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Original article

Incidence and effect of variant histology on oncological outcomes in patients with bladder cancer treated with radical cystectomy

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Abstract

Introduction: We sought to describe incidence of histological variants after radical cystectomy (RC) due to bladder cancer (BCa). Moreover, we investigated survival outcomes accounting for this parameter.

Methods: We retrospectively evaluated data from 1,067 patients with BCa treated with RC between 1990 and 2013 at a single tertiary care referral center. All specimen were evaluated by dedicated uropathologists. Univariable and multivariable Cox regression analyses tested the effect of different histopathological variant on recurrence, cancer-specific mortality (CSM), and overall mortality (OM) after accounting for all available confounders.

Results: Of 1,067 patients, 729 (68.3%) harbored pure urothelial BCa while 338 (31.7%) were found to have a variant. Considering uncommon variants, 21 (2.0%) were sarcomatoid, 10 (0.9%) lymphoepitelial, 19 (1.8%) small cell, 109 (10.2%) squamous, 89 (8.3%) micropapillary, 23 (2.2%) glandular, 34 (3.2%) mixed variants, and 33 (3.1%) were found with other types of variants. With a median follow-up of 6.2 years, 343 recurrence, 365 CSM, and 451 OM were recorded, respectively. At multivariable Cox regression analyses, the presence of small cell variant was associated with higher recurrence (hazard ratio [HR] = 3.47, $P < 0.001$), CSM (HR = 3.30, $P < 0.04$), and OM (HR = 2.97, $P < 0.003$) as compared with pure urothelial cancer. Conversely, no survival differences were recorded considering other histological variants (all $P > 0.1$).

Conclusion: Our study confirms that histological variant is not an infrequent event at RC specimen. However, in our single-center series, only patients found with small cell variant were associated with a negative effect on survival after RC. © 2016 Elsevier Inc. All rights reserved.

Keywords: Bladder cancer; Radical cystectomy; Histological variants

1. Introduction

Bladder cancer (BCa) may present with several different morphological features that deviate from the urothelial common aspect [1–3]. It has been estimated that approximately 80% of BCa is represented by pure urothelial carcinoma (UCb), whereas the remaining is the result of urothelial and nonurothelial variants [4,5]. In this perspective, WHO 2016 [6] has recently highlighted the importance of the morphology characteristics in BCa as a determinant of survival and driver of clinical and therapeutic

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managements. Morphological characteristics are directly related to molecular alterations, and in this perspective, the most frequently altered pathways are PI3K/AKT/mammalian [7], the FGFR3/RAF/RAS pathway [8], the TP53/RB1 pathway [9], immune response checkpoint modulators [10], and chromatin-regulating and remodeling genes [11]. However, in the absence of a validated tissue-based genetic test, assessing morphological features from hematoxylin and eosin-stained pathologic sections can provide information on their biologic characteristics.

However at the time, there is a paucity of data evaluating morphological tumor characteristics after radical cystectomy (RC). With this in mind, our hypothesis is to confirm that defining histological variants can affect survival outcomes after RC, and moreover could drive therapy and follow-up schemes after surgery. Therefore, we evaluated incidence and survival outcomes of a large single-center experience of patients treated with RC due to BCa.

2. Materials and methods

A total of 1,067 patients treated with RC and pelvic lymph node dissection between 1990 and 2013 at a single tertiary referral center were included in the study. The procedures were approved by the institutional review board (Vescica, 2010), and an informed consent was obtained by all patients. Patients were evaluated preoperatively with pelvic/abdominal computed tomography scan or magnetic resonance imaging, bone scan, and chest x-ray. RC with pelvic lymph node dissection was performed using standard techniques by various surgeons over the time frame of the study. Pathological stages were classified according to the 2009 TNM classification [12]. Tumor grade was assessed according to 1998 WHO/International Society of Urologic Pathology (ISUP) consensus classification [13]. Dedicated genitourinary pathologists examined all surgical specimens. Immunohistochemical markers panel consisting of neuroendocrine markers, chromogranin, synaptophysin, and CD56 were used when small cell neuroendocrine was suspected. Dedicated uropathologists evaluated BCa specimens assigning variant histology. Variant histology classification used in our analyses were sarcomatoid, lymphoepitelial, small cell, squamous, micropapillary, and glandular. When more than one variant histology was assessed by uropathologists, it was classified as mixed variants. Variant histology defined as plasmacitoid, nested, rhabdoid, or adenocarcinoma was included in the "others" group as a consequence of the rarity of these findings in our series. We did not use a percentage of threshold for variant histology, as we assumed in conformity with previous findings that any component of variant histology would drive outcomes [14]. All patients had a complete follow-up data. Clinical and radiological follow-up consisted of a baseline visit at 3 to 4 months after surgery. Subsequently, the minimum follow-up consisted of at least 2 annual visits. Examinations included radiological imaging with computed tomography in all patients. In addition to physical examination with laboratory testing, intravenous pyelography, neocystoscopy, urine cytology, urethral washings, and bone scan were carried out if indicated.

3. Statistical analyses

Descriptive statistics of categorical variables were focused on frequencies and proportions. Means, medians, and interquartile ranges (IQR) were reported for continuously coded variables. The Mann-Whitney test and chi-square test were used to compare the statistical significance of differences in medians and proportions, respectively. Univariable and multivariable Cox regression analyses tested the effect of different histopathological variant on recurrence, cancer-specific mortality (CSM), and overall mortality (OM) after accounting for all available confounders. The Kaplan-Meier method was used to compare recurrence-, CSM-, and OM-free rates after RC in overall population and after stratifying according to histological type. Statistical significance was considered at $P < 0.05$. Statistical analyses were performed using SPSS v.22.0 (IBM Corp., Armonk, NY) and STATA 13 (Stata Corp., College Station, TX).

4. Results

4.1. Baseline characteristics

In total, 1,067 patients were included in the study. Of these, 68.3% ($n = 729$) were found with urothelial BCa, whereas the remaining 31.7% ($n = 338$) were found with a variant. Of the 31.7% patients, 2.0% ($n = 21$) were found with sarcomatoid variant, 0.9% ($n = 10$) with lymphoepitelial, 1.8% ($n = 19$) with small cell, 10.2% ($n = 109$) with squamous, 8.3% ($n = 89$) with micropapillary, 2.2% ($n = 23$) with glandular, 3.2% ($n = 34$) with mixed variants, and 3.1% ($n = 33$) with other variants. Descriptive characteristics of the cohort were depicted in Table 1. The median age was 68 years, and most patients were male ($n = 894$, 83.8%). No differences considering age, sex, body mass index, or Charlson comorbidity index were reported between different histological variants (all $P > 0.2$). Pathologic outcomes are shown in Table 2. Overall, 38% ($n = 410$), 40% ($n = 429$), and 21% ($n = 228$) were found with pT0–T2 vs. pT3 vs. pT4 BCa disease. Lymphovascular invasion, carcinoma in situ and node metastases were found in 8.8% ($n = 94$), 25.0% ($n = 267$), and 36.5% ($n = 389$) of patients, respectively. Pathologic T stage, number of positive nodes, positive surgical margin rates, concomitant carcinoma in situ, and pathologic N stage varied within the cohort (all $P < 0.04$).

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