Concordance and Clinical Significance of Uncommon Variants of Bladder Urothelial Carcinoma in Transurethral Resection and Radical Cystectomy Specimens

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OBJECTIVE To evaluate the concordance and prognostic role of histologic variants of bladder urothelial carcinoma in transurethral resection of bladder tumor (TURBT) and radical cystectomy (RC) specimens.

METHODS Clinicopathologic information available at the time of RC and follow-up data from 4110 RC specimens, collected between January 2000 and December 2009 at 17 tertiary referral centers were retrospectively analyzed and evaluated for the presence or absence of uncommon variants of bladder urothelial carcinoma. The presence or absence of uncommon variants of bladder urothelial carcinoma was evaluated on previous TURBT specimens of patients undergoing RC. Cox regression was used to assess the impact of these parameters on cancer-specific survival, and the Kaplan-Meier test for disease-free survival was plotted for survival estimate.

RESULTS Of 4110 patients, 579 were found to have uncommon variants of bladder urothelial carcinoma at RC (14.1%), whereas 266 (6.4%) at TURBT. A lack of agreement about uncommon variants was observed between TURBT and RC specimens in the entire population ($P < .001$). The presence of uncommon variants at TURBT was associated with an increased risk of pathologic upstage (hazard ratio, 3.24; confidence interval, 1.19-6.37; $P < .003$) and significant decrease in cancer-specific survival and recurrence-free survival ($P < .001$).

CONCLUSION Although the concordance of presence of uncommon histologic variants of urothelial bladder carcinoma between TURBT and RC is low, the presence of uncommon histologic variants of urothelial bladder carcinoma at TURBT is associated with a less favorable clinical outcome. UROLOGY 84: 1141–1146, 2014. © 2014 Elsevier Inc.

Urothelial carcinoma of the urinary bladder is known to exhibit unusual morphologic features (variants) that deviate from conventional appearance.[1,2] This propensity for divergent differentiation may have potential diagnostic, prognostic, and therapeutic implications.[3,4] The recognition of histologic variants of urothelial carcinoma is important because (1) awareness of the unusual pattern may be critical in avoiding diagnostic misinterpretations, (2) some types may be associated with different clinical outcome, and (3) some may require a different therapeutic approach.[5-7] Although several studies investigated the prognostic role of histologic variants of

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urothelial carcinoma at radical cystectomy (RC),[7,8] there are no data available regarding the clinical significance of uncommon variants of urothelial carcinoma at transurethral resection of bladder tumor (TURBT). We aimed to evaluate the concordance and prognostic significance of histologic variants of bladder urothelial carcinoma in TURBT and RC specimens.

MATERIALS AND METHODS

Study Design and Patient Selection

After centralized institutional review board approval, we retrospectively reviewed all the collected data of 4110 patients treated with RC and lymph node dissection at 17 tertiary referral centers between January 2000 and December 2009. Clinicopathologic and instrumental data at the time of TURBT and RC were collected.

Patient Population

Anamnestic information and clinicopathologic data available at the time of RC were assembled by reviewing all dedicated databases sent by participating investigators. If any data were missing, we asked all investigators to review the medical charts or to recall the patients or contact the next of kin or family members. Patients with incomplete clinicopathologic information were excluded from the analysis. The clinical data included were date of birth, age at first presentation of bladder cancer, number of tumor recurrences, time at progression, use of intravesical treatment, presence of uncommon histotypes at TURBT before surgery, age at RC, clinical and pathologic stage, type of urinary diversion after cystectomy, presence of variant histology, and use of adjuvant or neoadjuvant chemotherapy. Patient status at follow-up (alive with no evidence of disease, alive with disease, death from other causes, or death from disease) was assessed by means of dedicated database systems or telephone interviews.

