

Impact of Histopathological Variant on the Outcome of Patients Treated by Radical Cystectomy

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Purpose: It is well established that muscle-invasive urothelial carcinoma (UC) has a marked propensity for divergent differentiation, a fact that has significant diagnostic, prognostic, and therapeutic implications. This work is designed to assess the impact of different histopathologic variants of bladder cancer on morbidity and mortality in patients undergoing radical cystectomy (RC) as compared to the impact in patients with conventional UC.

Materials and Methods: We reviewed records of 201 patients treated with RC and pelvic lymph node dissections. Demographics as well as clinico-pathologic parameters, including histopathological variant, tumor stage, and nodal status, were reviewed. Multivariate analyses were used to evaluate these parameters for overall survival (OS). Kaplan-Meier curves for overall and cancer-specific survival were plotted.

Results: The majority of patients were male (84%), and the mean age was 61±13.1 years (range, 27–87 years). The mean follow-up was 67 months (range, 6–132 months). A histological variant of UC tumor was found in 19 patients (11%). The OS was 55%, and the cancer-specific survival was 35%. The histopathologic variance showed significant impact on morbidity and mortality ($p=0.02$ and $p=0.05$, respectively). Patients with divergent histopathology of bladder tumor have poorer survival than do those with UC in a multivariate analysis.

Conclusions: The pathologic stages at RC and lymph node involvement are predictors for OS. Because of its aggressive nature, histopathologic variance is an independent risk factor determining the outcome in terms of both morbidity and mortality.

Keywords: Epithelial neoplasms; Malignant; Urinary bladder neoplasms

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INTRODUCTION

Bladder cancer is the second-most-common malignancy of the genitourinary tract [1]. In our previously reported work [2], approximately 90% of bladder cancers are pure urothelial carcinoma (UC), and the remaining 5% to 10% consisted of UC with aberrant differentiation or non-UC. UC may exhibit a diverse array of morphologies. This propensity of divergent differentiation may manifest as squamous or glandular cancers. Conventional UC, particularly the high-grade and high-stage cancer, may exhibit full range of variant morphology. The term “variant” is used to describe these distinctively different histomorphologic phe-

notypes of a certain type of neoplasm [2,3]. In recent years, several variants have been described, along with their clinical significance at various levels, to avoid diagnostic misinterpretation, aid in risk prognostication, and present differences in therapeutic approach [4]. Multiple case series and case reports on the aggressive nature of these tumors are available in the literature, but there are few data comparing the outcomes of various types of these tumors with non-UC as well as conventional UC. A single large series has documented that histologic variants are common in high-grade UCs of the renal pelvis; they made up 40% of the cases in the series [5].

This study is focused on a comparison of the outcome of

patients who underwent radical cystectomy (RC) for bladder cancers of different histopathologic types. Divergent histopathology has different clinical course and survival outcomes, as shown in several case series [4-6]. There is a dearth of data on the subject, and reported series have variable incidence; however, one factor common to all series is that variant histology increases the likelihood of locally advanced disease and metastasis. The aim of this study is to compare the clinical outcomes in different variants of bladder tumor that have not previously been reported in the literature.

MATERIALS AND METHODS

Between January 1988 and December 2010, 201 patients underwent RC for treatment of bladder cancer. These patients were identified through the hospital database by using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9CM). Thirty-one patients were excluded, of whom 18 were lost to follow-up, while 13 had missing records. Data were sealed in 2010 for follow-up and production of a final data set for analysis.

Bladder cancer was diagnosed by cystoscopy, which was followed by transurethral resection of the bladder tumor. The preoperative staging work-up included a complete history and a physical examination, followed by complete laboratory work-up, chest roentgenogram, computed tomography scan, and magnetic resonance imaging or ultrasound of abdomen and pelvis. A radio-isotopic bone scan was done only if indicated. Indications for RC were based on clinical and pathologic staging of the disease, including muscle-invasive bladder cancer, high-grade tumor, high-volume superficial cancer, invasive tumor refractory to radiotherapy and/or systemic chemotherapy, or highly recurrent superficial cancer refractory to endoscopic resection and intravesical chemotherapy. All patients underwent standard bilateral pelvic lymphadenectomy with RC and urinary diversion. The tumors were staged according to TNM 1997 classification. The retrospective nature of this current work precluded a standardized postoperative follow-up protocol in all patients. However, patients were initially seen at one week after RC, after a month, then after every 3 months for 1 year, and, finally, every 6 months until disease progression or death. Except for the initial follow-up, patients were followed with complete physical examination, complete renal profile and blood count and electrolytes, chest x-ray, computed tomography of the abdomen and pelvis, and bone scan if indicated.

