



Original article

Macroscopic sessile tumor architecture is a pathologic feature of biologically aggressive upper tract urothelial carcinoma

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Abstract

Objective: Macroscopic sessile tumor architecture was associated with adverse outcomes after radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC). Before inclusion in daily clinical decision-making, the prognostic value of tumor architecture needs to be validated in an independent, external dataset. We tested whether macroscopic tumor architecture improves outcome prediction in an international cohort of patients.

Material and methods: We retrospectively studied 754 patients treated with RNU for UTUC without neoadjuvant chemotherapy at 9 centers located in Asia, Canada, and Europe. Tumor architecture was macroscopically categorized as either papillary or sessile. Univariable and multivariable Cox regression analyses were used to address recurrence-free (RFS) and cancer-specific survival (CSS) estimates.

Results: Macroscopic sessile architecture was present in 20% of the patients. Its prevalence increased with advancing pathologic stage and it was significantly associated with established features of biologically aggressive UTUC, such as tumor grade, lymph node metastasis, lymphovascular invasion, and concomitant CIS (all P values < 0.02). The median follow-up for patients who were alive at last follow-up was 40 months (IQR: 18–75 months, range: 1–271 months). Two-year RFS and CSS for tumors with papillary architecture were 85% and 90%, compared with 58% and 66% for those with macroscopic sessile architecture, respectively (P values < 0.0001). On multivariable Cox regression analyses, macroscopic sessile architecture was an independent predictor of both RFS (hazard ratio {HR}: 1.5; $P = 0.036$) and CSS (HR: 1.5; $P = 0.03$).

Conclusion: We confirmed the independent prognostic value of macroscopic tumor architecture in a large, independent, multicenter UTUC cohort. It should be reported in every pathology report and included in post-RNU predictive models in order to refine current clinical decision making regarding follow-up protocol and adjuvant therapy. © 2010 Elsevier Inc. All rights reserved.

Keywords: Tumor architecture; Upper urinary tract; Urothelial carcinoma; Nephroureterectomy; Growth pattern

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1. Introduction

Upper urinary tract urothelial carcinoma (UTUC) comprises approximately 5% of all urothelial tumors and 10% of all renal tumors [1]. Radical nephroureterectomy (RNU) with bladder cuff resection and regional lymphadenectomy is regarded as the standard treatment in most of the patients with UTUC [2]. Biological markers for UTUC are lacking. Only tumor stage, lymph node metastasis, and grade have been documented as major prognostic factors [3–11], while the prognostic value of potential important features, such as tumor architecture, presence of necrosis, and lymphovascular invasion, remains to be proven [6,7,12–15].

Macroscopic sessile tumor architecture has been independently associated with adverse outcomes after RNU for UTUC in a single large multi-institutional retrospective study [14]. Before inclusion in daily clinical decision-making, the prognostic value of macroscopic tumor architecture needs to be validated in an independent, external dataset.

2. Materials and methods

This was an institutional review board approved study with all participating sites providing the necessary institutional data sharing agreements before initiation of the study. A total of 9 academic centers worldwide provided data. None of these institutions participated in the mentioned study by Remzi et al. [14]. A computerized database was generated for data transfer. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Before final analysis, the database was frozen, and the final data set was produced for the current analysis.

The database comprised 785 patients treated with RNU with ipsilateral bladder cuff resection between 1987 and 2008. No patient received preoperative chemotherapy or radiation therapy. Patients with concurrent urothelial carcinoma of the urinary bladder (UCB) and those in whom the macroscopic tumor architecture was not mentioned in the histopathologic report were also excluded. This left 754 patients for analysis.

Surgery was performed by several surgeons according to the standard criteria for RNU, i.e., extrafascial dissection of the kidney with the entire length of ureter and adjacent segment of the bladder cuff. The hilar and regional lymph nodes adjacent to the ipsilateral great vessel generally were resected along with enlarged lymph nodes if abnormal on preoperative computed tomography scans or palpable intra-operatively. Extended lymphadenectomy was not routinely performed.