Inclusion and Exclusion Criteria

To enroll a homogeneous group of patients, we only considered patients who underwent to RC with standard bilateral pelvic lymphadenectomy and urinary diversion. Indications for RC included muscle-invasive bladder cancer, superficial bladder cancer refractory to intravesical therapy, multifocal stage pT1 G3, and diffuse carcinoma in situ before the availability of intravesical bacille Calmette-Guérin therapy.[9] All patients with metastasis at diagnosis were excluded. All operations were performed by an expert qualified uro-oncology consultant in each center. RC was carried out according to the procedure suggested by the International Consultation on Bladder Cancer.[9] Lymph node dissection included the removal of all lymphatic tissues around the common iliac, external iliac, internal iliac arteries, and from the obturator region bilaterally and the presacral region. After cystectomy and urinary diversion, all patients were followed up at each center, in accordance with the European Association of Urology guidelines.[10] In brief, all patients were subjected to chest x-ray and abdominal ultrasonography every 3 months, computerized tomography of the abdomen every 6 months, and bone scan and excretory urography every 12 months. Additional examinations were required for symptomatic disease.[10] Follow-up was calculated from the date of cystectomy to the last date of contact, death, or recurrence.[11] Concomitant urethrectomy was performed only in patients who had preoperative histologically proven urothelial carcinoma of the prostate and/or urethra.[9] No other exclusion criteria were used to achieve clinically relevant results useful in everyday clinical practice. Moreover, the Charlson comorbidity index was calculated by using the software purposed in the Web site of the Institute for Algorithmic Medicine (a Texas nonprofit corporation; http://www.medal.org/OnlineCalculators/ch1/ch1.13/ch1.13.01.php).[12]

Pathologic Considerations

All specimens were examined by a dedicated uropathologist at each center. Problematic cases were discussed in a joint consultation session of pathologists and histotypes were recorded. Pathologic findings were collected in a dedicated database and submitted for statistical analysis. Diagnosis of urothelial bladder carcinoma with divergent differentiation was based on the identification of characteristic histopathologic features according to the World Health Organization histologic classification.[5] Pathologic staging was established using the current American Joint Committee on Cancer (TNM) system.[13]

Statistical Analysis and Ethical Consideration

Data were entered into a Microsoft Excel (version 14.0) database and transferred to SPSS 11.0 for Apple-Macintosh (SPSS, Inc., Chicago, IL, 2011). Continuous and non-normally distributed variables are presented as medians with interquartile ranges (IQRs). Comparisons were made across groups using the *t* test and the chi-square test. Agreement of uncommon variants of urothelial carcinoma presence was determined using the McNemar test. Kaplan-Meier and the log-rank test estimate of cancer-specific survival (CSS) were plotted for survival analysis. The 95% confidence intervals were calculated for survival probability for Kaplan-Meier estimates. Univariate and multivariate relative risk was calculated by using Cox proportional hazards regression to evaluate CSS. The following parameters were included in the univariate analysis: age at diagnosis, gender, presence of uncommon urothelial variants at TURBT, presence of uncommon urothelial variant at RC, pathologic stage of the primary bladder cancer (pT2, pT3, and pT4), lymph node metastasis (N0, N1, N2, or N3), concomitant carcinoma in situ (yes or no), presence of pure or mixed feature, adjuvant chemotherapy, or radiochemotherapy. All parameters found to be statistically significant at the univariate analysis were included in the multivariate analysis. Correlations were assessed by the Pearson or Spearman test. Statistical significance was achieved when P was $<.05$.

RESULTS

A total of 4369 patients were collected, whereas 259 were excluded from the analysis, because of the lack of clinical information. Finally, 4110 patients (mean age, 70.8 years) were analyzed. The anamnestic and clinical characteristics of the patients at the time of surgery are summarized in Table 1.

Concordance Between TURBT and RC Specimens

Of 4110 patients, 579 were found to have uncommon variants of bladder urothelial carcinoma at RC (14.1%), whereas 266 at TURBT (6.4%). A lack of agreement about uncommon variants was observed between TURBT and RC specimens in the entire population ($P <.001$). No

Table 1. Summary of anamnestic and clinical characteristics of the enrolled patients

Characteristic	Value
No. of radical cystectomies	4110
No. of uncommon variants of UCC, n (%)	579 (14.2)
Age, y	
Mean (IQR)	70.8 (57-78)
≤65, n (%)	203 (35.1)
>65, n (%)	376 (64.9)
Gender, n (%)	
Male	492 (84.9)
Female	87 (15.1)
Cigarette smokers, n (%)	260 (44.9)
Charlson comorbidity index, n (%)	
<2	463 (79.9)
2	75 (12.9)
≥3	41 (7.2)
Presentation, n (%)	
First presentation	214 (36.9)
Recurrence	365 (63.1)
Number of recurrence (365 patients), n (%)	
1	146 (40.0)
2	102 (27.9)
≥3	117 (32.1)
Uncommon variants of UCC at TURBT, n (%)	266 (45.9)
Urinary diversion, n (%)	
Cutaneous ureterostomy	254 (43.9)
Ileal conduit	265 (45.8)
Neobladder	60 (10.3)
No. of lymph nodes removed, median (IQR)	19.3 (11-28)
Adjuvant chemotherapy, n (%)	69 (11.9)
Adjuvant radiochemotherapy, n (%)	32 (5.5)

IQR, interquartile range; No, number; TURBT, Transurethral resection of bladder tumor; UCC, urothelial cell carcinoma.