All specimens were re-reviewed in consultation with pathologists, and the presence or absence of histologic differentiation was recorded. Patients were divided into four groups on the basis of their histopathologic type—that is, UC, squamous cell carcinoma (SCC), adenocarcinoma (ADC), and other, a type that includes small-cell carcinoma, large-cell carcinoma, and micropapillary variant; UC with squamoid, glandular, or sarcomatoid differentiation; and signet cell carcinoma.

The variables evaluated were age, gender, tumor cell type, pathologic stage, and nodal involvement. The chi-square test and independent sample t-test were used for statistical analysis. The association of histopathologic variance with categorical variables was assessed by using the Fisher exact test or the chi-square test, while the Mann-Whitney U test was used for continuous variables. Results were presented as mean±standard deviation for quantitative variables and as number (%) of patients for qualitative variables. Univariate and multivariate analyses were performed to determine the impact of different clinicopathologic variables on survival outcome. Survival estimates were constructed by using the Kaplan-Meier product limit methods, and the log rank test was applied to determine statistical significance. All data were analyzed by using SPSS ver. 16 (SPSS Inc., Chicago, IL, USA). For all tests, $p < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

The mean age of the patients was 61±13.1 years (range, 27–87 years); males greatly outnumbered (143, 84%) females (27, 16%). Mean follow-up was 67 months (range, 6–132 months). Clinicopathologic features are described in Table 1. Nineteen patients had histopathologic variants: seven (37%) each with squamoid differentiation and large-cell variant, two (11%) with sarcomatoid differentiation, and one each with signet cell, glandular differentiation, or micropapillary variant.

The majority of the patients had advanced disease at the time of presentation, with 18% of them having invasion of the surrounding pelvic structures. The overall survival (OS) was 55%, while cancer-specific survival (CSS) was

TABLE 1. Clinicopathologic details of patients after radical cystectomy

Variable	No. (%)
T stage	
T0	19 (11.2)
T1	31 (18.2)
T2	52 (30.6)
T3	37 (21.8)
T4	31 (18.2)
N stage	
N0	116 (68.2)
N1	36 (21.2)
N2	15 (8.8)
N3	3 (1.8)
Histopathological type	
UC	133 (78.2)
SCC	10 (5.9)
ADC	8 (4.7)
Variant	19 (11.2)

UC, urothelial carcinoma; SCC, squamous cell carcinoma; ADC, adenocarcinoma.

TABLE 2. Subgroup analysis of clinicopathologic features

Variable	UC	SCC	ADC	Variant	p-value
Age (y), mean±SD	61.58±12	60±12	65±8.4	59±13	0.552
Sex, n (%)					
Male	109 (82)	6	6	13	0.174
Female	24 (18)	4	2	6	
ASA score					0.190
1	24	3	2	9	0.393
2	87	5	4	6	
3	20	2	2	4	
4	2	0	0	0	
Functional class					0.393
1	107	7	5	17	
2	24	3	3	2	
3	2	0	0	0	0.038
Pathological distribution, n (%)					
T1	26 (19.5)	0	2	3	
T2	38 (28.5)	5	1	8	
T3	28 (21)	3	4	2	
T4	25 (19)	1	0	5	0.013
T0	16 (12)	1	1	1	
Node status, n (%)					0.013
Positive	28 (21)	2	0	6	
Negative	105 (79)	8	8	13	0.962
Histological features					
G1	15 (11)	2	1	3	
G2	82 (62)	6	5	11	
G3	36 (27)	2	2	5	0.070
Adjuvant chemotherapy	20	4	1	6	
Radiation (%)	13	0	0	1	0.935
Recurrence rate (%)	1.5	0	0	5.3	0.524
Metastasis (%)	6	10	0	21	0.102
Morbidity rates (%)	33.8	50.0	25.0	68.4	0.022
Mortality rates (%)	21.0	30.0	37.5	47.3	0.050

UC, urothelial carcinoma; SCC, squamous cell carcinoma; ADC, adenocarcinoma; SD, standard deviation; ASA, American Society of Anaesthesiologists.

