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Clinical Outcomes of Patients with Histologic Variants of Urothelial Cancer Treated with Trimodality Bladder-sparing Therapy

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Abstract

Background: Trimodality bladder-sparing therapy (TMT) is an acceptable treatment for selected patients with muscle-invasive urothelial cancer. Outcomes of TMT in histologic variants remains largely unknown.
Objective: To compare outcomes of pure urothelial carcinoma (PUC) to variant urothelial carcinoma (VUC) after TMT.
Design, setting, and participants: Retrospective study of patients treated with TMT at a single cancer center from 1993 until 2013.
Outcome measurements and statistical analysis: Kaplan-Meier survival probabilities, and univariate and multivariable Cox regression analysis.
Results and limitations: Of 303 patients treated with TMT, 66 (22%) had VUC. Fifty (76%) had VUC with squamous and/or glandular differentiation and 16 (24%) had other forms. Complete response rate after induction TMT was 83% in PUC and 82% in VUC ($p = 0.9$). The 5-yr and 10-yr disease-specific survival (DSS) was 75% and 67% in PUC versus 64% and 64% in VUC. The 5-yr and 10-yr overall survival (OS) was 61% and 42% in PUC versus 52% and 42% in VUC. On multivariable analysis VUC was not associated with DSS (hazard ratio: 1.3, 95% confidence interval: 0.8–2.2, $p = 0.3$) or OS (hazard ratio: 1.2, 95% confidence interval: 0.8–1.7, $p = 0.4$). Salvage cystectomy rates were similar (log-rank $p = 0.3$). Limitations include retrospective design and restriction to variants of urothelial cancer.
Conclusions: VUC responded to TMT, and there was no significant difference in complete response, OS, DSS, or salvage cystectomy rates compared with PUC. The presence of VUC should not exclude patients from TMT.
Patient summary: The response of histologic variants of bladder cancer to bladder-sparing chemoradiation is largely unknown. We compared the outcomes of histologic variants of urothelial cancer to pure urothelial cancer in a large series of patients from a single institution. We found that variant histology does not significantly influence outcomes.

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1. Introduction

The outcomes of patients with histologic variants of urothelial carcinoma is an emerging topic. While much of bladder cancer histology is pure urothelial carcinoma (PUC), 10–53% of bladder cancer is composed of variant histology [1–3]. Variant histology refers to either histologic variations of urothelial carcinoma (VUC) as well as distinct histologic subtypes. While some studies suggest that histologic variants may exhibit more aggressive behavior and poorer clinical outcomes [4,5], other studies suggest that the clinical course of VUC is similar to PUC after adjusting for stage and grade [2,6–9]. Recent reports have largely focused on VUC in the setting of radical cystectomy (RC).

Trimodality therapy (TMT) entails maximal transurethral resection of the bladder tumor (TURBT), chemotherapy, and radiotherapy, and has been shown to be effective in the definitive treatment of muscle-invasive bladder cancer (MIBC) [10–17]. While there has not been a completed prospective, randomized trial comparing TMT to RC, published studies suggest that excellent outcomes may be achieved in properly selected patients. However, the outcomes of patients with histologic variants following TMT is largely unknown.

The purpose of this study was to compare the long-term outcomes of patients with VUC and PUC who underwent TMT as their primary treatment.

2. Materials and methods

We evaluated patients from 1993 to 2013 who underwent TMT for MIBC at the Massachusetts General Hospital. The characteristics and outcomes of these patients are prospectively entered into an institutional review board-approved database. Patients were treated on or as per various Radiation Therapy Oncology Group protocols [10–17].

Patients underwent TURBT to maximal completeness followed by induction chemoradiation. For those with any residual tumor, indicating a less than a complete response (CR) on postinduction cystoscopy, cytology, or tumor site biopsy, immediate RC was recommended. Complete responders went on to receive consolidation chemoradiation and adjuvant chemotherapy. Patients were followed with cystoscopy, cytology, and cross-sectional imaging as previously described [13,17]. Surveillance occurred every 3 mo in the 1st yr, 3–4 mo in the 2nd yr, every 6 mo in the 3rd yr, and annually thereafter.