2.1. Pathologic evaluation

All surgical specimens were processed according to standard pathologic procedures at each institution. Tumors were staged according to the American Joint Committee on Cancer–Union Internationale Contre le Cancer (UICC) TNM classification [16]. Tumor grading was assessed according to the 1998 WHO/International Society of Urologic Pathology (ISUP) consensus classification. Tumor architecture is defined based on the predominant macroscopic feature by pathologic gross examination. If present, macroscopic sessile growth was defined as being predominant. The information on macroscopic architecture was taken from the histopathologic report. Microscopic tumor architecture like trabecular, nodular, or infiltrative pattern of invasion or inverted papillary architecture was not judged [17].

2.2. Follow-up regimen

Patients were generally observed every 3 to 4 months for the first year after RNU, every 6 months from the second through the fifth years, and annually thereafter. Follow-up consisted of a history, physical examination, routine blood work and serum chemistry studies, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Elective bone scans, chest computed tomography, and magnetic resonance imaging were performed when clinically indicated.

Disease recurrence was defined as local failure in the operative site, regional lymph nodes, or distant metastasis. Bladder recurrences were not considered in the analysis of recurrence-free survival rate. Cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or by death certificates alone. Most patients who were identified as having died of UTUC had progressive, widely disseminated metastases at the time of death. Patients who died in the perioperative period (i.e., death within 30 days of surgery) were censored at time of death for UTUC-specific survival analyses.

2.3. Statistical analysis

The Fisher's exact test and the χ^2 test were used to evaluate the association between categorical variables. Differences in variables with a continuous distribution across dichotomous categories were assessed using the Mann-Whitney U test. The Kaplan-Meier method was used to calculate survival functions, and differences were assessed with the log-rank statistic. Univariable and multivariable Cox regression models addressed time to recurrence and cancer-specific mortality after RNU. Statistical significance in this study was set as $P \leq 0.05$. All

Table 1

Association of tumor architecture with clinical and pathologic characteristics of 754 patients treated with radical nephroureterectomy and bladder cuff excision for upper tract urothelial carcinoma

| | No. of patients (%) | Architecture | | P |
|----------------------|---------------------|-----------------------------------|---------------------------------|---------|
| | | Papillary (%) (n = 604, 80.1%) | Sessile (%) (n = 150, 19.9%) | |
| Age (median and IQR) | 68 (60.6–75) | 68 (60–74.4) | 69 (63–77) | 0.203 |
| Sex | | | | 0.75 |
| Male | 516 (68.4) | 415 (80.4) | 101 (19.6) | |
| Female | 238 (31.6) | 189 (79.4) | 49 (20.6) | |
| Stage | | | | <0.0001 |
| Ta | 162 (21.5) | 159 (98.2) | 3 (1.8) | |
| Tis | 9 (1.2) | 9 (100) | 0 (0) | |
| T1 | 187 (24.8) | 182 (97.3) | 5 (2.7) | |
| T2 | 142 (18.8) | 118 (83.1) | 24 (16.9) | |
| T3 | 211 (28) | 110 (52.1) | 101 (47.9) | |
| T4 | 43 (5.7) | 26 (60.5) | 17 (39.5) | |
| Grade | | | | <0.0001 |
| Low | 138 (18.3) | 135 (97.8) | 3 (2.2) | |
| High | 616 (81.7) | 469 (76.1) | 147 (23.9) | |
| Regional lymph nodes | | | | <0.0001 |
| N0 | 131 (17.8) | 114 (87) | 17 (13) | |
| Nx | 574 (76.1) | 462 (80.5) | 112 (19.5) | |
| N+ | 49 (6.5) | 28 (57.1) | 21 (42.9) | |
| Predominant location | | | | 0.10 |
| Renal pelvis | 402 (59.4) | 325 (80.8) | 77 (20.2) | |
| Ureter | 275 (40.6) | 208 (75.6) | 67 (24.4) | |

Nx = lymphadenectomy not performed.

reported *P* values are two-sided. Analyses were performed with SAS ver. 9.2 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Association of macroscopic tumor architecture with clinical and pathologic characteristics

Macroscopic sessile architecture was present in 150 (19.9%) patients. It increased with advancing pathologic stage (2.7%, 16.9%, and 87.4%, for T1, T2, and non-organ-confined, respectively; $P < 0.001$) and it was associated with established features of biologically aggressive UTUC, such as higher tumor grade and lymph node metastasis (P values < 0.02 , Table 1).