The table shows all patients' anamnestic and clinical characteristics at enrollment time.

Data in parentheses are percentage unless otherwise specified.

statistically significant difference in the rate of histologic variants was recorded among the centers (median, 13.9%; IQR, 13.6-14.3). Moreover, the presence of uncommon urothelial variants at TURBT was associated with an increased risk of pathologic upstage (hazard ratio [HR], 3.24; 95% confidence interval [CI], 1.19-6.37; $P < .003$). Finally, even if patients with squamous differentiation showed a higher agreement between TURBT and RC specimens, no statistically significant differences have been observed between all uncommon variants.

Pathologic Findings at TURBT

Of 4110 patients, 3844 showed conventional urothelial carcinoma, whereas 266 showed uncommon histologic variants with the following spectrum: 82 squamous (30.8%), 44 sarcomatoid (16.5%), 24 clear cell (9%), 23 glandular (8.6%), 24 micropapillary (9%), 21 small cell (7.8%), 23 undifferentiated (8.6%), 18 osteoclast-like giant cell (6.7%), and 7 nested (2.6%).

Pathologic Findings at RC

At pathologic examination of RC specimens, 579 (14.1%) uncommon histologic variants were found. The spectrum of variant histologic components included 172 squamous (29.7%), 97 sarcomatoid (16.8), 55 clear cell (9.4%), 54 glandular (9.3%), 54 micropapillary (9.3%), 49 small cell (8.4%), 31 undifferentiated (5.4%), 32 osteoclast-like giant cell (5.6%), 25 lymphoepithelioma-like (4.3%), and 10 nested (1.8%). A median of 19.3 lymph nodes were removed (IQR, 11-28). Furthermore, we found 23 pT1, 82 pT2, 113 pT3a, 134 pT3b, and 227 pT4 and 66 N1, 41 N2, and 28 N3 tumors. Finally, 29 patients exhibited associated carcinoma in situ. Pathologic findings are detailed in Table 2. Squamous differentiation was the most common variant and correlated with higher stage ($r = 0.79$ and $r = 0.81$, respectively: $P < .003$).

Follow-up Results

With a mean follow-up of 65.6 months, cumulative CSS rates of all enrolled patients at 1 year, 3 years, and 5 years were 92.3%, 66.5%, and 39.8%, respectively. The 1-, 3-, and 5-year CSS rates in patients with the conventional urothelial variant were 91.6%, 78.1%, and 56.9%, respectively, vs 78.5%, 36.5%, and 34.3%, respectively, for those with uncommon urothelial variants (HR, 3.53; 95% CI, 2.03-5.54; $P < .001$). The 1-, 3-, and 5-year CSS probabilities in patients with uncommon urothelial variants at TURBT were 69.1%, 35.4%, and 32.1%, respectively, vs 86.8%, 44.4%, and 37.8%, respectively, for those with conventional urothelial carcinoma (mean survival, 15.1 months with 95% CI, 11.9-20.1 months vs 23.4 months with 95% CI, 19.3-24.9 months; HR, 2.45; 95% CI, 1.89-3.49; $P < .0001$; Fig. 1).

Univariate and Multivariate Analysis Results

The presence of uncommon urothelial variants at TURBT, pathologic stage pT2 or higher, lymph node status N1 or higher, patient age <65 years at diagnosis, and concomitant carcinoma in situ were identified as independent predictors of dismal clinical outcome at univariate analysis. The following parameters have been confirmed as independent predictors of dismal clinical outcome at the multivariate analysis: the presence of uncommon urothelial variants at TURBT, pathologic stage pT2 or higher, lymph node status N1 or higher, and patient age <65 years at diagnosis (Table 3).

