Outcomes Following Radical Cystectomy for Nested Variant of Urothelial Carcinoma: A Matched Cohort Analysis

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Abbreviations and Acronyms

CSS = cancer specific survival

NV = nested variant

RC = radical cystectomy

UC = urothelial carcinoma

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Purpose: We evaluated oncological outcomes after radical cystectomy in patients with the nested variant of urothelial carcinoma and compared survival to that in patients with pure urothelial carcinoma of the bladder.

Materials and Methods: We identified 52 patients with the nested variant who were treated with radical cystectomy between 1980 and 2004. Pathological specimens were re-reviewed by a single genitourinary pathologist. Patients were matched 1:2 by age, gender, ECOG (Eastern Cooperative Oncology Group) performance status, pathological tumor stage and nodal status to patients with pure urothelial carcinoma. Survival was estimated using the Kaplan-Meier method and compared with the log rank test.

Results: Patients with the nested variant had a median age of 69.5 years (IQR 62, 74) and a median postoperative followup of 10.8 years (IQR 9.3, 11.2). Nested variant cancer was associated with a high rate of adverse pathological features since 36 patients (69%) had pT3–T4 disease and 10 (19%) had nodal invasion. Eight patients (15%) with nested variant cancer received perioperative chemotherapy. When patients with the nested variant were matched to a cohort with pure urothelial carcinoma, no significant differences were noted in 10-year local recurrence-free survival (83% vs 80%, $p = 0.46$) or 10-year cancer specific survival (41% vs 46%, $p = 0.75$).

Conclusions: The nested variant of urothelial carcinoma is associated with a high rate of locally advanced disease at radical cystectomy. However, when stage matched to patients with pure urothelial carcinoma, patients with the nested variant did not have an increased rate of recurrence or adverse survival. Further studies are required to validate these findings and guide the optimal multimodal treatment approach to these patients.

Key Words: urinary bladder, carcinoma, cystectomy, urothelium, mortality

The incidence of bladder cancer in the United States in 2012 was estimated to be 73,150 cases.[1] While typical or pure UC is the most common bladder cancer histology, various pathological subtypes have been described.[2] One such entity, the NV of UC, was first described by Stern as having deceptively bland histological features[3] with a resemblance to benign lesions, such as von Brunn nests.[4,5] However, despite a bland histological appearance, several reports suggest aggressive biological behavior for the NV of UC with a high rate of extravesical and metastatic disease.[6–9] Nevertheless, given the rarity of this histological subtype, there is a paucity of data

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specifically addressing treatment in these patients. Reported series to date have been limited by relatively small sample size and/or limited followup as well as by the lack of a consistent comparison group of patients with pure UC. Therefore, to our knowledge the independent impact of NV histology on survival remains to be established.

We evaluated oncological outcomes in patients undergoing RC for NV bladder cancer and compared the survival of patients with the NV to that of a matched cohort of patients treated with RC for pure UC.

METHODS

After obtaining institutional review board approval, we reviewed the cystectomy registry at our clinic and identified 2,208 patients who underwent RC at our institution between 1980 and 2004. RC was performed by various surgeons using standard techniques. The extent of lymph node dissection varied by individual surgeon during the study period. It currently extends from the mid common iliac artery proximally to the Cooper ligament distal, laterally to the genitofemoral nerve and inferiorly to the internal iliac vessels.

A single urological pathologist (JCC) re-reviewed RC pathological specimens and 52 patients with the NV (2.4%) were identified. Patients were considered to have the NV if re-review demonstrated any NV component, including confluent small nests of varying shapes with irregular architecture, usually lacking intervening lamina propria (fig. 1).[4,5] RC was completed in all patients with NV histology and none died within 90 days of surgery. Clinicopathological variables recorded included age, gender, ECOG performance status, receipt of perioperative (neoadjuvant or adjuvant) chemotherapy, pathological tumor stage, lymph node status, surgical margin status, percent of NV features and the presence or absence of lymphovascular invasion. Tumors were staged according to the 2010 American Joint Committee on Cancer/UICC TNM classification, 7th edition.[10] Lymphovascular invasion was defined as tumor cells within an endothelial lined space without an underlying muscular wall.[11] Pathological grade was assigned according to 2004 WHO criteria. It was not reported separately since most patients treated with RC had high grade disease.

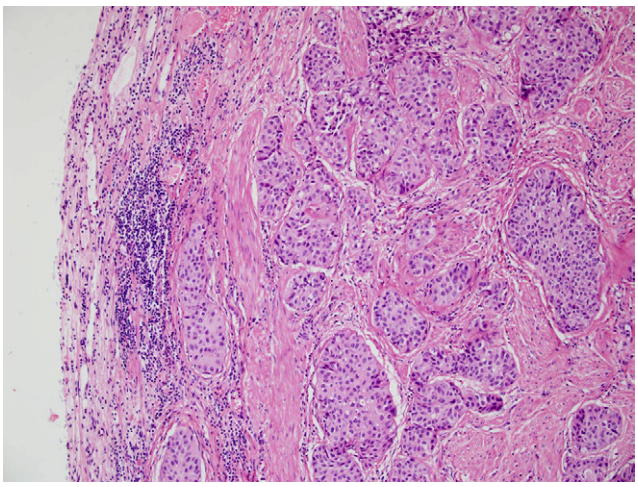

Figure 1. Representative high power image of NV. H&E, reduced from ×100.

The retrospective nature of this study precluded a standardized followup protocol in all patients. However, followup after RC at our institution has generally been recommended quarterly for the first 2 years after surgery, semiannually for the next 2 years and annually thereafter in patients without evidence of disease recurrence. Oncological evaluation includes history, physical examination, urine cytology and imaging of the chest/abdomen/pelvis.

We defined local recurrence as tumor recurrence in the soft tissue of the initial surgical bed or lymph node metastasis within the dissection template. Distant metastasis included metastasis in viscera, bone or lymph nodes outside the pelvis. Vital status was identified from death certificates or physician correspondence. Of the 52 patients with NV cancer 43 (83%) were followed at our institution. For patients followed elsewhere the cystectomy registry at our institution monitors outcomes annually by correspondence with the patient and treating physician.

The clinicopathological demographics of patients with the NV were reported and compared to those of 675 with pure UC. Patients with nonUC histology, ie squamous cell carcinoma or adenocarcinoma, and those with UC and variant histology other than the NV, ie squamous/glandular differentiation, were excluded from analysis. Patients who refused research authorization and those without tissue available for pathological review were also excluded. Given noted differences in pathological tumor stage between the NV and pure UC cohorts, to facilitate analysis of comparative survival outcomes based on histology we used a matched cohort study design to individually match the 52 patients with NV bladder cancer in a 1:2 ratio to patients with pure UC of the bladder based on age, gender, ECOG performance status, pathological tumor stage and pathological nodal status.

Comparison of features between cases and controls was evaluated using conditional logistic regression and summarized with the OR and 95% CI. Survival was estimated as time from RC to the event of interest using the Kaplan-Meier method and compared with the log rank test. Statistical analysis was performed with SAS® software. All statistical tests were 2-sided with $p < 0.05$ considered statistically significant.

RESULTS

Table 1 lists the clinicopathological demographics of the 52 patients with NV bladder cancer and the 675 unmatched patients with pure UC who were treated with RC at our institution. Patients with the NV were significantly more likely to have extravesical disease at RC than patients with pure UC (69% vs 37%, $p < 0.0001$). In patients with the NV outcomes