

# Tumour architecture is an independent predictor of outcomes after nephroureterectomy: a multi-institutional analysis of 1363 patients

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Accepted for publication 12 June 2008

Study Type – Prognosis (retrospective cohort study)  
Level of Evidence 2b

## OBJECTIVE

To assess whether tumour architecture can help to refine the prognosis of patients treated with nephroureterectomy (NU) for urothelial carcinoma (UC) of the upper urinary tract (UT), as the prognostic value of tumour architecture (papillary vs sessile) in UTUC remains elusive.

## PATIENTS AND METHODS

The study included 1363 patients with UTUC and treated with radical NU at 12 centres worldwide. All slides were re-reviewed according to strict criteria by genitourinary pathologists who were unaware of the

findings of the original pathology slides and clinical outcomes. Gross tumour architecture was categorized as sessile vs papillary.

## RESULTS

Papillary growth was identified in 983 patients (72.2%) and sessile growth in 380 (27.8%). The sessile growth pattern was associated with higher tumour grade, more advanced stage, lymphovascular invasion, and metastasis to lymph nodes (all  $P < 0.001$ ). In multivariable Cox regression analyses that adjusted for the effects of pathological stage, grade and lymph node status, tumour architecture (sessile or papillary) was an independent predictor of cancer recurrence (hazard ratio 1.5,  $P = 0.002$ ) and cancer-specific mortality (1.6,  $P = 0.001$ ). Adding tumour architecture increased the predictive accuracy of a model that comprised pathological stage, grade

and lymph node status for predicting cancer recurrence and cancer-specific death by a minimal but statistically significant margin (gain in predictive accuracy 1% and 0.5%, both  $P < 0.001$ ).

## CONCLUSION

The tumour architecture of UTUC is associated with established features of biologically aggressive disease, and more importantly, with prognosis after radical NU. Including tumour architecture in predictive models for disease progression should be considered, aiming to identify patients who might benefit from early systemic therapeutic intervention.

## KEYWORDS

urothelial carcinoma, urinary tract cancer, architecture, recurrence, survival

## INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is an uncommon malignancy accounting for ≈5% of urothelial malignancies, and <10% of renal tumours [1]. Presently, radical nephroureterectomy (RNU) with removal of a

bladder cuff is the primary treatment for UTUC. Of patients with UTUC, 20–55% develop metastases and eventually die from their disease [1–4]. Tumour stage, grade, lymph node (LN) invasion and extent of surgery have been established as significant prognostic factors [4–6].

The prognostic importance of tumour architecture (papillary vs sessile) has not been conclusively investigated in UTUC. In bladder UC, sessile tumour architecture has been suggested to predict a worse outcome [7]. The aim of the current study was to assess whether tumour architecture

TABLE 1 The clinical and pathological characteristics of 1363 patients treated with RNU for UTUC

Variable	All	Tumour architecture		P
		Papillary	Sessile	
No. of patients	1363	938	380	
Mean (median, range) age, years	68.3 (69.7, 27–97)	67.7 (68.5, 27–97)	69.9 (71.4, 34–91)	0.001*
n (%):				
Gender				
Men	921 (67.6)	673 (73.1)	248 (26.9)	
Women	442 (32.4)	310 (70.1)	132 (29.9)	0.273†
Pathological T stage				
T0/Ta/Tis	301 (22.1)	274 (91)	27 (9)	
T1	299 (21.9)	273 (91.3)	26 (8.7)	
T2	252 (18.5)	192 (76.2)	60 (23.8)	
T3	443 (32.5)	233 (52.6)	210 (47.4)	
T4	68 (4.9)	11 (16.2)	57 (83.8)	<0.001†
Pathological grade				
Low	495 (36.3)	466 (94.1)	29 (5.9)	
High	868 (63.7)	517 (59.6)	351 (40.4)	<0.001†
LN status				
Unknown	788 (57.8)	586 (76)	187 (24)	
Negative	440 (32.3)	340 (75)	115 (25)	
Positive	135 (9.9)	57 (42)	78 (58)	<0.001†
LVI				
Negative	1025 (75)	818 (79.8)	207 (20.2)	
Positive	338 (25)	165 (48.8)	173 (51.2)	<0.001†
Concomitant CIS				
Negative	972 (71)	760 (78.2)	212 (21.8)	
Positive	391 (29)	223 (57.0)	168 (43.0)	<0.001†

\*Mann–Whitney U-test; †Pearson chi-square test.

could help to refine the prognosis of patients with UTUC.

