.

3.3. Sequential multivariable analysis of recurrence-free survival

The results of the sequential multivariate Cox proportional hazards regression analysis are presented in Table 3. In Model 1, which evaluated only preoperative clinical parameters, male sex (HR 2.57, 95% CI 1.27–5.22) and tumor size ≥ 40 mm (HR 4.67, 95% CI 2.85–7.66) were associated with worse RFS.

In Model 2, which integrated postoperative pathological findings, tumor size ≥ 40 mm remained associated with shorter RFS (HR 2.67, 95% CI 1.56–4.56). Notably, the association between the male sex and RFS was attenuated after adjusting for pathological features (HR 1.89, 95% CI 0.92–3.86). LVI was also associated with a shorter RFS in Model 2 (HR 4.94; 95% CI, 2.87–8.52). Conversely, histological subtype (HR 0.59, 95% CI, 0.27–1.29), pathological upstaging to pT3a (HR 2.26, 95% CI, 0.85–6.02), and surgical margin status (HR 1.79, 95% CI, 0.39–8.19) were not associated with postoperative RFS.

3.4. Risk stratification as a post hoc analysis

In the post hoc analysis, patients were stratified into three risk tiers (range 0–2) based on the number of associated factors present, namely tumor size ≥40 mm and LVI. This risk-stratification framework demonstrated clear differences in RFS across the three groups in the entire cohort (log-rank p < 0.0001) (Figure 2). The 5-year RFS rate decreased sequentially according to the coexistence of these adverse features: 98.3% for patients with zero factors (n = 630), 93.4% for those with one factor (n = 264), and 76.1% for those with two factors (n = 114). Notably, the presence of both these factors delineates a distinctly high-risk population with a markedly inferior RFS timeline.

3.5. Subgroup analysis in the clear cell RCC cohort

Targeted multivariate Cox regression analysis was performed within the ccRCC subgroup (n = 810) to elucidate the prognostic relevance of the Fuhrman grading system. In the adjusted model, after controlling for all preoperative and postoperative clinicopathological parameters, tumor size ≥ 40 mm (HR 2.32, 95% CI 1.32–4.09), LVI (HR 4.65, 95% CI 2.54–8.49), and a high Fuhrman grade (Grade 3–4) (HR 2.44, 95% CI 1.42–4.19) were associated with worse RFS (Table 4).

Building on the factors identified in the ccRCC subgroup, we evaluated the combined association of these factors in this population. Patients were stratified into four distinct risk categories (range, 0–3) based on the total number of these three factors. This cumulative risk stratification demonstrated clear differences in RFS outcomes (log-rank p < 0.0001) (Figure 3). The 5-year RFS rates sequentially and substantially declined with the coexistence of these factors: 98.2% for patients with zero factors (n = 436), 95.4% for those with one factor (n = 210), 87.0% for those with two factors (n = 115), and 66.9% for those with three factors (n = 49).

4. Discussion

In this study of > 1,000 patients with long-term follow-up, we showed that RAPN provides durable oncological outcomes while identifying distinct prognostic factors through a sequential multivariable approach. This retrospective analysis of a large contemporary cohort treated at a single high-volume center revealed that 67 (6.7%) of the 1,008 patients developed recurrence. The 5-year RFS rate after RAPN has been reported to range from 92.8% to 94.8% in a landmark large-scale series. [17, 18] The 5-year RFS rate of 94.5% in our cohort is comparable to these results. Our analysis identified larger tumor size and LVI as the primary prognostic factors for worse long-term RFS.

Through a hierarchical sequential adjustment approach, this study clarified the evolving prognostic contributions of factors from the preoperative to the postoperative pathological phases. In Model 1 (preoperative clinical factors), male sex and larger tumor size were significantly associated with an increased risk of recurrence. However, upon additional adjustment for postoperative pathological features in Model 2, the association between male sex and RFS was attenuated, suggesting that the observed association might be mediated by an underlying aggressive tumor biology that is more prevalent in male patients. Our findings that tumor size and LVI are associated with long-term RFS are consistent with those of a prior surgical series, indicating that intrinsic pathological features dictate

oncological outcomes after nephron-sparing surgery. [19-23] Specifically, the presence of LVI demonstrated an overwhelmingly high HR, underscoring its pivotal role in microscopic vascular spread and early systemic dissemination, which cannot be captured by anatomical TNM staging alone. Furthermore, a larger tumor volume increases the probability of subclinical micrometastasis.

