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Recurrence After Endoscopic Management of Upper Tract Urothelial Carcinoma: Incidence, Predictors, and Clinical Consequences in an International Multicenter Cohort

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Abstract

Background: Endoscopic kidney-sparing management has become an established treatment option for selected patients with upper tract urothelial carcinoma (UTUC). However, recurrence remains common, and its predictors in contemporary practice are incompletely defined.

Objective: To evaluate recurrence patterns, predictors of recurrence-free survival (RFS), and the clinical consequences of recurrence following endoscopic management of UTUC.

Design, Setting, and Participants: A retrospective multicenter cohort study was performed across five tertiary referral institutions (three Italian centers, one Spanish center, and one United States center). Consecutive patients undergoing primary endoscopic treatment for localized UTUC between 2019 and 2023 were included. All analyses were conducted using a single locked dataset comprising 277 patients.

Outcome Measurements and Statistical Analysis: The primary endpoint was any recurrence. Secondary endpoints included progression, delayed radical nephroureterectomy (RNU), metastasis, overall survival, and cancer-specific survival. Kaplan–Meier analyses and Cox proportional hazards models were performed.

Results: Recurrence occurred in 96 patients (34.7%), whereas delayed RNU was required in 31 patients (11.2%). High-grade biopsy histology was significantly associated with inferior RFS and represented the strongest predictor of recurrence on multivariable analysis (adjusted HR 3.27, 95% CI 1.91–5.60; $p<0.001$). Tumor size, multifocality, and hydronephrosis demonstrated weaker associations and did not remain independently predictive. Although recurrence increased the likelihood of progression and delayed RNU, most recurrent tumors remained amenable to further kidney-sparing treatment.

Conclusions: Recurrence following endoscopic management of UTUC is common but heterogeneous. High-grade biopsy histology remains the dominant predictor of recurrence and should guide surveillance intensity and patient counseling.

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) comprises approximately 5–10% of urothelial cancers and carries an inherent risk of recurrence, progression, and cancer-specific mortality. Standard treatment has historically involved radical nephroureterectomy (RNU), but nephroureterectomy with bladder cuff removal may lead to significant loss of renal function and limit candidacy for systemic therapies in older patients with comorbidities. [1–5]

Improvements in flexible ureteroscopy, digital imaging, laser technology, and endoscopic platforms have led to increasing adoption of kidney-sparing management. Current European Association of Urology (EAU) and American Urological Association (AUA) guidelines recommend endoscopic management of patients with low-risk disease as well as select imperative indications such as solitary kidney, bilateral disease, and chronic kidney disease.[1, 6] Several institutional series have described favorable renal

preservation and oncologic outcomes after ureteroscopic or percutaneous treatment in select patients. [7–11]

Despite these advances, recurrence remains the primary limitation of kidney sparing management. Published recurrence rates range from 25% to 60%, depending on patient selection, treatment indications, surveillance intensity, and tumor biology. [7–12] Recurrence is a heterogeneous endpoint, however, and while some patients may require delayed RNU for persistent or recurrent disease, others can be successfully treated with repeat endoscopic management without immediate loss of renal unit. For this reason, recurrence should not be considered a treatment failure in itself. [13–15]

Current risk stratification is derived from clinicopathologic variables obtained at the time of diagnosis, including biopsy grade, tumor size, multifocality, hydronephrosis, urinary cytology, and imaging characteristics. [1, 16, 17] The independent predictive ability of these variables has been inconsistent across recent studies, especially in patients who undergo kidney-sparing management. Further, recent enthusiasm for machine-learning models has underscored the critical need for rigorous event accounting, model calibration assessment, and transparent reporting standards. [18–22]

The goal of this study was to evaluate patterns of recurrence, predictors of recurrence-free survival, and clinical consequences of recurrence after endoscopic management of UTUC using a contemporary multicenter cohort. We hypothesized that while recurrence would be frequent, heterogenous, and that biopsy histology would remain the strongest predictor of adverse outcomes. Emphasis was placed on deriving reproducible analyses from a single locked dataset and clinically relevant endpoints such as delayed progression and delayed radical nephroureterectomy.

MATERIALS AND METHODS

Study design and patient population

This was a retrospective multicenter cohort study consisting of consecutive patients who underwent primary endoscopic treatment of localized upper tract urothelial carcinoma (UTUC) from January 2019 through December 2023 at five tertiary referral centers (three Italian centers, one Spanish center, and one United States center). Institutional review board approval was obtained at each participating institution in accordance with local guidelines.

Patients eligible for inclusion had pathologically confirmed UTUC treated with kidney-sparing endoscopic management and at least one postoperative follow-up examination. Patients with metastatic disease at presentation, prior history of radical nephroureterectomy, immediate salvage nephroureterectomy within three months, or missing baseline characteristics were excluded. After data harmonization and quality control review, the final analytical cohort consisted of 277 patients.

Endoscopic management and surveillance

Treatment was carried out at the discretion of the treating clinician using standard ureteroscopic or, less commonly, percutaneous techniques. Ablation was performed using contemporary laser technology including holmium:YAG or thulium-fiber platforms. Biopsy samples and/or selective upper tract cytology was obtained when feasible.