35% at a median follow-up of 58 months (range, 6–162 months). The OS for the pathologic stage pT₀–pT₁ was 83%, compared to 60% for the group with stage pT₂–pT₄ (p=0.03). The OS for node-positive patients was 16%, compared to 60% for node-negative patients (p<0.01). The subgroup analysis and univariate analysis showed no significant difference (p>0.05) in the overall mortality of the patients with variant pathology compared to UC, SCC, and ADC (Table 2). Univariate and multivariate analyses showed that age, gender distribution, T stage, and nodal status are not statistically significant in predicting survival, whereas variant pathology was an independent predictor of CSS (Table 3). On Cox regression analysis, variant pathology was also shown to have a significant impact on OS (hazard ratio, 2.81; 95% confidence interval, 1.32–5.97).

The Kaplan-Meier curve (Figs. 1, 2) plotted for OS and CSS in different histopathologic variants showed a statistically significant difference (log-rank Mantel-Cox test p=0.02 and p=0.01, respectively).

DISCUSSION

Bladder cancer is a heterogeneous disease with an array of histologic findings. High-grade and muscle-invasive bladder cancers treated with RC have varied prognoses [6,7]. In recent years, several “variant” morphologies have been described, and most were recognized in the 2004 World Health Organization Classification [8]. These histologic variants of UC have clinical significance for diagnosis, prognosis, and therapy. Awareness of the morphologic variant is essential to avoiding diagnostic misinterpretations. It has been shown that variant pathologic tumors are aggressive, a fact that has significant prognostic implications. In view of this factor, early recognition may require novel therapeutic interventions, such as the administration of a therapy distinctive from that used for conventional invasive UC [6].

Currently, clinical stage is the strongest predictor of 5-year progression-free survival. Patient risk stratification is essential for optimal management of patients

TABLE 3. Impact of gender, age, nodal status, and pathology on survival in univariate

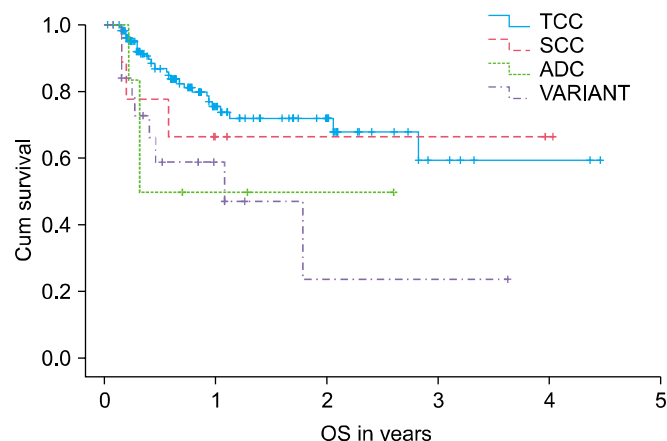
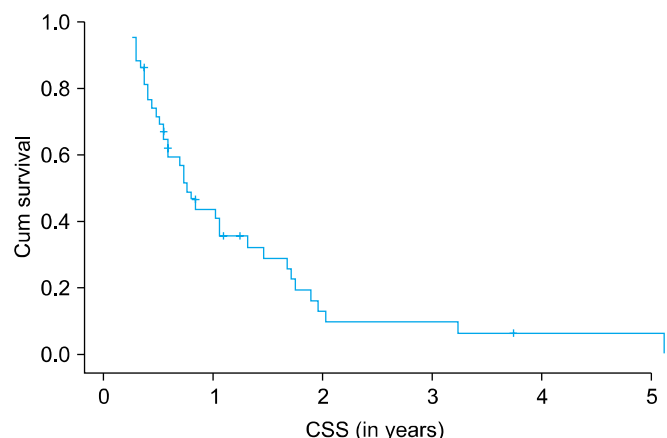
Variable	Univariate analyses	Multivariate analysis		
	p-value	Hazard ratio	95% CI	p-value
Sex	0.174			
Male				
Female		-	-	-
Age	0.552			
≥ 60		-	-	-
< 60		-	-	-
T stage	0.038			>0.050
T0		-	-	
T1		-	-	
T2		-	-	
T3		-	-	
T4		-	-	
Nodal status	0.013			
Node (-)				
Node (+)		1.25	1.15-2.26 ^a	0.018
Pathology	0.050			
UC				
SCC				
Adenocarcinoma		2.81	1.32-5.97 ^a	0.008
Variant histology				