An important clinical insight derived from our cohort was the chronological distribution of recurrence events; approximately half of all recurrences (32/67, 47.8%) occurred beyond 3 years after surgery. While many traditional surveillance protocols focus intensively on the first 24–36 months postoperatively, our long-term follow-up data (median 82.2 months) clearly indicate that a 3-year recurrence-free interval does not guarantee a definitive cure, particularly for patients with adverse tumor biology. In our fully adjusted model, LVI exhibited the highest HR for recurrence (HR, 4.94). The presence of LVI may signify a high propensity for dormant circulating tumor cells or subclinical micrometastases, which can manifest as clinical recurrence after an extended latent period. Similarly, a larger tumor size contributes to a sustained and continuous risk of relapse over time. Collectively, these observations suggest that patients with these pathological prognostic factors require extended and individualized surveillance strategies well beyond the conventional 3-year window.

A relevant methodological consideration in our study was the histology-specific evaluation of tumor grade. Although pathological nuclear grading is a well-established prognostic factor for RCC, its universal application across histologically heterogeneous RCC cohorts may be difficult to interpret, particularly because the Fuhrman grading system lacks robust biological validation in various non-clear-cell RCC lineages. To reduce this clinicopathological heterogeneity, we intentionally excluded Fuhrman grade from the primary whole-cohort multivariate analysis and instead conducted an additional evaluation within the biologically uniform ccRCC subgroup (n = 810). In this selective population, a high Fuhrman grade (grades 3–4) emerged as an important factor associated with recurrence (HR, 2.44). This finding aligns with previous landmark studies demonstrating that nuclear grading remains a highly reliable surrogate for intrinsic tumor aggressiveness when restricted to the ccRCC phenotype. [22, 23]

Current risk stratification models and clinical guidelines from the AUA, EAU, and NCCN primarily rely on the pathological T stage, tumor grade, and surgical margin status to determine the intensity of postoperative imaging. [24-26] While these established criteria are important for predicting early oncological events, our study suggests that tumor size and LVI may provide relevant information for long-term oncological surveillance after RAPN. By evaluating the cumulative presence of these two prognostic factors (tumor size ≥40 mm and LVI positivity), clinicians may effectively stratify long-term RFS into distinct risk tiers, as shown in Figure 2. This stratification framework may help to identify low-risk patients harboring zero or one factor who may safely undergo de-escalated surveillance, while identifying high-risk patients harboring both factors who require vigilant long-term radiographic monitoring. Furthermore, in the ccRCC population, the integration of Fuhrman grade with these two factors provided further separation of RFS curves (Figure 3), identifying an ultra-high-risk subset harboring all three factors with a 5-year RFS of only 66.9%.

This study had some limitations that warrant consideration. First, its retrospective, single-center design may have introduced a selection bias, which may limit the generalizability of our findings. However, the use of a large consecutive cohort of over 1,000 patients managed at a high-volume center using a standardized robotic approach may reduce the heterogeneity in surgical management and follow-up practices. Second, although our sequential multivariate approach provided structured insights into the associations between pre-and postoperative factors and RFS, the median follow-up of 82.2 months may still be insufficient to capture very late recurrences occurring beyond 10 years. Third, we used the Fuhrman grading system, which has been largely replaced by the International Society of Urological Pathology/World Health Organization classification in contemporary practice. [27] Nevertheless, given the historical nature and long-term follow-up of our cohort, Fuhrman grade remains clinically important and informative for interpreting long-term outcomes, particularly within the ccRCC subgroup. Finally, the relatively low absolute number of recurrence events (n = 67) limited the statistical power. Although this low event rate reflects the favorable long-term oncological effectiveness of RAPN, it restricted our ability to perform more granular subgroup analyses of specific anatomical sites of distant metastasis or further stratify pathological variables.

