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Seminar article

Surgical management of bladder urothelial carcinoma with squamous differentiation

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Abstract

Background: Urothelial carcinoma (UC) with squamous differentiation (UC w/SD) is the most common variant bladder cancer histology.

Main Findings: Accurate identification at the time of transurethral resection is critical although current barriers exist, which include tumor heterogeneity, sampling limitation during resection, and pathologic interpretation of specimens. Although many cases of UC w/SD present with muscle-invasive bladder cancer, those cancers that are confirmed to be truly non−muscle invasive can be managed with endoscopic resection, adjuvant intravesical therapies (i.e., Bacillus Calmitte Guerin), and close surveillance. Radical cystectomy series suggest that UC w/SD tends to present at a more advanced stage than pure UC does although survival outcomes are similar when controlling for standard clinicopathologic factors.

Principal Conclusions: Future basic science and clinical studies are requisite to better investigate the biology of urothelial carcinoma with squamous differentiation and response to multimodal therapies. © 2015 Elsevier Inc. All rights reserved.

Keywords: Bladder cancer; Transurethral resection; Variant histology; Survival outcomes

Introduction

Bladder cancer is the seventh most prevalent cancer worldwide, accounting for 3.2% of all malignancies [1]. At present, it is the fifth leading new cancer diagnosis in the United States with most patients (>75%) presenting with non−muscle-invasive (NMI) disease [2]. In the United States, 90% to 95% of bladder cancers are histologically pure urothelial carcinoma (UC) with the remaining tumors consisting of UC with aberrant differentiation or non-urothelial histologies [3]. The most common aberrant differentiation patterns include squamous differentiation (SD) or glandular differentiation (GD) or both in 10% to 60% of patients [4,5], small cell carcinoma in 0.5% to 1.2% [6,7], micropapillary carcinoma in 0.7% [8], and sarcomatoid carcinoma in 0.2% [9]. All of these variant histologies are believed to be derived from common urothelial progenitor cells that give rise to either pure tumor cell populations or mixed urothelial and variant patterns [10,11].

Among the histologic variants described earlier, UC with squamous differentiation (UC w/SD) remains the most common pathologic entity. Nonetheless, the literature to date remains conflicting regarding the biology of this variant particularly when compared with pure UC or squamous cell carcinoma (SCC). Specific considerations include appropriate recognition of this entity at the time of transurethral resection, management of NMI bladder UC w/SD, as well as outcomes of muscle-invasive bladder disease treated by radical surgery.

We focus on these aforementioned issues with a specific focus on the surgical management of UC w/SD. Moreover, these presented observations dovetail with the subsequent article discussing integration of multimodal therapies for the advanced disease.

Methods

The Pubmed and Medline databases were queried for all relevant articles published between 2000 and 2015 that

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focused on the surgical management of UC w/SD. Original articles, editorial comments, as well as review articles were all used as source documents for creation of this review. Given the focus of this article, search terms of interest included "UC w/SD," "variant histology," "radical cystectomy" (RC), "transurethral resection," and "outcomes." Other topic areas including pathologic evaluation and multimodal treatments (chemotherapy and radiation treatment) are addressed in accompanying articles of this seminars series.

Challenges associated with transurethral resection

Transurethral resection of bladder tumors (TURBT) is the referent standard for establishing a histologic diagnosis of bladder cancer. Beyond diagnosis, however, TURBT provides detailed pathologic information regarding clinical grade and stage. Both of these latter 2 variables are critical in the management algorithm for bladder cancer and dictate the need for adjuvant therapies with or without more radical surgery.

Identification of bladder cancer−variant histologies (when present) at TURBT is also a critical component of diagnostic information necessary in the patient with bladder cancer. Indeed studies have suggested therapeutic implications when variant histologies are present, which in turn serve as predictors of treatment response and patient outcomes [12–14]. However, accurate recognition and diagnosis of variant histologies including UC w/SD has proven to be challenging with barriers related both to transurethral technique as well as pathologic interpretation.

In 2013, el-Latif et al. [12] investigated the sensitivity of initial TUR or transurethral biopsy for detecting bladder cancer variants recognized at the time of RC. In this retrospective study of 302 patients, 159 (53%) had variant histology either at endoscopic bladder biopsy, TURBT, or RC. Among the variant histologies, UC w/SD was the most common, accounting for 45% of cases. Overall, initial bladder biopsy/TURBT sensitivity was only 39% for predicting variant morphology at RC. Furthermore, subset analysis revealed that the sensitivity for UC w/SD was 47%. The authors concluded that sensitivity of endoscopic bladder sampling for variant histologies is relatively low and suggested that such observations were likely owing to sampling and tumor heterogeneity rather than to an inaccurate pathological diagnosis.

Clearly, however, experienced pathologic review is associated with increased likelihood of identifying variant histologies when present. In 2013, Shah et al. [13] presented data on 589 TUR specimens, which were re-reviewed at a tertiary care medical center before instituting definitive therapy. Of the 589 TUR specimens, 115 (19.5%) were UC demonstrating variant histologic differentiation with UC w/SD being the most common type (32% of variant cases). Most specimens demonstrated only a single variant pattern (90%) with more than half having an extensive amount of variant pathology in the specimen. Overall, variant histologic differentiation was not reported by the referring institution in 44% of cases, among which 47% were extensive in nature. The authors emphasized the importance of central pathologic review of TUR specimens to ensure adequate identification of variant patterns.

The implications for appropriate recognition of variant histologies are highlighted by the series demonstrating pathologic outcomes of these entities at the time of RC. One such study by Wasco et al. [14] reviewed pathologic specimens from 448 consecutive TURBT specimens and 295 subsequent RC specimens. This group found that 25% of TURBT specimens contained variant histologies, with UC w/SD (40%) and UC with GD (18%) being the most common. Tumors with mixed histologies were of almost uniformly high grade and invasive. Additionally, when compared with pure UC, mixed histology tumors were more likely to have muscle-invasive disease at TUR ($P < 0.0001$) and extravesical disease at RC ($P = 0.0001$).

In summary, although TURBT specimens currently present the optimal means to identify UC with variant differentiation, significant challenges both from surgical sampling and pathologic interpretation exist when attempting to characterize this entity. Given the implications of aggressive disease, additional molecular markers may be crucial to aid characterization at TUR before proceeding with more definitive therapy.

NMI bladder cancer and variant histologies

Data regarding management of NMI bladder cancer (NMIBC) and variant histologies are limited owing to the aggressive biology of disease. Indeed, as highlighted earlier, many cases of UC with differentiation present at a higher grade and stage compared with pure urothelial tumors. Therefore, meticulous TURBT with appropriate restaging is critical to accurately characterize such a tumor as being NMI. Furthermore, axial imaging with either computed tomography or magnetic resonance imaging is needed for accurate staging to confirm that disease is indeed confined to the bladder.

For UC with variant histologies, the incidence of NMI tumors is approximately 20% to 30% with many of these lesions being of high grade and cT1 stage [15,16]. Analysis of the Netherlands Cancer Registry between 1995 and 2006 by Ploeg et al. [15] identified more than 28,000 cases of T1 or greater bladder cancer. Of these cases, 7.7% had non−pure urothelial histologies and 23% were T1 with the remainder being of higher stage.

Shapur et al. [16] explored this similar concept albeit in a single-institution series with treatment considerations. In this series of 760 patients treated by initial TUR, 79 (10.4%) had evidence of variant histologic tumors of which 57 (72%) had muscle-invasive bladder cancer (MIBC) or extensive NMIBC whereas 22 (28%) had NMIBC managed by TUR and adjuvant intravesical Bacillus Calmitte Guerin

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