COMMENT

By using a large multicentre cohort of patients, we found that the concordance of the presence of uncommon histologic variants of urothelial bladder carcinoma between TURBT and RC is low. On the other hand, when uncommon histologic variants of urothelial bladder carcinoma are identified in a transurethral bladder tumor resection sample, they are associated with an increased risk of pathologic upstage and dismal clinical outcome. The low concordance between TURBT and RC specimens can be partially explained by difficulties in staging accuracy based on TURBT specimens and in part because of the recognition of these entities as neoplastic, as suggested by Hansel et al.[14] Moreover, the same authors stated that the presence or absence of muscularis propria

Table 2. Pathologic findings at the time of radical cystectomy

Histologic Variant	Histologic Feature			*P* Value
	Pure	Mixed	Associated Cis	
Squamous (172)	118	54	3	—
Sarcomatoid (97)	70	27	3	—
Micropapillary (54)	35	19	2	—
Clear cell (55)	35	20	4	—
Glandular (54)	33	21	1	—
Small cell (49)	38	11	3	—
Undifferentiated (31)	22	9	6	—
Osteoclast-like giant cell (32)	21	11	2	—
Lymphoepithelioma like (25)	20	5	3	—
Nested type (10)	8	2	2	—
Total	400	179	29	

Histologic Variant	Pathologic Stage					*P* Value
	pT1	pT2	pT3a	pT3b	pT4	
Squamous (172)	—	18	46	63	45	.003
Sarcomatoid (97)	1	12	46	31	7	—
Micropapillary (54)	8	32	11	3	—	—
Clear cell (55)	3	28	19	4	1	—
Glandular (54)	—	29	12	8	5	—
Small cell (49)	—	23	9	12	5	—
Undifferentiated (31)	—	10	1	8	12	—
Osteoclast-like giant cell (32)	—	12	5	10	5	—
Lymphoepithelioma like (25)	8	9	4	4	—	—
Nested type (10)	3	—	2	3	2	—
Total	23	182	113	134	127	

Histologic Variant	Lymph Node Involvement				*P* Value
	N0	N1	N2	N3	
Squamous (172)	101	39	21	11	—
Sarcomatoid (97)	35	34	12	16	—
Micropapillary (54)	43	11	—	—	—
Clear cell (55)	33	22	—	—	—
Glandular (54)	31	19	4	—	—
Small cell (49)	38	11	—	—	—
Undifferentiated (31)	13	15	2	1	—
Osteoclast-like giant cell (32)	17	15	—	—	—
Lymphoepithelioma like (25)	25	—	—	—	—
Nested type (10)	8	—	2	—	—
Total	344	166	41	28	—

Cis, carcinoma in situ.

The table shows all detailed pathological findings at the radical cystectomy time. Data in parentheses are number of cases.

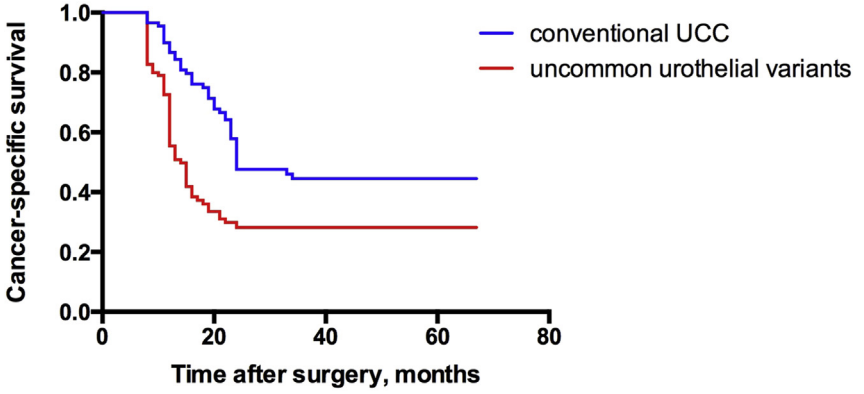

Figure 1. Cancer-specific survival in 579 patients with uncommon histologic variants of urothelial bladder carcinoma after radical cystectomy, stratified by the presence of uncommon urothelial variants at transurethral resection (TURBT) before radical cystectomy: conventional urothelial cell carcinoma (UCC) or uncommon urothelial variants; $P < .0001$; HR, 2.45; 95% CI, 1.89-3.49. (Color version available online.)