5. Conclusion

In conclusion, tumor size and LVI were associated with long-term recurrence after RAPN in patients with clinical T1 RCC. The prognostic relevance of the Fuhrman grade is histology-specific, and it should not be applied universally across heterogeneous histologies, but remains informative for precise risk stratification within the clear cell variant. Evaluating the cumulative presence of tumor size ≥40 mm and LVI may provide a simple risk stratification framework for differentiating long-term oncological outcomes. This approach may help clinicians tailor individualized postoperative surveillance plans, minimizing unnecessary imaging for low-risk patients while ensuring vigilant monitoring for those at highest risk.

Declarations

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This study did not receive any funding.

Conflict of interest statement

Kenji Omae received lecture fees from Ono Pharmaceutical and Pfizer outside the submitted work. The other authors declare no conflicts of interest.

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Author contributions

SW: Conceptualization, Methodology, Formal analysis, data curation, writing – original draft, writing – review, and editing. KO: Conceptualization, Methodology, Formal analysis, Supervision, Validation, Writing – review and editing, and project administration. YK: Writing, review, and editing. HI: Writing, review, and editing. HF: Writing, reviewing, and editing. TN: Writing, reviewing, and editing. KY: Writing, reviewing, and editing. TK: Writing, review, and editing. TT: Project administration, supervision, writing, reviewing, and editing.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request and are subject to institutional ethical approval and privacy regulations.

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Tables

Tables 1 to 4 are available in the Supplementary Files section.

Figures

Figure 1

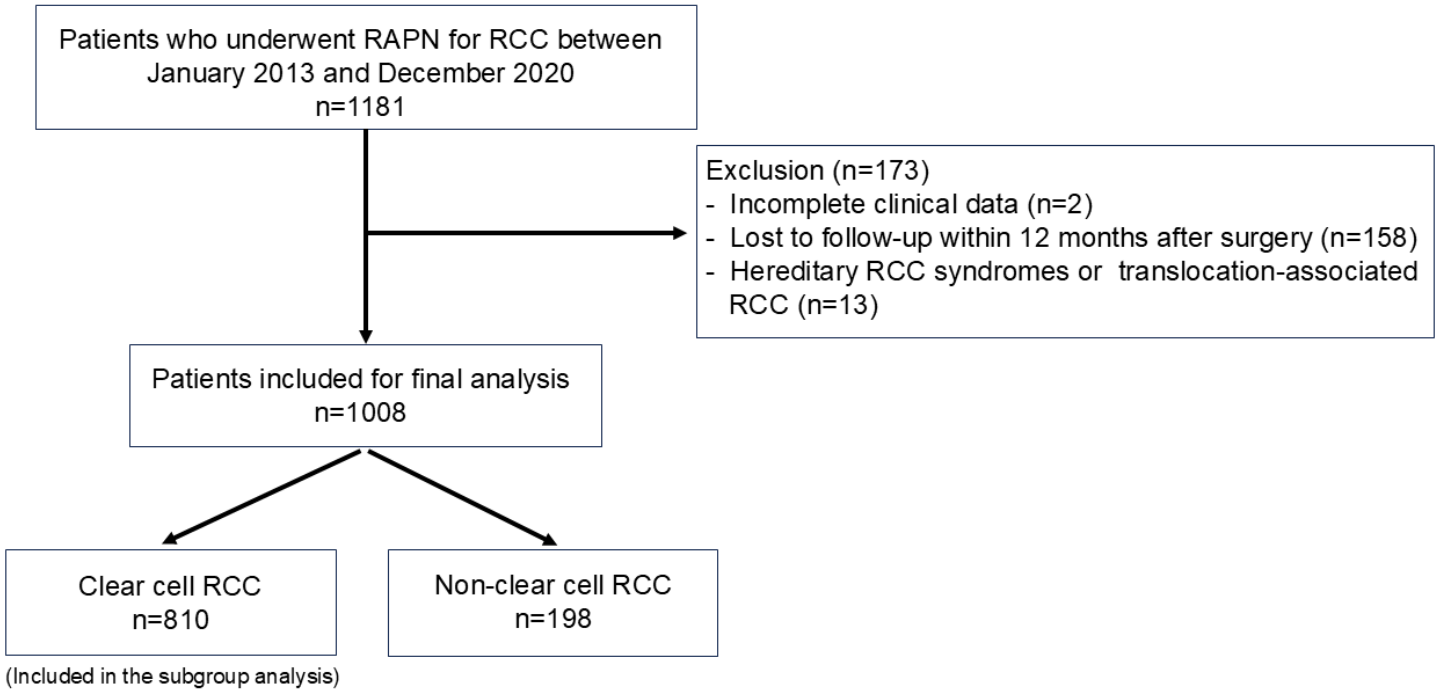


Figure 1

Study flowchart illustrating the patient selection and exclusion process.

