ELSEVIER

CrossMark

Urologic Oncology: Seminars and Original Investigations 33 (2015) 18.e15–18.e20

UROLOGIC ONCOLOGY

Original article

Contemporary bladder cancer: Variant histology may be a significant driver of disease

M. Francesca Monn, M.D., M.P.H.[a,*], Hristos Z. Kaimakliotis, M.D.[a], Jose A. Pedrosa, M.D.[a], K. Clint Cary, M.D., M.P.H.[a], Richard Bihrle, M.D.[a], Liang Cheng, M.D.[b], Michael O. Koch, M.D.[a]

[a] *Department of Urology, Indiana University School of Medicine, Indianapolis, IN*
[b] *Department of Pathology, Indiana University School of Medicine, Indianapolis, IN*

Abstract

Objectives: To evaluate pathologic and survival outcomes among patients with variant histology (VH) urothelial carcinoma of the bladder.

Methods: A retrospective review of an institutional database was performed to identify all patients who underwent radical cystectomy with curative intent for urothelial carcinoma between 2008 and June 2013. VH was assigned by genitourinary pathologists. Descriptive statistics comparing clinicopathologic outcomes were performed using the Pearson chi-square test and analysis of variance. Survival was evaluated using the Kaplan-Meier methodology and the Cox proportional hazards regression.

Results: In total, 624 patients were identified. Overall, 26% ($n = 162$) had VH, with the most common being squamous differentiation ($n = 68$), micropapillary variant (MPV, $n = 28$), plasmacytoid variant (PCV, $n = 25$), and sarcomatoid variant ($n = 15$); 64% of MPV and 72% of PCV had positive lymph nodes. Compared with 8% of patients with a non VH, 44% of those with VH were categorized as pT4 ($P < 0.001$). MPV and PCV were independently associated with twice the risk of all-cause mortality compared with nonvariant, when adjusting for demographics, American Society of Anesthesiologists class, transurethral resection of bladder tumor stage, cystectomy stage, positive lymph nodes, and reception of chemotherapy (odds ratio = 2.20, 95% CI: 1.28–3.78; $P = 0.004$; odds ratio = 2.42, 95% CI: 1.33–4.42; $P = 0.004$, respectively). There was no difference in risk of mortality associated with squamous differentiation or sarcomatoid variant ($P > 0.05$ each).

Conclusions: MPV and PCV are associated with increased risk of mortality. Improved recognition of VH will enable larger cohorts of study and better prognostic understanding of the significance of specific VH involvement.

Keywords: Radical cystectomy; Variant histology; Urothelial bladder cancer; Survival; Clinical outcomes

1. Introduction

When the World Health Organization (WHO) published its 2004 guidelines for classification of urothelial carcinoma (UC) and chose to recognize distinct variant histology (VH), one of its aims was increasing identification of these variants on pathology specimens [1]. Better understanding of these VH forms of UC leads to greater knowledge of prognosis and treatment strategies specific to individual variants. Despite initial descriptions of variants more than 20 years ago, molecular pathways for the divergent development of specific VH within primary urothelial bladder carcinoma have not been elucidated [2,3]. Divergent differentiation is poorly understood; although, Cheng et al. [4] have suggested sarcomatoid urothelial cancer developing as the final common pathway in UC differentiation. The true prevalence of VH has likely not increased over the past decade, although this is difficult to prove retrospectively [5]. Rather, increased pathologic awareness of the possible morphologic variants is likely the driver of increased variant diagnosis.

Recognizing the increased identification of less common VH at our institution since 2008, we sought to evaluate clinicopathologic outcomes of patients with VH UC within a contemporary cohort of patients in an attempt to better delineate treatment algorithms.

These authors contributed equally to the manuscript.

* Corresponding author. Tel.: +1-317-847-5647; fax: +1-317-948-2619.
E-mail address: mmonn@iupui.edu (M.F. Monn).

http://dx.doi.org/10.1016/j.urolonc.2014.10.001
1078-1439/

2. Methods

Using an institutional database, we conducted a retrospective review of all patients who underwent radical cystectomy for UC of the bladder at our institution between 2008 and June 2013 ($n = 698$). As the current WHO guidelines recommend that patients with any component of small cell histology be managed as primary small cell carcinoma, we eliminated all patients with small cell variant ($n = 22$). Patients with locoregional metastatic disease that underwent cystectomy after preoperative chemotherapy or with a history of management under a bladder-preservation protocol were excluded ($n = 52$). Dedicated genitourinary pathologists assigned all UC VH using centralized pathology review, which included regular review of all malignant histology and variant classification to ensure standardization within the group. Outside hospital transurethral resection (TUR) specimens underwent VH reassignment by this same group of genitourinary pathologists. Histologic descriptions of VH are available from prior studies [2].