## PATIENTS AND METHODS

The study was approved by an institutional review board, with all participating sites providing the necessary institutional data-use agreements before starting the study. In all, 12 academic centres worldwide provided data; a computerized databank was generated for data transfer. After combining the datasets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, all identified anomalies were resolved before data analysis. Before the final analysis the database was 'frozen' and the final dataset was produced for the current analysis. This study comprised 1363 patients who had RNU with a bladder cuff between 1987 and 2007.

All surgical specimens were processed according to standard pathological procedures, and all slides were re-reviewed by genitourinary pathologists according to identical strict criteria and who were unaware of the clinical outcomes. Tumours were staged pathologically according to the 2002 TNM classification of the American Joint Committee on Cancer, and tumours were graded according to the 1998 WHO/International Society of Urologic Pathology consensus classification. Tumour architecture (papillary vs sessile) was defined based on the predominant feature [7].

Patients were generally followed every 3–4 months for the first year after RNU, every 6 months from 2–5 years, and annually thereafter. The follow-up consisted of a history, physical examination, routine blood 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 CT or MRI were used when clinically indicated. The mean (median, range) follow-up for these patients was 51.1 (35.8, 1.2–250) months.

The cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or by death certificates alone. Perioperative mortality (any death within 30 days of surgery or before discharge) was censored at time of death for urothelial disease-specific survival analyses.

The chi-squared test was 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. Univariable recurrence and survival probabilities after RNU were estimated using the Kaplan–Meier method. Univariable

TABLE 2 Univariable and multivariable Cox regression analyses predicting disease recurrence and cancer-specific death in 1363 patients treated with RNU for UTUC

Variable	HR; P	
	Univariable	Multivariable
<i>Disease recurrence</i>		
Pathological T stage	-; <0.001	-; <0.001
T1 vs T0/Ta/Tis	1.72; 0.05	1.38; 0.25
T2 vs T0/Ta/Tis	4.05; <0.001	2.89; <0.001
T3 vs T0/Ta/Tis	9.23; <0.001	5.56; <0.001
T4 vs T0/Ta/Tis	36.9; <0.001	16.89; <0.001
Pathological grade	4.36; <0.001	1.91; <0.001
<i>LN status</i>		
Positive vs negative/Nx	4.83; <0.001	2.01; <0.001
<i>Architecture</i>		
Sessile vs papillary	3.65; <0.001	1.45; 0.002
<i>Predictive accuracy, %</i>		
Base model	78.4	
Base model + tumour architecture	78.9	
Gain including tumour architecture	+0.5; <0.001	
<i>Cancer-specific death</i>		
Pathological T stage	-; <0.001	-; <0.001
T1 vs T0/Ta/Tis	1.51; 0.19	1.29; 0.42
T2 vs T0/Ta/Tis	4.07; <0.001	2.93; <0.001
T3 vs T0/Ta/Tis	9.14; <0.001	5.35; <0.001
T4 vs T0/Ta/Tis	34.37; <0.001	13.12; <0.001
Pathological grade	3.99; <0.001	1.67; 0.003
<i>LN status</i>		
Positive vs negative/Nx	4.83; <0.001	1.74; <0.001
<i>Architecture</i>		
Sessile vs papillary	3.92; <0.001	1.58; 0.001
<i>Predictive accuracy, %</i>		
Base model	78.3	
Base model + tumour architecture	79.3	
Gain including tumour architecture	+1.0; <0.001	

and multivariable Cox regression models addressed time to recurrence and disease-specific mortality after RNU. In all models, proportional hazards assumptions were systematically verified, using the Grambsch-Therneau residual-based test. The change in predictive accuracy resulting from adding the variable of interest to standard predictor variables was quantified with Harrell's concordance index [8,9]. Internal validation was performed using 200-bootstrap re-samples [8,9]. Predictive accuracy estimates were expressed as proportions and compared with the Mantel-Haenszel test. All reported *P* values are two-sided and statistical significance was set at  $\leq 0.05$ . Nominal *P* values are given; no adjustments were made for the number of *P* values calculated.