Routine postoperative follow-up consisted of interval ureteroscopy, urinary cytology, cystoscopy, and cross-sectional imaging per institutional protocols and contemporary guideline recommendations.

Variables and outcomes

Clinicopathologic variables included age, sex, body mass index (BMI), Charlson Comorbidity Index (CCI), baseline estimated glomerular filtration rate (eGFR), smoking status, prior history of bladder cancer, chronic kidney disease (CKD), baseline tumor size, tumor location, multifocality, hydronephrosis on imaging, urinary cytology, biopsy grade, and presenting symptoms.

The primary outcome of interest was any recurrence following index endoscopic treatment. Recurrence was defined as ipsilateral upper-tract recurrence, bladder recurrence, contralateral upper tract recurrence, or pathologic confirmation of residual/recurrent disease. Secondary endpoints included clinical progression, delayed radical nephroureterectomy (RNU), metastatic progression, overall survival, and cancer-specific survival.

Statistical analysis

Continuous variables are reported as median with interquartile range (IQR), while categorical variables were summarized as frequencies and percentages. Group comparisons were performed using Mann–Whitney U tests, $\chi 2$, or Fisher's exact tests where appropriate.

Recurrence-free survival (RFS) was estimated using Kaplan–Meier analysis and compared between groups using log-rank statistics (Figs. 1–3). Univariable Cox proportional hazards regression was initially performed for prespecified clinicopathologic variables (Table 3). To reduce overfitting, multivariable analysis was restricted to include only baseline variables with clinical importance selected prior to model construction; namely biopsy grade, tumor size, multifocality, hydronephrosis, symptomatic presentation, and prior history of bladder cancer (Table 4; Fig. 5).

All analyses were performed using STATA version 18.0 (StataCorp, College Station, TX). A p-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 277 patients treated with primary endoscopic management for localized upper tract urothelial carcinoma between 2019 and 20 were included in the final locked analysis dataset. Baseline

demographic, clinical, and tumor characteristics are summarized in Table 1.

Median age at diagnosis was 73.6 years (IQR 68.6–79.5), and 173 patients were male (62.5%). Median baseline estimated glomerular filtration rate (eGFR) was 61.0 mL/min/1.73m^2. High-grade biopsy histology was identified in 92 cases (33.2%), while 77 tumors (27.8%) were multifocal, 144 kidneys exhibited hydronephrosis (52.0%), and 40 tumors measured > 2 cm at largest dimension (14.4%).

Patients with recurrence were significantly more likely to have high-grade tumors on biopsy compared to those who did not experience recurrence during follow-up (52.1% vs 23.2%, $p < 0.001$). Positive urinary cytology and symptomatic presentation were also more common among patients with recurrence. There were no significant differences in age at diagnosis, sex, baseline renal function, comorbidity score, or hydronephrosis on imaging (Table 1).

Recurrence patterns and oncologic outcomes

After a median follow-up period of 48.5 months, any recurrence developed in 96 patients (34.7%). The distribution of recurrence events and subsequent oncologic outcomes are outlined in Table 2 and Fig. 4.

The most common recurrence phenotype was ipsilateral upper tract recurrence, followed by bladder recurrence and contralateral upper tract recurrence. Progression of grade/stage occurred in 30 patients (10.8%), whereas 31 patients (11.2%) underwent delayed RNU. Metastatic progression was observed in 9 patients (3.2%), and 3 deaths due to cancer were recorded.

Kaplan–Meier recurrence analyses

Kaplan-Meier recurrence free survival (RFS) analysis demonstrated a significant difference in RFS when stratified by biopsy grade (Fig. 1). Patients with high-grade tumors on biopsy experienced inferior RFS compared to patients with low-grade disease on univariable analysis (log-rank $p < 0.001$). Separation of survival curves occurred shortly after treatment and persisted for the duration of follow-up.

When patients were stratified by tumor size, those with disease measuring greater than 2 cm had numerically lower RFS compared to tumors 2 cm or less (Fig. 2). This difference was smaller than that observed for biopsy grade.

Multifocal tumors had lower RFS than patients with unifocal disease (Fig. 3). There was significant overlap in the confidence intervals of these curves, suggesting a weaker association with outcomes than biopsy grade.

Univariable Cox regression analysis

The results of univariable Cox regression analysis are summarized in Table 3.

High-grade biopsy pathology was strongly associated with recurrence after kidney-sparing management of UTUC (HR 3.27, 95% CI 1.91–5.60; $p < 0.001$). Positive high-grade urinary cytology, multifocal disease,

tumor size greater than 2 cm, and presenting with symptoms were also significantly associated with recurrence in univariable analysis.

Age at diagnosis, sex, baseline eGFR, chronic kidney disease, and CCI were not significantly associated with RFS.

Restricted multivariable Cox regression analysis

To limit model over-fitting, a restricted multivariable Cox proportional hazards model was used that included prespecified baseline variables thought to be clinically relevant. The results of this analysis are displayed in Table 4 and Fig. 5.