3.2. Association of macroscopic tumor architecture with clinical outcomes

The median follow-up of the whole color was 34 months (interquartile range (IQR) 16–65). At follow-up, 179 (24%) patients experienced disease recurrence, 151 (20%) had died of UTUC, and 99 (13%) of other disease. The median follow-up of those patients alive at last follow-up was 40 months (IQR 18–75).

On univariable Cox regression analyses macroscopic sessile architecture was significantly associated with RFS

and CSS (Tables 2 and 3, respectively). Two-year RFS and CSS estimates for patients with papillary architecture tumors were 85% (SE 2%) and 90% (SE 1%), respectively, compared with 58% (SE 4%) and 66% (SE 4%) for those with sessile architecture tumors, respectively (Figs. 1A and B, respectively).

On multivariable Cox regression analyses that adjusted for the effects of age, stage, grade, lymph node status, and adjuvant chemotherapy, sessile architecture was an independent predictor of both RFS (hazard ratio {HR} 1.5, 95% confidence interval {95% CI} 1.03–2.1, $P = 0.036$), and CSS (HR 1.5, 95% CI 1.03–2.2, $P = 0.03$).

Analyses were rerun after excluding 324 patients who were alive and disease-free at follow-up < 60 months. Tumor architecture was significantly associated with RFS (HR 3.1; $P < 0.0001$) and CSS (HR 3.3; $P < 0.0001$) in univariable analyses. However, in multivariable analyses that adjusted for the same covariates included in the other models, only a non-statistically significant trend was observed (RFS: HR 1.3; 95% CI: 0.9–1.8; $P = 0.199$; CSS: HR 1.3; 95% CI 0.9–1.9; $P = 0.184$).

4. Discussion

In the current study, we found that macroscopic sessile architecture was present in 20% of patients treated with RNU and it was associated to other established features

Table 2

Univariable and multivariable Cox regression analysis of tumor architecture for prediction of disease recurrence in 754 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma (179 recurrences)

| Parameter | Univariable analysis | | | Multivariable analysis | | |
|-----------------------|----------------------|------------|---------|------------------------|------------|---------|
| | HR | 95% CI | P | HR | 95% CI | P |
| Age | 1.02 | 1.003–1.03 | 0.02 | 1.02 | 1.005–1.04 | 0.01 |
| Stage | | | <0.0001 | | | <0.0001 |
| Ta/Tis | 1 | — | — | 1 | — | — |
| T1 | 1.1 | 0.6–2.1 | 0.8 | 1.1 | 0.5–2.1 | 0.86 |
| T2 | 3.1 | 1.7–5.6 | 0.0003 | 2.5 | 1.3–4.7 | 0.006 |
| T3 | 5.9 | 3.4–10.2 | <0.0001 | 3.6 | 1.9–6.6 | <0.0001 |
| T4 | 33.8 | 18.1–63.3 | <0.0001 | 14.1 | 6.7–29.6 | <0.0001 |
| Grade | 3.1 | 1.7–5.4 | 0.0001 | 1.5 | 0.8–2.8 | 0.17 |
| pN | | | <0.0001 | | | 0.49 |
| N0 | 1 | — | — | 1 | — | — |
| Nx | 0.9 | 0.6–1.3 | 0.58 | 1 | 0.64–1.5 | 0.91 |
| N+ | 5.6 | 3.4–9.3 | <0.0001 | 2.0 | 1.1–3.5 | 0.01 |
| Sessile architecture | 2.9 | 2.1–4.0 | <0.0001 | 1.5 | 1.03–2.1 | 0.036 |
| Adjuvant chemotherapy | 6.2 | 4.4–8.7 | <0.0001 | 2.7 | 1.8–4.1 | <0.0001 |

Nx = lymphadenectomy not performed.

of biologically aggressive UTUC such as advanced pathological T and N stages. Tumor grade was no significant prognostic factor in the multivariate model. This might be explained by its close association with macroscopic tumor architecture. Once adjusted for the effects of standard covariates, macroscopic tumor architecture was an independent predictor of both RFS and CSS but, due to the small number of cases, it only showed a non-statistically significant trend for RFS and CSS in the subgroup analyses limited to patients with follow-up longer than 5 years.

