ELSEVIER

Urologic Oncology: Seminars and Original Investigations xx (2010) xxx

UROLOGIC ONCOLOGY

Original article

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

Hans-Martin Fritsche, M.D.,[a] Giacomo Novara, M.D.,[b] Maximilian Burger, M.D.,[a] Amit Gupta, M.D.,[c] Kazumasa Matsumoto, M.D.,[d] Wassim Kassouf, M.D.,[e] Kanishka Sircar, M.D.,[e] Filiberto Zattoni, M.D.,[b] Tom Walton, M.D.,[f] Stefan Tritschler, M.D.,[g] Shiro Baba, M.D.,[d] Patrick J. Bastian, M.D.,[g] Juan I. Martínez-Salamanca, M.D.,[h] Christian Seitz, M.D.,[i] Wolfgang Otto, M.D.,[a] Wolf Ferdinand Wieland, M.D.,[a] Pierre I. Karakiewicz, M.D., M.P.H.,[j] Vincenzo Ficarra, M.D.,[b] Arndt Hartmann, M.D.,[k] Shahrokh F. Shariat, M.D., Ph.D.[l,*]

[a] *Caritas St. Josef Medical Center, University of Regensburg, Regensburg, Germany*
[b] *University of Padua, Padua, Italy*
[c] *University of Texas Southwestern Medical Center, Dallas, TX 75390, USA*
[d] *Kitasato University School of Medicine, Sagamihara, Japan*
[e] *McGill University Health Centre, Montréal, Canada*
[f] *Nottingham City Hospital, Nottingham, United Kingdom*
[g] *Ludwig Maximilians University, Klinikum Grosshadern, Munich, Germany*
[h] *Hospital Universitario Puerta de Hierro-Majadahonda, Universidad Autónoma de Madrid, Madrid, Spain*
[i] *General Hospital Bolzano, Bolzano, Italy*
[j] *University of Montréal, Montréal, Canada*
[k] *Institute of Pathology, University of Erlangen, Erlangen, Germany*
[l] *Weill Medical College of Cornell University, New York, NY 10021, USA*

Received 14 May 2010; received in revised form 13 July 2010; accepted 16 July 2010

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.

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

* Corresponding author. Tel.: (469) 363-8500; fax: (212) 746-0975.
E-mail address: sfshariat@gmail.com (S.F. Shariat).

1078-1439/$ – see front matter
doi:10.1016/j.urolonc.2010.07.010

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 databank 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

		Architecture		
		Papillary (%)	Sessile (%)	
	No. of patients (%)	(n = 604, 80.1%)	(n = 150, 19.9%)	P
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)

	Univariable analysis			Multivariable analysis		
Parameter	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.

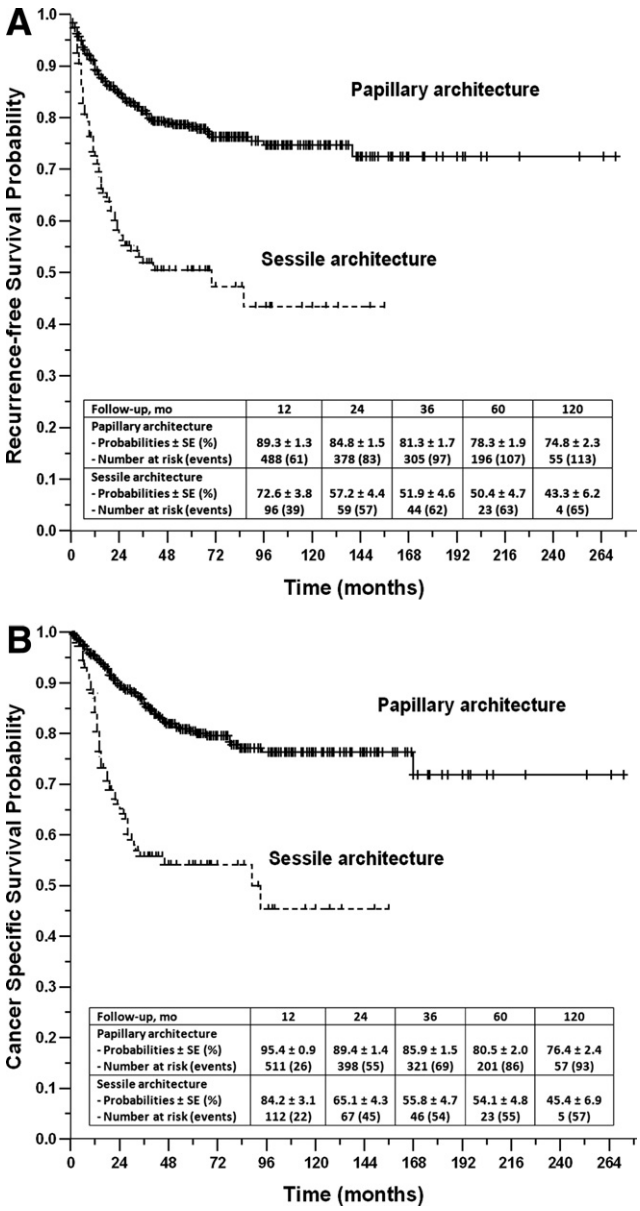
Nearly 30% of patients with UTUC die due to metastatic disease within 5 years after RNU [6]. Early identification of the patients at high risk of failing surgery alone could help tailor follow-up surveillance after RNU and/or select appropriate patients for adjuvant therapy. While standard prognostic 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)

	Univariable analysis			Multivariable analysis		
Parameter	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.