Histologic variants of urothelial carcinoma were identified retrospectively. Eligible patients had cT2-T4aN0M0 disease treated with TMT. We identified patients with PUC and VUC based on their pretreatment TURBT findings. Patients with pure variant subtypes such as adenocarcinoma or squamous cell carcinoma were excluded. All pathology was reviewed prior to treatment by seven dedicated genitourinary pathologists over the study period. VUC was categorized according to the 2004 World Health Organization classification of bladder cancer [18]. All available variant histology specimens were re-reviewed by three genitourinary pathologists (CW, SW, and JZ) to confirm the histology and quantify the amount of differentiation in the specimens. Tumor staging was standardized according to the American Joint Committee on Cancer TNM standard [19].

The primary outcome was disease specific survival (DSS). Secondary outcomes included overall survival (OS), response to induction chemoradiation, salvage cystectomy rate, and *bladder intact* DSS. Patients without visible tumor on cystoscopy and negative tumor-site rebiopsy following induction TMT were considered to have a CR. Cause of death was investigator defined, reported in follow-up case report forms, and confirmed by a convened panel of investigators [13,17]. For DSS, an event was defined as death due to the disease (including death due to toxicity of treatment), and *bladder intact* DSS was defined as DSS and freedom from a RC.

2.1. Statistical analysis

The PUC and VUC cohort were compared using the Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. DSS, OS, and *bladder intact* DSS were estimated according to the Kaplan-Meier method and compared using the log-rank test with the start date being the date of TURBT. We utilized a multivariable Cox proportional hazard model to estimate the effect on OS and DSS. The multivariable model was created using previously described clinically relevant covariates with the addition of PUC and VUC [17]. Hazard ratios (HR) were calculated along with 95% confidence intervals (CI) and p values. All calculations were two sided, and a p value <0.05 was considered to be significant. Analysis was performed using Stata v.14.1 (StataCorp, College Station, TX, USA).

3. Results

Between 1993 to 2013, 303 patients underwent TMT for clinical stage T2–T4a urothelial carcinoma. The median age was 68 yr with an interquartile range of 61–75. Of those patients 77% were men. The median tumor size was 3.5 cm (interquartile range: 2.0–4.9).

The patient demographics and pretreatment characteristics are outlined in Table 1. Within the cohort, 66/303 (22%) patients had variant histology. Most variants were of squamous and/or glandular differentiation (50/66, 76%). Eight patients exhibited sarcomatoid differentiation (8/66, 12%). Other variants were less frequent (Table 2). The chemotherapy regimens given to patients with PUC and VUC are listed in Table 3. There were no significant differences in terms of age, race, smoking status, tumor size, neoadjuvant chemotherapy, grade, stage, hydronephrosis, presence of carcinoma in situ, and fractionation between the two groups. The median follow-up for surviving patients was 6.0 yr in PUC and 6.8 yr in VUC. Twenty-five patients with VUC had slides available for pathology re-review and quantification of the amount of variant histology in the specimen (Supplementary Table 1).

A CR to induction chemoradiation was seen in 250 patients (83%). There was no difference in the rates of response to induction chemoradiation between PUC and VUC (196/237, 83% vs 54/66, 82%, $p = 0.9$). Of the 53 patients who had an incomplete response to induction, 25 (47%) did not receive immediate, salvage RC due to poor performance status ($n = 4$, 16%), need for palliative care ($n = 4$, 16%), refusal of RC ($n = 11$, 44%), and unknown reasons ($n = 6$, 25%). No patient required a RC for treatment-related toxicity. One-year, 5-yr, and 10-yr salvage cystectomy rates were 10% (95% CI: 7–15%), 19% (95% CI: 14–26%), and 24% (95% CI: 17–32%) in PUC compared with 15% (95% CI: 8–27%), 28% (95% CI: 18–42%), and 28% (95% CI: 18–42%) in VUC, and these rates were not significantly different (log-rank $p = 0.3$).

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