Nearly 30% of patients with UTUC die due to metastatic disease within 5 years after RNU [6]. Early identification of the patients at high risk of failing surgery alone could help tailor follow-up surveillance after RNU

and/or select appropriate patients for adjuvant therapy. While standard prognostic factors, such as pathological T stage, N stage, and grade are associated with outcomes after RNU, their accuracy is not sufficient for clinical decision-making. Other predictors that are easily obtainable and measurable are necessary for improved management of patients with UTUC. Macroscopic tumor architecture is readily available and a reproducible pathologic feature that adds independent prognostic information beyond that available from standard histopathologic characteristics.

Recently, there has been an increased interest in microscopic tumor growth pattern in urothelial carcinoma (Table 4). Jimenez et al. described tumor growth patterns for muscle invasive UCB as an independent predictor of

Table 3

Univariable and multivariable Cox regression analysis of tumor architecture for prediction of cancer-specific mortality in 754 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma (151 cancer-specific deaths)

| Parameter | Univariable analysis | | | Multivariable analysis | | |
|-----------------------|----------------------|------------|---------|------------------------|------------|---------|
| | HR | 95% CI | P | HR | 95% CI | P |
| Age | 1.02 | 1.006–1.04 | 0.008 | 1.03 | 1.007–1.04 | 0.007 |
| Stage | | | <0.0001 | | | <0.0001 |
| Ta/Tis | 1 | — | — | 1 | — | — |
| T1 | 1.05 | 0.5–2.3 | 0.9 | 1 | 0.44–2.3 | 0.99 |
| T2 | 3.3 | 1.6–6.6 | 0.001 | 2.5 | 1.2–5.3 | 0.01 |
| T3 | 7.4 | 3.9–13.9 | <0.0001 | 4.5 | 2.2–9.1 | <0.0001 |
| T4 | 45.5 | 22.4–92.4 | <0.0001 | 19.5 | 8.4–45.6 | <0.0001 |
| Grade | 3.6 | 1.9–7.1 | 0.0002 | 1.7 | 0.8–3.4 | 0.17 |
| pN | | | <0.0001 | | | 0.67 |
| N0 | 1 | — | 1 | — | — | — |
| Nx | 1.0 | 0.6–1.6 | 0.96 | 1.2 | 0.7–1.9 | 0.55 |
| N+ | 6.5 | 3.7–11.5 | <0.0001 | 2 | 1.06–3.7 | 0.03 |
| Sessile architecture | 3.3 | 2.4–4.6 | <0.0001 | 1.5 | 1.03–2.2 | 0.03 |
| Adjuvant chemotherapy | 6.4 | 4.4–9.2 | <0.0001 | 2.5 | 1.6–4.0 | <0.0001 |

Nx = lymphadenectomy not performed.