Once again, high-grade biopsy histology was the strongest independent predictor of recurrence following treatment (adjusted HR 3.27, 95% CI 1.91–5.60; $p < 0.001$). Although multifocal disease, tumor size greater than 2 cm, and hydronephrosis trended towards significance, these variables were not robustly predictive of recurrence after adjustment for other variables.

Biopsy grade accounted for the majority of predictive information in this model.

Clinical consequences of recurrence

While patients who experienced recurrence were more likely to undergo delayed RNU and experience grade/stage progression, recurrence did not uniformly portend cancer-specific mortality.

SUMMARY OF PRINCIPAL FINDINGS

The principal findings from our analysis can be summarized into three major points. First, kidney-sparing management of UTUC carries a significant risk of recurrence, with approximately one-third of patients experiencing recurrence during follow-up. Second, high-grade biopsy histology was the dominant predictor of recurrence and remained significantly associated with worse RFS after adjustment for other variables. Third, recurrence should not be considered synonymous with failure. While recurrence did increase the likelihood of delayed progression and RNU, most patients could still be treated successfully with repeat endoscopic management without requiring loss of renal unit.

DISCUSSION

Recurrence after kidney-sparing management of upper tract urothelial carcinoma (UTUC) is frequent but should not be considered synonymous with treatment failure. Endoscopic management was performed on 277 patients between 2019 and 20 across five high-volume tertiary referral centers. During a median follow-up of 48 months, recurrence developed in 34.7% of patients. Delayed radical nephroureterectomy was required in only 11.2% of patients after a median follow-up of 48 months.

In patients treated with endoscopic management for UTUC, recurrence was common but did not necessarily lead to cancer-specific mortality. High-grade biopsy histology was strongly associated with development of recurrence after treatment and should be considered during patient counseling and treatment selection.

The optimal management strategy for UTUC continues to evolve as technological improvements facilitate resection of previously challenging tumor locations. While radical nephroureterectomy has historically been the standard of care for patients with localized disease, kidney-sparing strategies may offer several advantages. Nephroureterectomy with bladder cuff inevitably leads to loss of at least one functioning renal unit and may render patients ineligible for cytotoxic therapy in the event of recurrence or progression. In high-risk patients with bilateral disease or existing chronic kidney disease, preservation of renal function may be of utmost importance.

Recent European Association of Urology (EAU) and American Urological Association (AUA) guidelines have expanded to include kidney-sparing management for select patients with low-risk UTUC and imperative indications such as bilateral disease, solitary kidney, and chronic kidney disease.[1, 2] Contemporary case series have further supported these recommendations by demonstrating promising renal preservation and oncologic outcomes after ureteroscopic or percutaneous management in carefully selected patients.[7–11]

The current analysis supports previous reports that recurrence is common but does not invariably lead to cancer-specific death, delayed nephroureterectomy, or loss of renal unit. Although clinicians should anticipate recurrence during counseling and surveillance planning, recurrence should not automatically be regarded as treatment failure. Rather, patients experiencing recurrence represent a heterogeneous population in which many may be successfully managed with endoscopic therapy while maintaining long-term renal function.

One of the primary findings of this manuscript is that recurrence remains exceedingly common following kidney sparing management of UTUC. In the current study, recurrence developed in 34.7% of patients during a median follow-up of 48 months. Scotland et al. reported a cumulative recurrence rate of 39% after ureteroscopic management, whereas Villa et al. demonstrated cumulative recurrence rates between 30% and 50% depending on tumor stage, grade, and follow-up duration.[11, 12] Similar rates of recurrence have been reported by several other endoscopic series.[13–15] Taken together, these data suggest that recurrence should be anticipated in a significant proportion of patients after kidney sparing management and is likely not an indicator of treatment failure.

Recurrence must be interpreted in the context of tumor biology and overall risk profile. While high-grade tumors on biopsy were significantly more likely to recur after treatment ($p < 0.001$), most recurrences were able to be managed successfully without nephroureterectomy or immediate loss of renal function. High-grade biopsy histology was the strongest independent predictor of recurrence in both univariable and multivariable analysis (Fig. 5, Table 4). These data support findings from several prior studies

demonstrating that biopsy grade remains one of the most important predictors of aggressive tumor behavior. [16–20]

Biopsy sampling error and grade discordance with final pathology after nephroureterectomy remain limitations of ureteroscopic biopsy. Despite these limitations, biopsy grade remains one of the most useful predictors of tumor biology that can be reliably ascertained before treatment. Multiple prior studies have demonstrated that high-grade disease on biopsy is associated with increased risk of recurrence, progression, invasive disease, and cancer-specific mortality. [16–19]

The main strength of our analysis is that biopsy grade on univariable analysis. Current EAU and AUA guidelines incorporate tumor size into risk classification because lesions larger than 2 cm have historically been associated with adverse pathology and progression at the time of diagnosis. [1, 2] However, our data suggest that tumor size alone may not be sufficient to predict recurrence in patients undergoing kidney-sparing management. Correspondingly, Matin et al. recently reported that while tumor size greater than 2 cm predicted failure of bladder preservation, the majority of recurrences were still successfully managed with repeat endoscopic management.[11] Similar results have been reported by Villa et al.[12] Although tumors > 2 cm did predict worse RFS on Kaplan-Meier analysis (Fig. 2), biopsy grade was significantly more predictive of recurrence than tumor size. These results highlight the need for further risk classification schemes that more accurately predict recurrence beyond size alone and current EAU/AUA guideline recommendations.