RESULTS

Table 1 lists the clinicopathological characteristics of the 1363 patients; papillary architecture was found in 983 patients (72.2%) and sessile architecture in 380 (27.8%). Regional lymphadenectomy was generally performed in patients with enlarged lymph nodes on preoperative axial imaging or with adenopathy detected during intraoperative examination. As such, 58% of patients in this cohort did not have a lymphadenectomy (pNx).

Sessile architecture was associated with advanced pathological stage, higher tumour grade, metastasis to lymph nodes, lymphovascular invasion (LVI) and

concomitant carcinoma in-situ (CIS) (all *P* < 0.001).

Disease recurrence is shown in Table 2; the 5-year recurrence-free survival (RFS) estimate was 70% (Fig. 1A). The median RFS for papillary vs sessile UTUC was 132 vs 26 months, respectively (*P* < 0.001). The 5- and 10-year RFS rates were significantly lower for sessile than for papillary tumours (40% and 32% vs 77% and 75%, respectively; Fig. 1B). On univariable and multivariable analyses, pathological stage, grade, LN status and tumour architecture (all *P* < 0.001; Table 2) were associated with disease recurrence. The predictive accuracy of the base model for disease recurrence that included pathological stage, grade and LN status was 78.4%; adding tumour architecture improved the predictive accuracy of this base model (0.5% gain, *P* < 0.001).

Cancer-specific survival (CSS) is also shown in Table 2; the 5-year CSS estimate was 74% (Fig. 1C). The median CSS for papillary vs sessile UTUC was 132 vs 45 months. The 5- and 10-year CSS rates were lower for sessile than for papillary tumours (45% and 34% vs 80% and 77%, respectively; Fig. 1D). On univariable and multivariable analyses, pathological stage, grade, LN status and tumour architecture (all *P* < 0.001; except multivariable, grade *P* = 0.003; Table 2). The predictive accuracy of the base model for CSS was 78.3%; adding tumour architecture improved the predictive accuracy of this base model by only 1.0% (*P* < 0.001).

DISCUSSION

As in UC of the urinary bladder, about two-thirds of patients treated with RNU for UTUC have a papillary growth pattern and a third a sessile growth pattern. A solid or sessile cancer is highly suggestive of muscle-invasive disease in bladder cancer [7,10]. However, to our knowledge, there is no study evaluating the predictive accuracy of the macroscopic description of tumour architecture with outcomes in patients with UTUC. Sessile tumour growth was associated with established features of biologically aggressive UTUC, e.g. higher tumour grade, advanced stage, LVI and LN metastasis. More importantly, tumour architecture was an independent predictor of cancer recurrence and cancer-specific mortality after RNU. Adding tumour architecture improved