From an initial screening of 1,181 consecutive patients who underwent robot-assisted partial nephrectomy (RAPN), a final cohort of 1,008 patients with clinical T1 renal cell carcinoma (RCC) was analyzed. To evaluate the histology-specific prognostic impact of tumor grade, a predefined subgroup analysis was restricted to patients with clear-cell RCC (n=810).

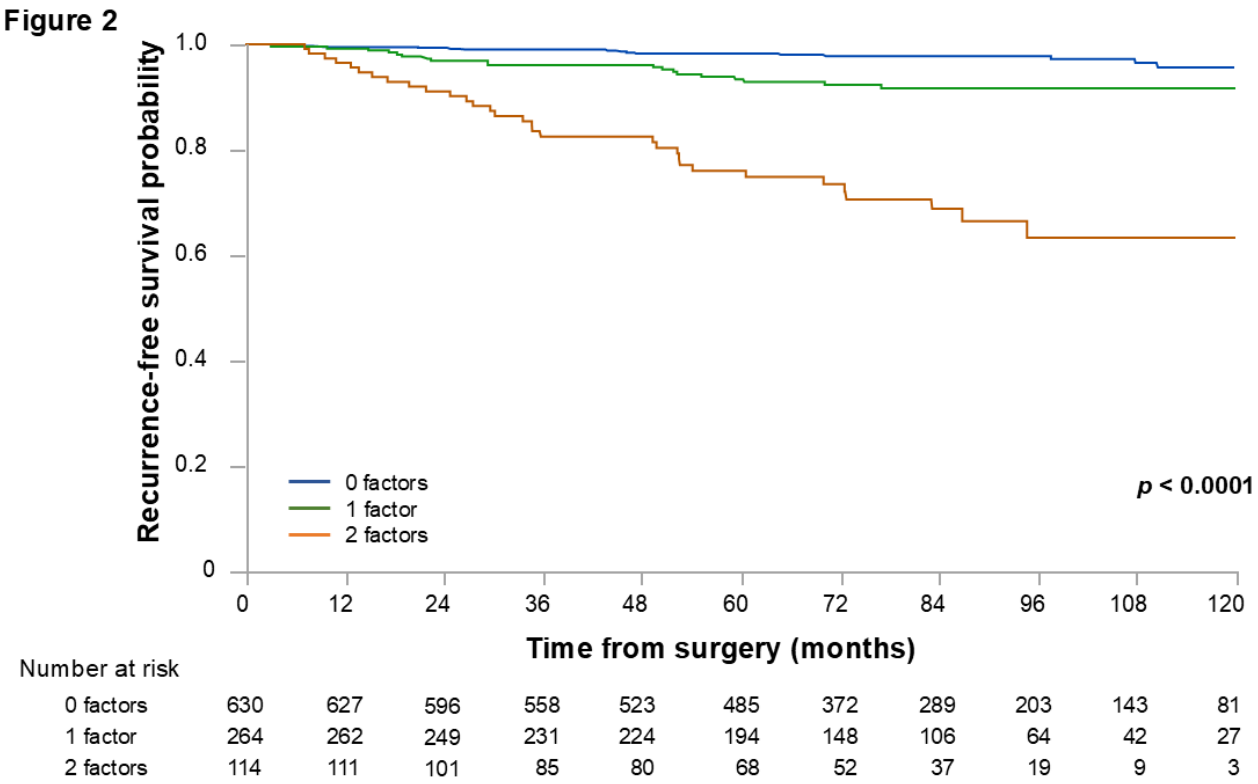


Figure 2

Kaplan–Meier curves for recurrence-free survival stratified by the cumulative number of prognostic factors in the entire cohort.