Surveillance protocols were heterogeneous among participating institutions.

Similarly, multifocality on imaging has traditionally been associated with field cancerization and urothelial instability. [23, 24] While multifocality was associated with inferior RFS on Kaplan-Meier analysis, the association between multifocal disease and recurrence weakened after multivariable adjustment. We suspect this is because multifocality is more reflective of recurrence burden than a direct predictor of treatment failure.

There were several limitations to this study. Firstly, data were collected retrospectively at each institution; as such, we cannot rule out selection bias or unmeasured confounding. Secondly, while all institutions follow protocols similar to current EAU/AUA guidelines, surveillance protocols were not standardized among centers. Thirdly, we were unable to perform a central pathology review to ensure uniform grading and staging. Fourth, molecular biomarkers and genomic sequencing data were not available for the current analysis. Finally, while this represents one of the largest contemporary series of endoscopic management for UTUC, the number of events for certain secondary endpoints, such as metastasis and cancer-specific mortality, was still relatively low.

Recurrence following endoscopic management of upper tract urothelial carcinoma (UTUC) is common but should not be considered treatment failure. Recurrence developed in approximately one-third of patients during a median follow-up of 48 months after treatment. High-grade biopsy histology was strongly associated with recurrence and represented the only variable significantly associated with

recurrence in multivariable analysis. While patients with recurrence were more likely to progress or undergo delayed RNU, the majority of patients did not require immediate nephroureterectomy and could be successfully managed with repeat endoscopic interventions.

Given these findings, clinicians should not hesitate to offer kidney-sparing management to appropriate patients. When counseling patients, it is important to make them aware that while kidney sparing management results in a significant rate of recurrence, most recurrences can still be managed without immediate loss of renal function. Despite these limitations, our findings highlight that recurrence should not be considered treatment failure and that kidney-sparing strategies can play an important role in the management of UTUC.

CONCLUSIONS

Approximately one-third of patients will experience recurrence after kidney sparing management of UTUC. High-grade biopsy histology is associated with increased risk of recurrence but does not preclude successful management without loss of renal unit. Clinicians should anticipate recurrence and counsel patients accordingly. Recurrence following endoscopic management of UTUC should not be considered synonymous with treatment failure.

DECLARATIONS

Conflict of Interest Statement

The authors declare that they have no competing financial or non-financial interests related to the present study.

None of the authors has received personal fees, consulting fees, honoraria, stock ownership, patent royalties, or other financial support that could be perceived as influencing the work reported in this manuscript.

All authors have completed the appropriate conflict-of-interest disclosures and confirm that no conflicts exist.

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No external funding was received for the conduct of this study, data collection, statistical analysis, manuscript preparation, or publication.

The study was performed using institutional resources available at the participating centers.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its subsequent amendments.

Institutional Review Board or Ethics Committee approval was obtained at each participating institution before commencement of the study. Given the retrospective nature of the investigation and the use of de-identified data, the requirement for written informed consent was waived where permitted by local regulations.

All patient information was anonymized before analysis.

Consent for Publication

The manuscript does not contain identifiable patient information, photographs, videos, or other materials requiring individual patient consent for publication.

Availability of Data and Materials

The datasets generated and analyzed during the current study are not publicly available because of institutional privacy regulations and data-sharing agreements among participating centers.

De-identified data may be made available from the corresponding author upon reasonable request and subject to institutional approval.

Author Contributions

Concept and design: [MB, MB, OZ ZD]

Acquisition of data: [AK, RP LS, MDM,]

Statistical analysis and interpretation of data: [TP]

Drafting of the manuscript: [all authors]

Critical revision of the manuscript for important intellectual content: All authors

Administrative, technical, or material support: [TP]

Study supervision: [Maurizio Buscarini]

All authors read and approved the final manuscript.

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Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request. Restrictions apply to the availability of these data because they were collected under institutional review board approvals and multicenter data-sharing agreements.

Use of Artificial Intelligence

No artificial intelligence tools were used in the acquisition, analysis, interpretation, or generation of the study data.

Any language assistance used during manuscript preparation was limited to editorial support. The authors take full responsibility for the content of the manuscript and all scientific conclusions presented.