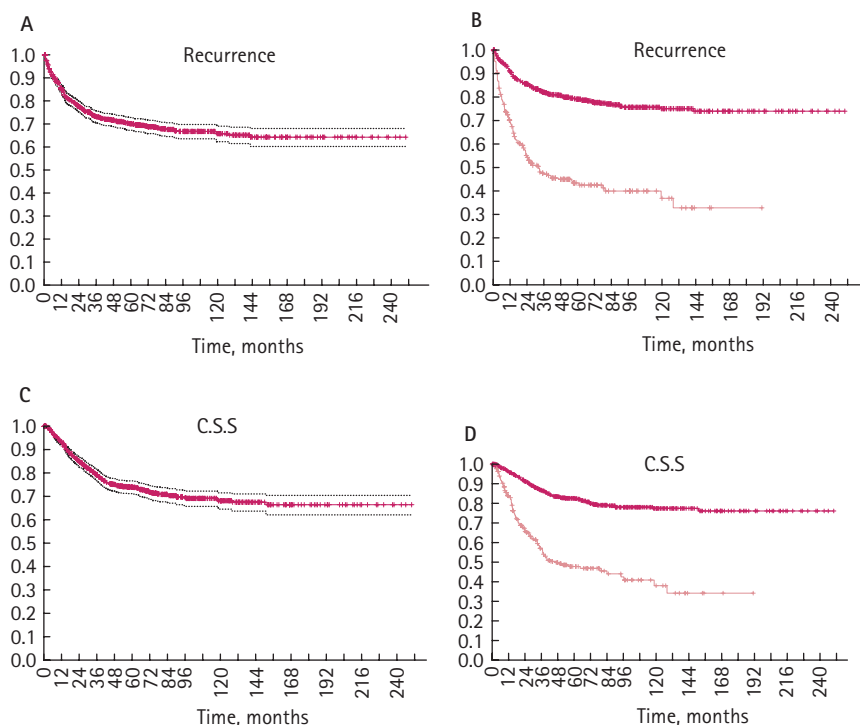
marginally but significantly the accuracy of a model based on established pathological features for predicting both cancer recurrence and cancer-specific death.

Tumour architecture was independently associated with clinical outcomes after RNU; while both papillary and sessile tumours can be invasive and high-grade, leading to disease recurrence, sessile tumours were more likely to behave aggressively. While small UTUCs are rarely muscle-invasive, having a nonpapillary architecture (sessile form) can predict muscle invasion. As such, 44% of papillary tumours vs 86% of sessile tumours were muscle-invasive. At 5 years after RNU, 40% of patients with papillary vs 77% with sessile tumours had disease recurrence. Langner *et al.* [11] showed that infiltrative UTUC were of higher stage and grade (both  $P < 0.001$ ). In multivariable analyses only tumour stage and tumour architecture were independent markers for metastasis-free survival. Usually sessile tumours also have a higher grade, because most infiltrative UC are high grade [12].

Although cancer architecture only marginally improved the predictive accuracy for disease recurrence and CSS after RNU it remained statistically significant. This feature is readily available, as it is generally reported in standard pathology reports. Moreover, the greatest advantage of this feature is that it is readily available during ureteroscopic evaluation and correlates very well with stage and grade, which are difficult to assess during endoscopic examination. Thus, it could be a useful marker in selected patients to guide conservative vs extirpative further therapy. Therefore its inclusion in predictive tools for UTUC should be considered. Such predictive tools could be helpful in patient counselling, planning the follow-up, and clinical trial design.

There are several limitations to the present study. First there are limitations inherent in retrospective analyses. In addition, the present patients had RNU by several surgeons at many sites, and had their specimens evaluated by many pathologists. While prognostic factors might perform well in the selected group of patients operated by one surgeon, it remains to be determined whether these are applicable to the greater population of patients with UTUC. All specimens were re-examined by dedicated genitourinary pathologists according to strict criteria agreed

FIG. 1. Kaplan-Meier estimates for RFS (A,B) and CSS (C,D) in 1363 patients treated with RNU for UTUC; (A,C) overall estimates and (B,D) estimates stratified by tumour architecture.



on by all participating pathologists. Thus, the multi-institutional nature of the study and the use of 'local' pathological interpretation might make the results more relevant and applicable in both the academic and community settings.

In conclusion, gross tumour architecture of UTUC is associated with established features of aggressive disease and clinical outcomes after RNU. While it is an independent risk factor for disease recurrence and cancer-specific mortality, considering this variable increases the predictive accuracy only marginally. After validation, inclusion of tumour architecture into predictive models for disease progression should be considered, aiming to identify patients who might benefit from early systemic therapeutic intervention.

CONFLICT OF INTEREST

None declared.

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**Abbreviations:** RNU, radical nephroureterectomy; UTUC, upper tract urothelial carcinoma; CSS, cancer-specific survival; CIS, carcinoma in-situ; RFS, recurrence-free survival; LVI, lymphovascular invasion; LN, lymph node.