The primary outcomes of interest were pathologic stage, lymph node involvement (pN+), and overall survival (OS). Additional variables included in the analysis were demographic characteristics, American Society of Anesthesiologists (ASA) class, TUR of bladder tumor (TURBT) stage, neoadjuvant and adjuvant chemotherapy, and pathologic stage. OS was determined from patient records and an institutional cancer registry. For the purpose of this study, we used cystectomy VH. VH classification used in the analysis was as follows: nonvariant (NV), squamous differentiation (SQD), micropapillary variant (MPV), plasmacytoid variant (PCV), sarcomatoid variant (SAV), and other variants (other). The other variant group was comprised of variants with less than 10 cases and included glandular differentiation (GLD), nested, lymphoepitheliomalike, rhabdoid, and clear cell variants. We did not use a percentage threshold for VH, as we assumed that any component of VH would drive pathologic outcomes. In the setting of mixed VH, patients were classified by the variant with the highest percentage present.

Descriptive statistical analysis was performed using the Pearson chi-square test for categorical variables and the analysis of variance for continuous variables. The Kaplan-Meier methodology with the log-rank test was used to assess OS. A Cox proportional hazards model was used to assess the effect of VH on overall mortality when adjusting for demographics, ASA class, pathologic stage, pN+, and chemotherapy. Schoenfeld residual plots were used to test the proportional hazards assumption, and all included variables met the assumption. Sensitivity analyses using only TURBT patients with muscle-invasive cancer and those who did not receive neoadjuvant chemotherapy were additionally performed. We chose $P < 0.05$ as our level of statistical significance for the study. All statistical analyses were performed using Stata 12.1 (Statacorp, College Station, TX). Institutional review board approval was gained before conduct of the study.

3. Results

In total, 624 patients were identified as meeting all inclusion criteria. Of these, 462 (74.0%) had NV histology, 68 (10.9%) had SQD, 28 (4.5%) had MPV, 25 (4.0%) had PCV, 15 (2.4%) had SAV, and 26 (4.2%) had other VH. Among the other VH, there were 9 GLD, 6 nested variant, 5 lymphoepitheliomalike, 4 clear cell, and 2 rhabdoid variant. Table 1 shows patient characteristics. The average age of patients was 67.0 years (range: 34–92 y), which varied by variant. Most patients were white men. Overall, 61% of patients with NV had evidence of muscle invasion on TURBT compared with 79.6% of those with VH ($P = 0.001$). At 68%, PCV had the lowest incidence of muscle-invasive disease on TURBT among the patients with VH. Overall, 13% of patients underwent neoadjuvant

Table 1
Demographic characteristics of patients with primary urothelial cancer undergoing radical cystectomy

Characteristics	NV	SQD	MPV	PCV	SAV	Other[a]	*P* value[b]
n	462	68	28	25	15	26	
Age, mean (SD), y	66.6 (11)	69.4 (11)	72.0 (9)	66.2 (9)	62.9 (13)	65.5 (8)	0.026
Gender (female)	98 (21.2)	17 (25.0)	4 (14.3)	5 (20.0)	6 (40.0)	6 (23.1)	0.491
Race (white)	441 (95.5)	64 (94.1)	28 (100)	22 (88.0)	14 (93.3)	24 (92.3)	0.431
TURBT muscle invasive	283 (61.3)	53 (77.9)	22 (78.6)	17 (68.0)	13 (86.7)	23 (88.5)	0.001
Neoadjuvant chemotherapy	65 (14.1)	4 (5.9)	5 (17.9)	5 (20.0)	0 (0)	4 (15.4)	0.195
ASA class[c]							
2	19 (4.2)	2 (3.0)	0	1 (4.0)	0	1 (4.0)	0.300
3	409 (91.1)	61 (92.4)	27 (96.4)	24 (96.0)	11 (78.6)	23 (92.0)	
4	21 (4.7)	3 (4.6)	1 (3.6)	0	3 (21.4)	1 (4.0)	

SD = standard deviation.
[a]Other comprises cystectomy variants with less than 10 cases, including glandular differentiation, nested, lymphoepitheliomalike, and clear cell.
[b]*P* values refer to the Pearson chi-square test for categorical variables and the analysis of variance (ANOVA) for continuous variables.
[c]ASA class was missing for 17 patients.