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TABLES

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

Figures

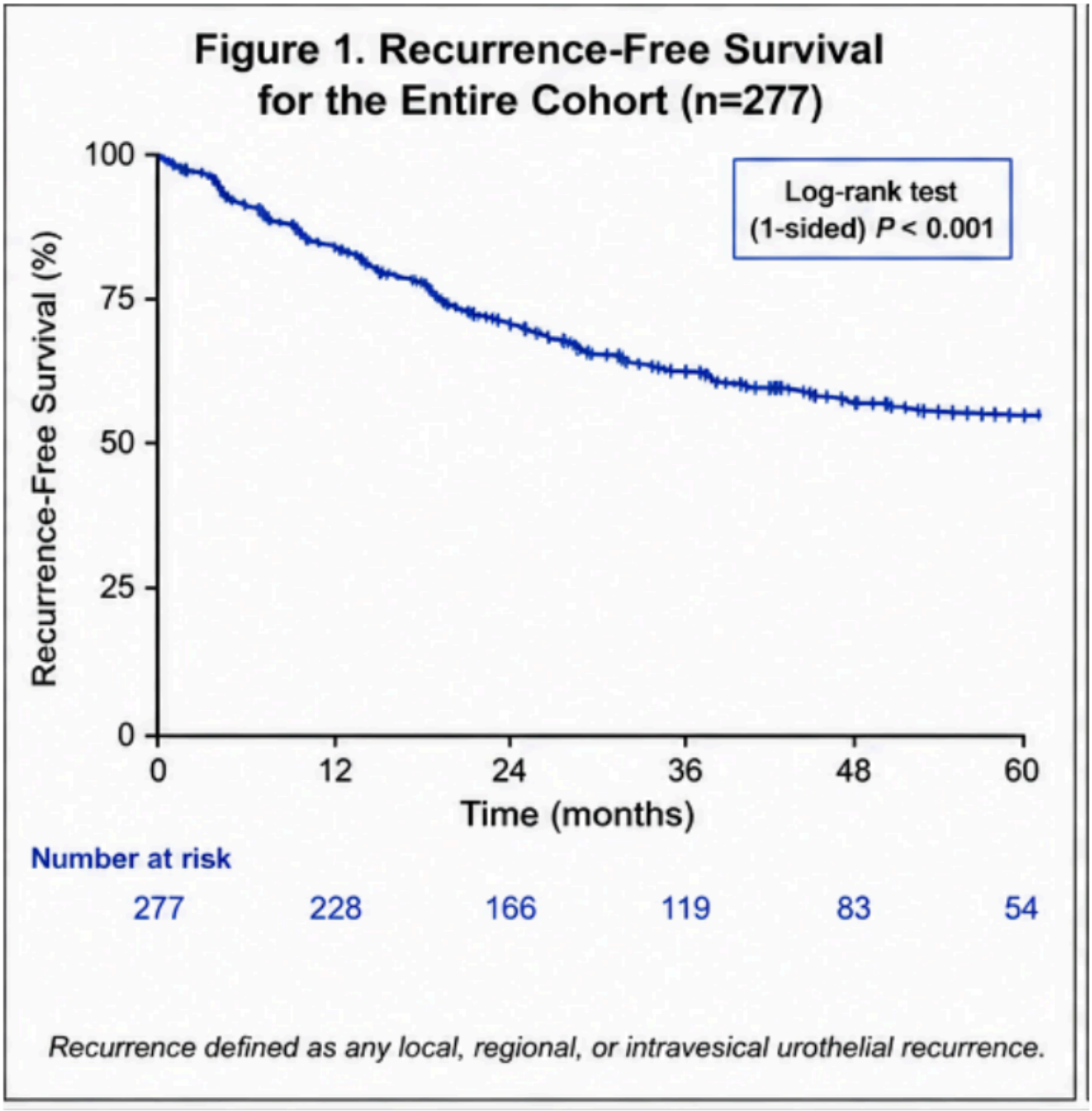

Figure 1

Kaplan–Meier recurrence-free survival according to biopsy grade. Shaded areas represent Greenwood 95% confidence intervals. Tick marks indicate censored observations. Number-at-risk tables are displayed beneath the survival curves. Log-rank testing compares recurrence-free survival between low-grade and high-grade tumors.