CI, confidence interval; UC, urothelial carcinoma; SCC, squamous cell carcinoma.

^a:On Cox regression analysis, variant pathology was also shown to have significant impact on overall survival (hazard ratio, 2.81; 95% CI, 1.32-5.97).

with bladder cancer. Risk status determines the application and timing of adjuvant/neoadjuvant systemic chemotherapy and RC. One of the major factors in risk stratification is the presence of variant histologic patterns in the bladder tumor. These histologic variants of UC have clinical significance at various levels, including the diagnostic level; that is, awareness of the morphologic variant is essential to avoidance of diagnostic misinterpretations, to prognosis for patient risk stratification, and to therapy, in which a diagnostic assignment of a particular variant may be associated with the administration of a therapy distinctive from that used in conventional invasive UC [9]. The differential diagnosis of UC with variant pathology includes SCC and ADC. Pure SCC shows an exclusive squamous cell component. Similarly, ADC of the bladder is a term reserved for pure ADC.

The vast majority of tumors are conventional UCs, and the rest consist of UC with aberrant differentiation (i.e., squamous/glandular differentiation, small-cell carcinoma, sarcomatoid carcinoma, and micropapillary carcinoma) or non-UC (SCC and ADC). A review of contemporary literature suggests that all of the variant histologies portend a poor prognosis as compared to that for conventional UC. In our series, there was a trend toward poorer out-

**FIG. 1.** Kaplan-Meier curve of overall survival (OS) in patient with conventional urothelial carcinoma (UC), squamous cell carcinoma (SCC), adenocarcinoma (ADC), or UC with variant pathology in a univariate analysis. TCC, transitional cell carcinoma (urothelial cancer).**FIG. 2.** Kaplan-Meier curve of cancer-specific survival (CSS).

comes with variant histology; however, overall mortality was not statistically significantly different ($p>0.05$). This finding could potentially be due to the smaller numbers in our series.

RC remains the mainstay of treatment in high-grade and muscle-invasive bladder cancers, and the use of systemic chemotherapy may have a beneficial effect on OS. The timing of systemic chemotherapy has the potential to alter the ultimate outcome in patients at high risk of recurrence. The use of neoadjuvant chemotherapy in high-risk UC is recommended [10] and should be considered for variant histology as it also impart high risk. Scosyrev et al. [11] assessed the effect of neoadjuvant chemotherapy and noted that the presence of squamous or glandular differentiation in locally advanced UC of the bladder does not confer resistance to neoadjuvant methotrexate, vinblastine, adriamycin and cisplatin (MVAC) chemotherapy (chemotherapy combining methotrexate, vinblastine, doxorubicin, and cisplatin) and may, in fact, be an indication for the use of such chemo-

therapy before RC. For small-cell carcinoma, there is good evidence that MVAC chemotherapy is an appropriate strategy.

The established predictors of prognosis such as T stage and nodal status were predictors of survival in a univariate analysis but were not found to have a significant impact on survival in a multivariate analysis. This difference could perhaps be due to the smaller numbers of patients in the subgroups. Our study clearly indicates that, in a multivariate analysis, variant pathology is an independent predictor of survival.

CONCLUSIONS

Pathologic stage at RC and lymph node involvement are predictors for OS. Because of its inherently aggressive nature, histopathologic variance is an independent risk factor determining the outcome in terms of both morbidity and mortality.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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