Table 3. Multivariate analysis results of factors affecting recurrence-free survival in enrolled patients

Categories (Variables)	No. of Recurrence-free Patients/No. of Total Patients (%)	Multivariate Analysis HR (95% CI)
Age, y		$P = .003$
<65	22/203 (10.8)	2.97 (1.50-3.67)
≥65	56/376 (14.8)	0.81 (0.17-1.23)
Gender		$P = .89$
Male	37/492 (7.5)	1.21 (0.65-1.53)
Female	41/87 (47.1)	1.14 (0.79-1.67)
Presence of uncommon urothelial variants at TURBT		$P = .001$
Yes	22/266 (8.2)	4.01 (1.67-8.21)
No	56/313 (17.8)	0.81 (0.12-1.30)
Pathologic stage		$P = .001$
pT1	37/23 (62.1)	0.09 (0.45-1.24)
pT2	25/182 (13.7)	0.78 (0.11-1.12)
pT3a	10/113 (8.8)	5.31 (2.3-9.7)
pT3b	6/134 (4.4)	6.72 (4.3-10.12)
pT4	0/127 (—)	8.91 (7.1-14.3)
Lymph node status		$P = .001$
N0	72/387 (—)	0.82 (0.34-1.11)
N1	6/98 (—)	1.35 (0.50-2.31)
N2	0/66 (—)	4.31 (3.36-5.85)
N3	0/28 (—)	5.11 (4.5-9.32)
Cis associated		$P = .72$
Yes	8/29 (27.5)	0.89 (0.50-1.21)
No	70/550 (12.7)	1.08 (0.25-1.70)
Presence of single or multiple histology pattern		$P = .09$
Single	67/400 (16.5)	0.45 (0.30-1.03)
Multiple	21/179 (11.7)	0.98 (0.55-1.50)
Adjuvant therapy		$P = .09$
Yes	38/201 (18.9)	0.81 (0.61-1.12)
No	40/378 (10.5)	1.02 (0.85-1.25)
Charlson comorbidity index		$P = .08$
<2	58/463 (12.5)	0.99 (0.63-1.13)
≥2	20/116 (17.2)	0.87 (0.51-1.02)

CI, confidence interval; HR, hazard ratio; other abbreviations as in Tables 1 and 2.
Data in parentheses are percentages.

(detrusor muscle) in the TURBT specimen, and its involvement is critical when diagnosing this aggressive variant.[14] Upstaging is then common and ranged from 52.7% to 79%.[15,16] In the present study, we observed an upstaging rate of 34.3%. Furthermore, we emphasize the importance of the presence of uncommon urothelial variants at TURBT. If sarcomatoid differentiation is detected at TURBT, a more aggressive treatment is recommended regardless of pathologic stage. Indeed, Black et al,[17] using a dedicated treatment algorithm for patients with resectable bladder cancer, suggested that patients with T1 or T2 disease and uncommon urothelial variants, such as sarcomatoid differentiation, at TURBT should be offered neoadjuvant chemotherapy. However, the retrospective nature of this study precluded any standardized therapeutic protocol with neoadjuvant or adjuvant chemotherapy. In this sense, future clinical trials are needed. In addition, Linder et al, recently, concluded that nested variant of urothelial carcinoma is associated with a high rate of locally advanced disease at RC but not with adverse survival when stage matched to patients with pure urothelial carcinoma.[18]

Even if supported by a large cohort of patients, this study shows a few limitations that should be taken into account. First is the lack of centralized pathologic review. However, all specimens were examined by a dedicated uropathologist at each center, and all problematic cases were discussed in a joint consultation session of pathologists. Furthermore, the quality of pathologic reporting was demonstrated by the absence of a significant difference in the rate of histologic variants among the centers and over the entire study period. Moreover, we must take into account the retrospective nature of the study that did not allow stratification of our findings in terms of specific therapeutic strategies. In conclusion, as suggested by Philipp Dahm,[3] "it will likely take the concerted effort of many institutions linked together by a national or international tumor registry to develop and evaluate effective treatment strategies in an attempt to optimize patient outcome in the future". Moreover, further prospective studies are needed to determine the usefulness of more aggressive treatment when uncommon histologic variants of urothelial bladder carcinoma are found at the time of TURBT.

CONCLUSIONS

The present study shows that the concordance of the presence of uncommon histologic variants of urothelial bladder carcinoma between TURBT and RC is low. Moreover, the

presence of uncommon urothelial variants at TURBT proved to be independent predictor of worse clinical outcome and potential therapeutic implications that should be taken into account in urologic clinical practice.

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