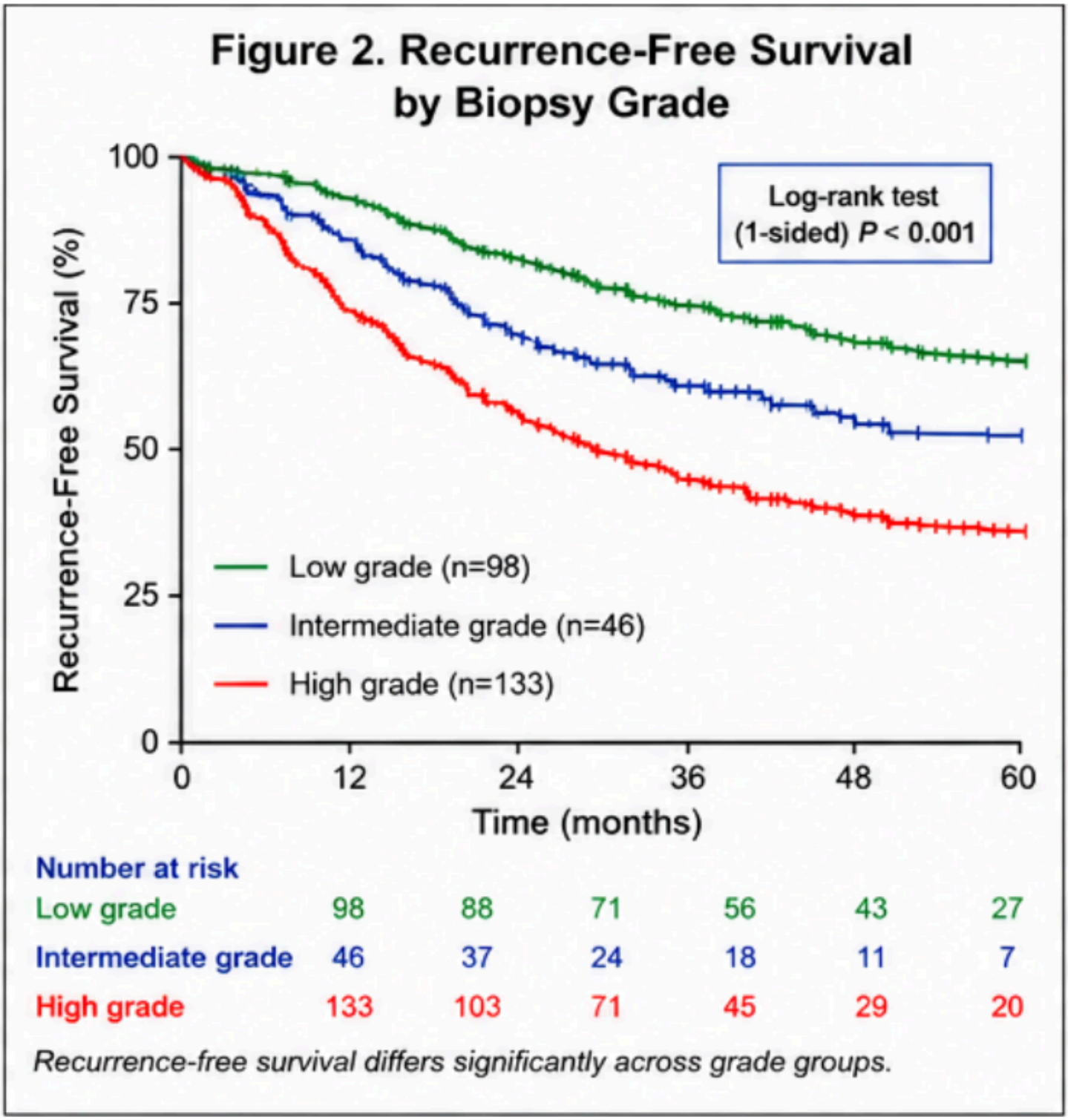

Figure 2

Kaplan–Meier recurrence-free survival stratified according to maximum tumor diameter (>2 cm versus ≤2 cm). Shaded areas represent 95% confidence intervals. Tick marks indicate censored observations. Number-at-risk tables are shown below the x-axis.