Patients were stratified into three distinct risk tiers based on the presence of two identified post-RAPN prognostic factors: tumor size ≥ 40 mm and LVI. The 5-year recurrence-free survival rates were 98.3% for patients with zero factors (n=630), 93.4% for those with one factor (n=264), and 76.1% for those with two factors (n=114).

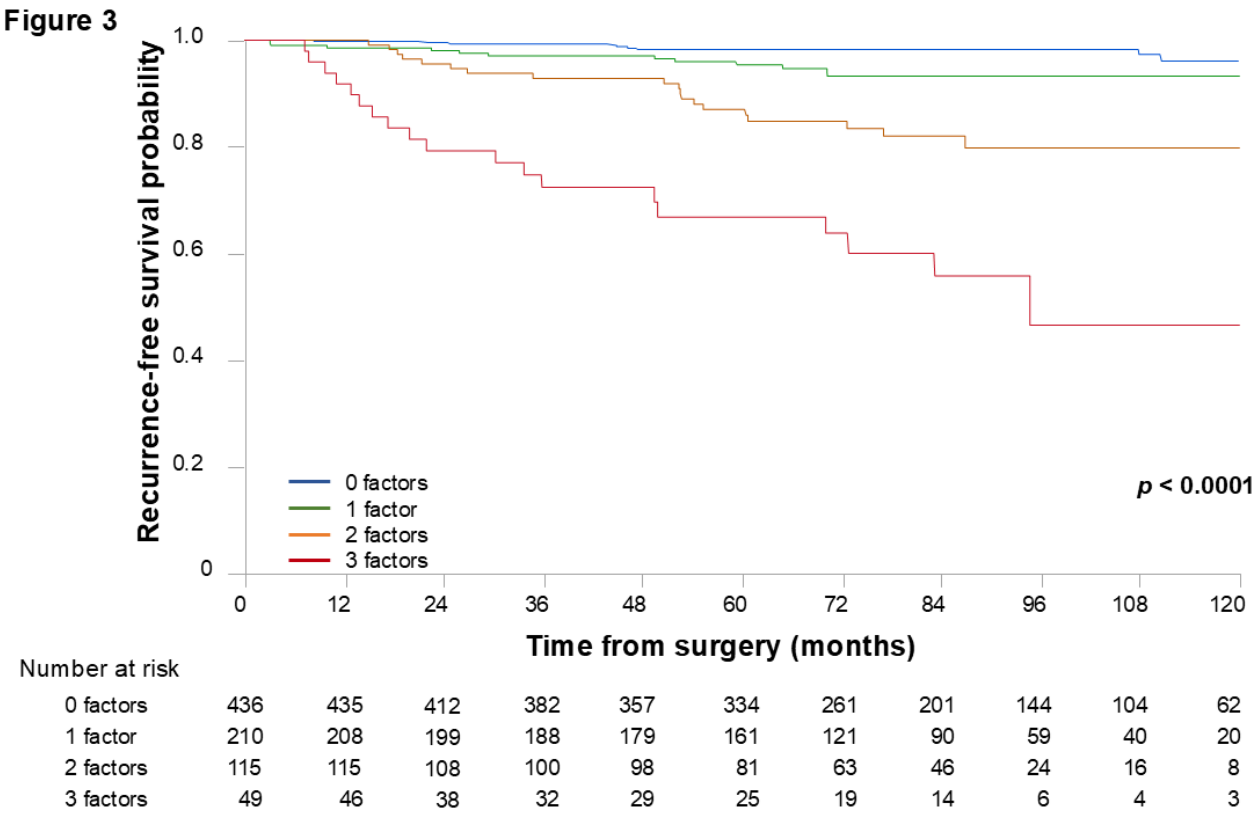


Figure 3

Kaplan–Meier curves for recurrence-free survival stratified by the cumulative number of prognostic factors in the clear cell renal cell carcinoma (ccRCC) subgroup.

Patients within the biologically homogeneous ccRCC subgroup were stratified according to the cumulative presence of three validated independent prognostic factors: tumor size ≥ 40 mm, lymphovascular invasion (LVI), and a high Fuhrman grade (grades 3–4). The 5-year recurrence-free survival rates were 98.2% for patients with zero factors (n=436), 95.4% for those with one factor (n=210), 87.0% for those with two factors (n=115), and 66.9% for those with three factors (n=49).

Supplementary Files

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