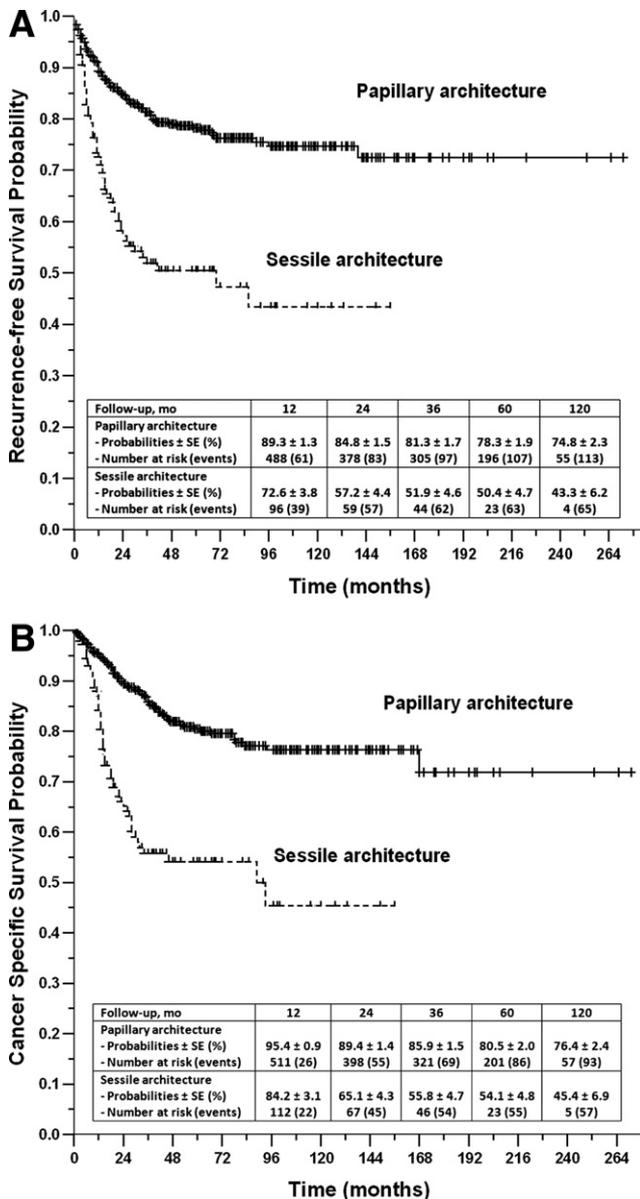


Fig. 1. (A) Kaplan-Meier curves of recurrence-free survival stratified by tumor architecture in 754 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma (P values $<$ 0.0001). (B) Kaplan-Meier curves of cancer-specific survival stratified by tumor architecture in 754 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma (P values $<$ 0.0001).

oncologic outcome in patients treated with radical cystectomy [17]. Kruger et al. found similar results in muscle-invasive UCB [18], while Denzinger et al. reported that microscopic tumor invasion pattern was a strong predictor of cancer-specific survival in T1G3 UCB [19], while Bircan et al. stated that these patterns have large impact on stage [20]. In UTUC, the evidence is weaker. Langner et al. found that the microscopic patterns of invasion in UTUC are independent predictors of metastasis-free survival [4]. There is no study evaluating the

correlation between macroscopic and microscopic architecture.

In a large multi-center series of UTUC patients including more than 1,300 patients treated with RNU at 12 different institutions, Remzi et al. showed that macroscopic sessile architecture was independently associated with oncologic outcomes. Specifically, the authors found that patients with sessile tumors had a 1.5-fold higher risk of both disease recurrence and cancer-related death once adjusted for the pathologic T stage, grade, N stage [14]. Before introduction into daily pathologic reporting and clinical decision-making, these findings needed to be externally validated in an independent cohort. We confirm the strong independent prognostic value of macroscopic tumor architecture in a large, international cohort of RNU patients. Therefore, we recommend that macroscopic tumor architecture should be routinely mentioned in pathologic reports from RNU specimens, and it should be considered for inclusion into risk-stratification models for patient counseling regarding follow-up protocols and identifying those at high risk of disease recurrence and cancer-related death for enrolment into clinical trials on adjuvant therapy.

There are several important limitations of the present study that must be discussed. First are the limitations inherent to retrospective analyses. Moreover, inter-observer variations have not been examined. Detailed definition criteria for macroscopic architecture are missing, and the present study fails to define such parameters. But in contrast to microscopic architecture, macroscopic judgment is easy and only bases on a simple aspect. Therefore, we believe that there is only a very small inter-investigator variation. Macroscopic architecture seems to be a simple surrogate parameter for tumor biology that currently cannot be expressed in a more effective way.

Furthermore, there is an inability to account for all the variables that might be decisive for the outcome, for example different surgical techniques and quality by multiple surgeons, different numbers of lymph nodes removed, and multiple pathologists evaluating the specimen. However, this can be interpreted as strength, as it stands for a real-world practice and the results may have high external validity in the general urology community. The study period spans more than 21 years, and the data in the present study may not represent current practice patterns. There was no inclusion of patients who have been treated by only endoscopic measures or distal ureterectomy without RNU. Finally and foremost, there are limitations concerning histopathologic assessment. Mixed papillary-sessile cases were not judged as independent category, macroscopic sessile growth was defined as being predominant. Secondly, it could be questioned whether the categories of papillary vs. sessile are reproducible, as there are no published data in support of the reproducibility of this gross growth designation. But