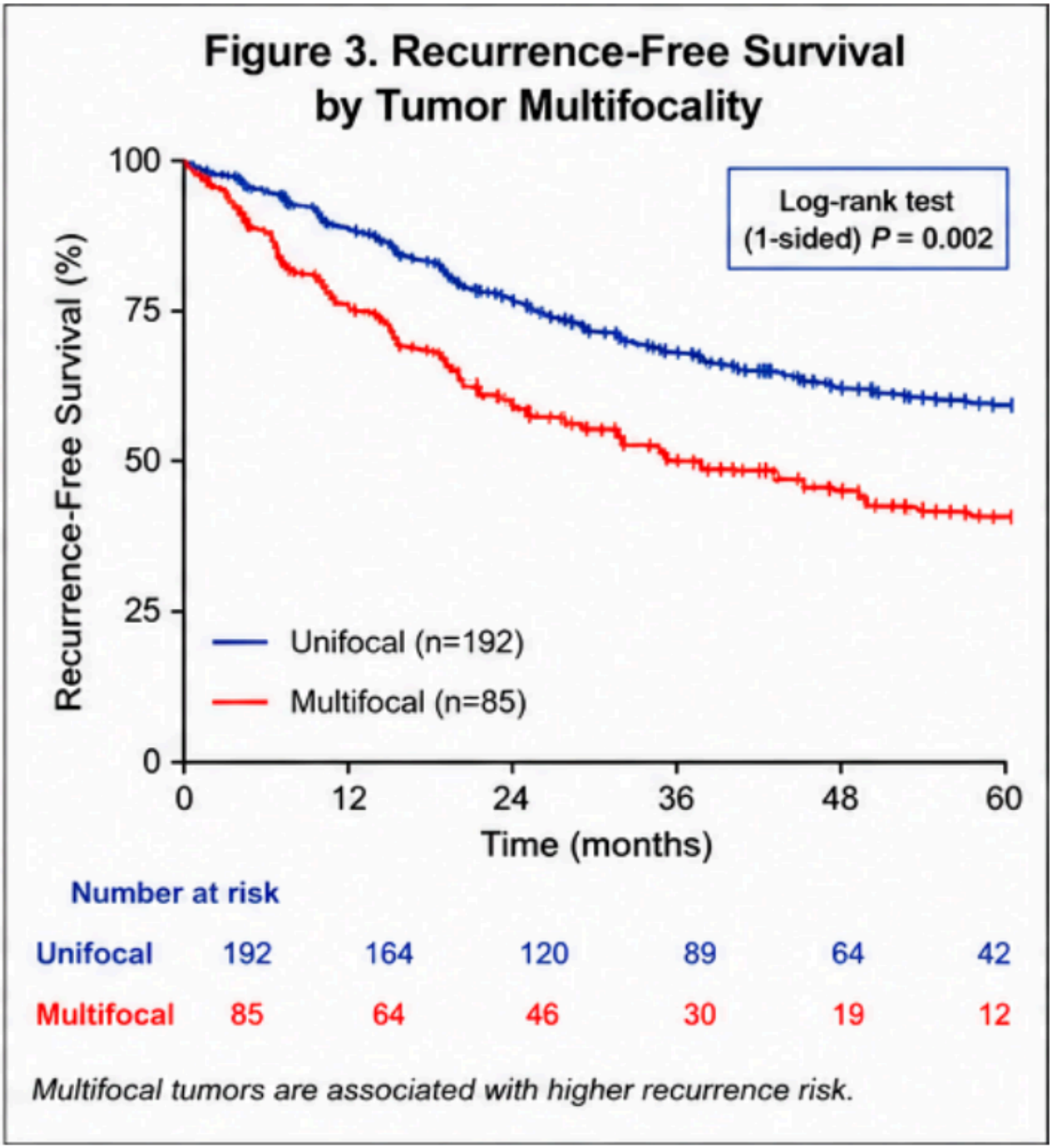

Figure 3

Kaplan–Meier recurrence-free survival according to tumor focality (unifocal versus multifocal disease). Shaded areas represent 95% confidence intervals. Tick marks indicate censored observations. Number-at-risk tables are displayed beneath the curves.