Follow-up, mo	12	24	36	60	120
Papillary architecture					
- Probabilities ± SE (%)	89.3 ± 1.3	84.8 ± 1.5	81.3 ± 1.7	78.3 ± 1.9	74.8 ± 2.3
- Number at risk (events)	488 (61)	378 (83)	305 (97)	196 (107)	55 (113)
Sessile architecture					
- Probabilities ± SE (%)	72.6 ± 3.8	57.2 ± 4.4	51.9 ± 4.6	50.4 ± 4.7	43.3 ± 6.2
- Number at risk (events)	96 (39)	59 (57)	44 (62)	23 (63)	4 (65)

Follow-up, mo	12	24	36	60	120
Papillary architecture					
- Probabilities ± SE (%)	95.4 ± 0.9	89.4 ± 1.4	85.9 ± 1.5	80.5 ± 2.0	76.4 ± 2.4
- Number at risk (events)	511 (26)	398 (55)	321 (69)	201 (86)	57 (93)
Sessile architecture					
- Probabilities ± SE (%)	84.2 ± 3.1	65.1 ± 4.3	55.8 ± 4.7	54.1 ± 4.8	45.4 ± 6.9
- Number at risk (events)	112 (22)	67 (45)	46 (54)	23 (55)	5 (57)

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-interpreter 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 ≥ 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 ≥ 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 ≥ 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.

References

[1] Jemal A, Siegel R, Ward E, et al. Cancer Statistics, 2008. CA Cancer J Clin 2009;59:225–49.

[2] NCCN clinical practice guidelines in oncology. Bladder cancer including upper tract tumors and urothelial carcinoma of the prostate. V. 1.2010

[3] Kang CH, Yu TJ, Hsieh HH, et al. The development of bladder tumors and contralateral upper urinary tract tumors after primary transitional cell carcinoma of the upper urinary tract. Cancer 2003; 98:1620–6.

[4] Langner C, Hutterer G, Chromecki T, et al. Tumor necrosis as prognostic indicator in transitional cell carcinoma of the upper urinary tract. J Urol 2006;176:910–4.

[5] Lughezzani G, Jeldres C, Isbarn H, et al. Nephroureterectomy and segmental ureterectomy in the treatment of invasive upper tract urothelial carcinoma: A population-based study of 2,299 patients. Eur J Cancer 2009;45:3291–7.

[6] Margulis V, Shariat SF, Matin SF, et al. The Upper Tract Urothelial Carcinoma Collaboration. Outcomes of radical nephroureterectomy: A series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer 2009;115:1224–33.

[7] Novara G, De Marco V, Gottardo F, et al. Independent predictors of cancer-specific survival in transitional cell carcinoma of the upper urinary tract: Multi-institutional dataset from 3 European centers. Cancer 2007;110:1715–22.

[8] Rabbani F, Perrotti M, Russo P, et al. Upper-tract tumors after an initial diagnosis of bladder cancer: Argument for long-term surveillance. J Clin Oncol 2001;19:94–100.

[9] Roscigno M, Shariat SF, Margulis V, et al. Impact of lymph node dissection on cancer specific survival in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy. J Urol 2009;181:2482–9.

[10] Roscigno M, Shariat SF, Margulis V, et al. The extent of lymphadenectomy seems to be associated with better survival in patients with nonmetastatic upper-tract urothelial carcinoma: How many lymph nodes should be removed? Eur Urol 2009;56:512–8.

[11] Zigeuner R, Pummer K. Urothelial carcinoma of the upper urinary tract: Surgical approach and prognostic factors. Eur Urol 2008;53: 720–31.

[12] Karam JA, Margulis V, Montorsi F, et al. Carcinoma in situ of the upper urinary tract treated with radical nephroureterectomy—results from a multicenter study. Eur Urol 2008;54:961–3.

[13] Raman JD, Ng CK, Scherr DS, et al. Impact of tumor location on prognosis for patients with upper tract urothelial carcinoma managed by radical nephroureterectomy. Eur Urol 2009 Jul 15. [Epub ahead of print]

[14] Remzi M, Haitel A, Margulis V, et al. Tumor architecture is an independent predictor of outcomes after nephroureterectomy: A multi-institutional analysis of 1363 patients. BJU Int 2009;103:307–11.

[15] Zigeuner R, Pummer K. Urothelial carcinoma of the upper urinary tract: Surgical approach and prognostic factors. Eur Urol 2008;53: 720–31.

[16] Greene FL, Page DL, Fleming ID, et al. American Joint Committee on Cancer (AJCC) Staging Manual, 6th ed. Philadelphia: Springer; 2002.

[17] Jimenez RE, Gheiler E, Oskanian P, et al. Grading the invasive component of urothelial carcinoma of the bladder and its relationship with progression-free survival. Am J Surg Pathol 2000;24:980–7.

[18] Krüger S, Noack F, Böhle A, et al. Histologic tumor growth pattern is significantly associated with disease-related survival in muscle-invasive transitional cell carcinoma of the urinary bladder. Oncol Rep 2004;12:609–13.

[19] Denzinger S, Burger M, Fritsche HM, et al. Prognostic value of histopathological tumor growth patterns at the invasion front of T1G3 urothelial carcinoma of the bladder. Scand J Urol Nephrol 2009;43: 282–7.

[20] Bircan S, Candir O, Kapucuoglu N. The effect of tumor invasion patterns on pathologic stage of bladder urothelial carcinomas. Pathol Oncol Res 2005;11:87–91.

[21] Epstein JI, Amin MB, Reuter VR, et al. The Bladder Consensus Conference Committee. The World Health Organization/International Society of Urological Pathology Consensus Classification of Urothelial (Transitional Cell) Neoplasms of the Urinary Bladder. Am J Surg Pathol 1998;22:1435–48.