Table 4
Summary of literature for microscopic growth pattern and macroscopic architecture for UTUC and UCB

| Authors | Publication | Patients | Type of UC | Aspect | Criteria | Results | Conclusion |
|---|---|----------|------------------------|---|---|--|--|
| Langner et al. Virchows Arch 2006 [4] | Patterns of invasion and histological growth as prognostic indicators in urothelial carcinoma of the upper urinary tract | 268 | Upper tract | Microscopic assessment of pattern of infiltration | 1. Most aggressive pattern (nodular<trabecular <infiltrative) 2. Three-tiered classification according to Jimenez [17] 3. Presence of glandular or squamous differentiation | Infiltrative 79%, trabecular 23%, nodular pattern 7% | Tumor stage and infiltrative pattern are independent predictors of metastasis-free-survival |
| Remzi et al. BJU Int 2008 [14] | Tumor architecture is an independent predictor of outcomes after nephroureterectomy | 1363 | Upper tract | Macroscopic assessment gross tumor architecture | Gross tumor architecture, based on predominant feature according to WHO criteria by Epstein [21] | 72% papillary, 28% sessile | Architecture is an independent predictor of cancer recurrence and cancer-specific mortality |
| Present study: Fritsche et al. Urol Oncol 2010 | Macroscopic tumor architecture is a pathologic feature of biologically aggressive upper tract urothelial carcinoma | 754 | Upper tract | Macroscopic assessment gross tumor architecture | Macroscopic aspect, judged by pathologist, microscopic inverted papillary type included in sessile group | 80% papillary, 20% sessile | Macroscopic architecture is an independent predictor of cancer recurrence and cancer-specific mortality |
| Jimenez et al. Am J Surg Pathol 2000 [17] | Grading the invasive component of urothelial carcinoma of the bladder and its relationship with progression-free survival | 93 | pT \geq 2 of bladder | Microscopic assessment of pattern of infiltration | 1. Patterns: nodular, trabecular, infiltrative 2. Grouping the cases according to the major pattern, the minor pattern, both major and minor patterns, and the presence of any pattern either as major or as minor | Major pattern: nodular 14%, trabecular 42%, infiltrative 44%; 45% infiltrative component, 55% noninfiltrative | Infiltrative growth pattern may be associated with a more dismal prognosis |
| Kruger et al. Oncol Rep 2004 [18] | Histologic tumor growth pattern is significantly associated with disease-related survival in muscle-invasive transitional cell carcinoma of the urinary bladder | 153 | Pt \geq 2 of bladder | Microscopic assessment of pattern of infiltration | 1. Assessment of dominant pattern 2. Two-tiered classification infiltrative component vs. noninfiltrative (trabecular and nodular) | Major pattern: nodular 22%, trabecular 63%, infiltrative 14%; 45% infiltrative component, 55% noninfiltrative | Independent predictor of disease-related survival |
| Bircan et al. Pathol Oncol Res 2005 [20] | The effect of tumor invasion patterns on pathologic stage of bladder urothelial carcinomas | 62 | pT \geq 1 of bladder | Microscopic assessment of pattern of infiltration | 1. Mayor pattern: nodular/trabecular/infiltrative 2. Homogeneity of pattern | Major pattern: nodular 77%, trabecular 72%, infiltrative 11% | Patterns have large impact on stage; invasion heterogeneity appears to be of value in determination of biologic aggressiveness |
| Denzinger et al. Scand J Urol Nephrol 2009 [19] | Prognostic value of histopathological tumor growth patterns at the invasion front of T1G3 urothelial carcinoma of the bladder | 205 | T1G3 of bladder | Microscopic assessment of pattern of infiltration | Single pattern at invasion front: nodular/trabecular/infiltrative, no grouping | Nodular 27%, trabecular 58%, infiltrative 15% | Growth pattern is an independent predictor of cancer recurrence and cancer-specific mortality |

as the present study reproduces the independent prognostic value of macroscopic architecture, there should be a minimal interobserver variability of this easily obtainable tumor characteristic.

5. Conclusion

The present study confirms the independent prognostic value of macroscopic tumor architecture in a large, independent, multicenter RNU cohort. Tumor architecture of RNU specimens should be mentioned in pathology reports and included in post-RNU prognostic models in order to refine current clinical decision making regarding follow-up protocol and adjuvant therapy.

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