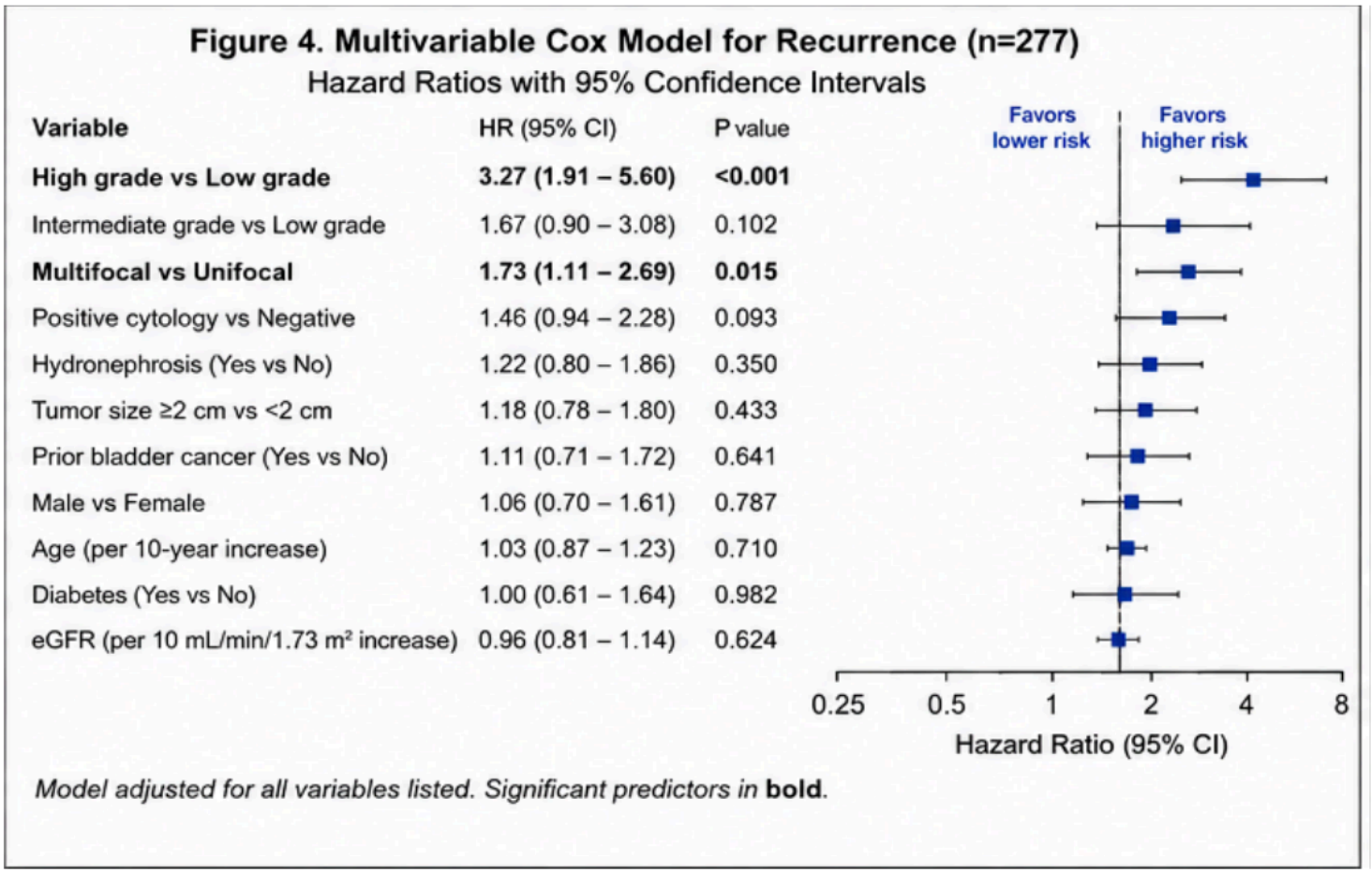

Figure 4

Distribution of recurrence phenotypes and downstream oncologic outcomes. Bars represent the number of patients experiencing ipsilateral upper tract recurrence, bladder recurrence, contralateral upper tract recurrence, grade/stage progression, and delayed radical nephroureterectomy.

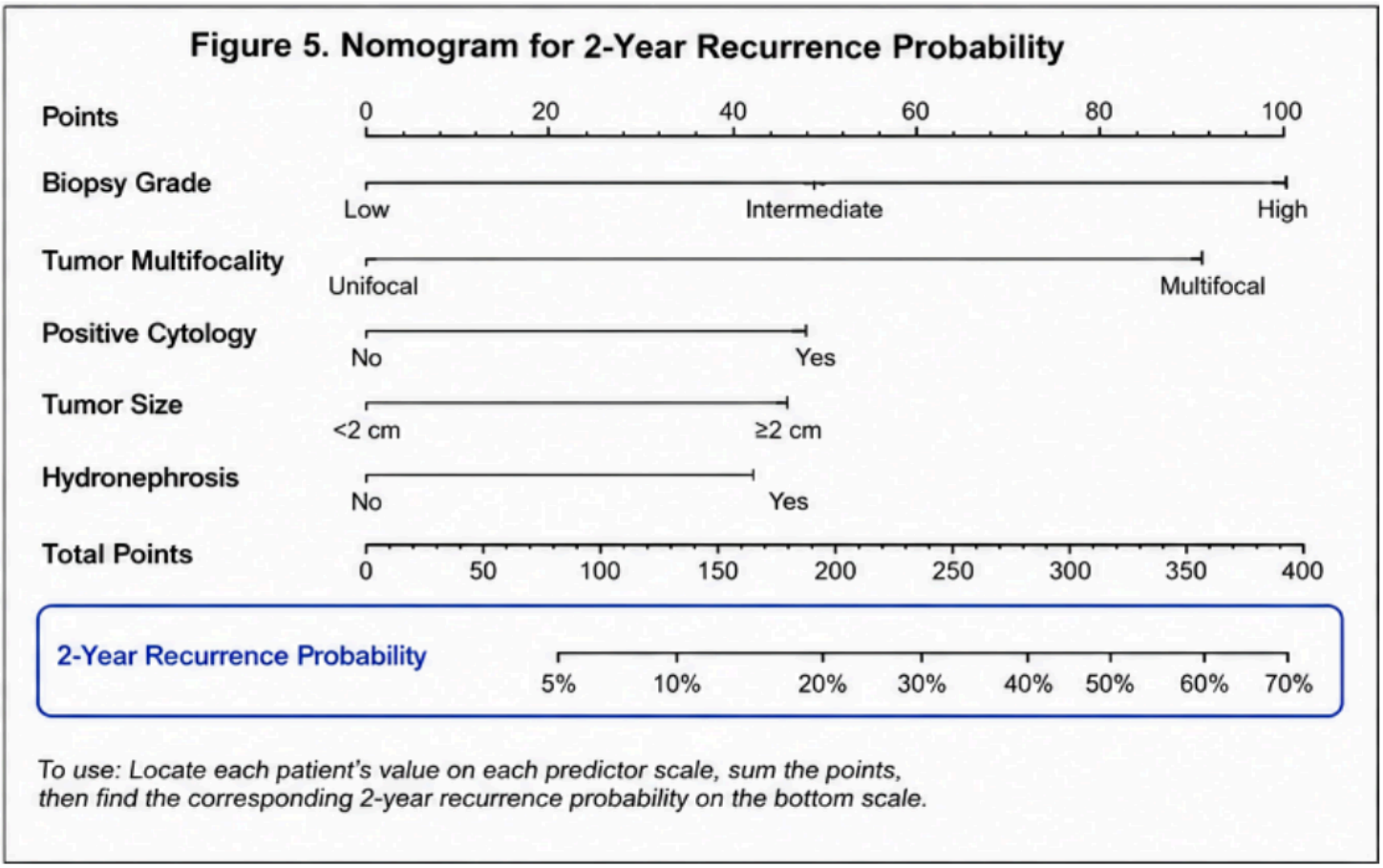

Figure 5

Forest plot of the restricted multivariable Cox proportional hazards model for recurrence-free survival. Hazard ratios are shown with 95% confidence intervals. The vertical reference line indicates a hazard ratio of 1.0.

Supplementary Files

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