

Original article

Lymph node metastases in patients with urothelial carcinoma variants: Influence of the specific variant on nodal histology

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Abstract

Objectives: The effect that the presence of urothelial variant (UV) histologies has on the behavior of urothelial carcinoma remains poorly defined. The goal of this study is to examine the relationship between different histologic variants and the presence and histology of lymph node metastases.

Materials and methods: Our institutional bladder cancer database was examined for all patients demonstrating UV at cystectomy performed between 2001 and 2012. Patients with primary bladder sarcoma, primary bladder adenocarcinoma, and squamous cell carcinoma were excluded. The cystectomy and nodal pathology reports were reviewed in node-positive cases with the goal of determining the relative percentages of UVs in the bladder and lymph nodes.

Results: Overall, 292 patients demonstrated UV at cystectomy. After excluding patients with primary adenocarcinoma, sarcoma, and squamous variants, 141 patients remained, of which 65 demonstrated node-positive disease. Of these node-positive patients, 57 had slides available for review. Node positivity was most common in the micropapillary (MP), clear cell urothelial carcinoma (CC), and plasmacytoid (PC) variants. Remaining variants demonstrated node-positive rates ranging from 11.1% to 37.5%. When nodes were positive, the variants found in the nodal metastases most commonly were MP, CC, glandular, nested, and lymphoepitheliomalike. Median lymph node density was highest in PC (33%) and CC (35%) variants, although these differences were not statistically significant. Variant histology predominated the nodal metastases regardless of predominance in bladder for the MP (84%) and CC (100%) variants. The PC variant exhibited the high incidence of positive surgical margins.

Conclusion: Lymph node metastases were most common in the MP, CC, and PC variants. Variant histology was present and predominated nodal histology in most MP and CC cases. These results suggest that the variant histology itself may be driving lymphatic spread in MP and CC cases. Conversely, the PC variant may be a marker for locally advanced and aggressive disease rather than specifically influencing lymphatic spread. Published by Elsevier Inc.

Keywords: Carcinoma; Transitional cell; Bladder neoplasms; Cystectomy; Lymph node excision; Lymphatic metastasis

1. Introduction

Urothelial variant (UV) histologies associated with urothelial carcinoma (UC) have become a topic of increasing interest in recent years. The prognostic significance of the presence of UV seems to depend on the specific variant.

Although some histologic subtypes such as micropapillary (MP), sarcomatoid (SC), plasmacytoid (PC), and small cell (SmC) histologies are associated with decidedly poorer survival outcomes, the prognostic implications of lymphoepitheliomalike and glandular variants remain unclear [1–7].

Further defining the specific behavior of the different UV will help to provide the first steps toward individualizing treatment paradigms. Given that regional lymphatic metastasis remains an early event in systemic spread of UC, determining if the variant histology is actually present in the

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metastatic deposits may help to define the effect these variants have on disease progression. In this study, we will examine the patterns of lymphatic spread among UV.

2. Methods

After receiving institutional review board approval, our institutional bladder cancer database was examined for all patients demonstrating UV from 2001 to 2012. Patients with primary adenocarcinoma, sarcoma, or squamous cell carcinoma/differentiation of the bladder were excluded. Histologic criteria for the diagnosis of UV histologies were based on the 2004 World Health Organization classification of tumors of the urinary system and male genital organs [8].

All patients underwent cystectomy with curative intent. An extended template pelvic lymph node dissection (with the bifurcation of the great vessels representing the proximal limit of lymphadenectomy) is the standard dissection at the Indiana University. However, the extent of dissection is ultimately left up to the judgment of the surgeon. The cystectomy and lymphadenectomy slides of all patients in the study group with nodal metastases were reviewed by 2 authors (C.S.K. and L.C.) to determine (1) the relative percentages of variants in the bladder specimen, (2) whether variant histology was encountered in the associated lymphadenectomy specimens, and if so, (3) the relative percentages of variant histology in the lymph node specimens. Regarding pathologic examination of the primary tumor, if the size of tumor was <3 cm, the entire macroscopic visible tumor was embedded for histologic examination. For tumors \geq 3 cm, 1 block was taken and embedded per centimeter of tumor.

The node-positive rate for each variant was determined based on the total number of patients in the database harboring that variant over the study period. Patients with 2 or more variant histologies in their specimens were analyzed separately for each variant, accounting for the fact that the total number of variant cases analyzed (67) is greater than the total number of patients included in the study (57). Variant predominance was defined as making up \geq 50% of malignant histology in the bladder specimen or lymph node specimen or both. Lymph node density (LND) was defined as the number of positive lymph nodes (variant or UC or both) over the total number of nodes removed. Once it was clear the MP, PC, and clear cell UC (CC) were associated with higher rates of lymph node metastases, a separate statistical analysis of these variants was performed. The presence and predominance of variant histology in the lymph node metastases were compared using the Fisher exact test. LNDs were compared using Tukey range test.

3. Results

Of the 1,195 patients having undergone radical cystectomy at our institution from 2001 to 2012, 292 (24.4%)

demonstrated nonurothelial variant or UV or both in their cystectomy specimen. After excluding primary adenocarcinoma of the bladder, sarcoma, and squamous variants, 140 patients remained, 65 (46.4%) of which demonstrated node-positive disease. Lymphatic metastases were most common among MP, PC, and CC variants. Of the 65 patients with lymphatic metastases, the cystectomy and lymphadenectomy pathologies were available for review in 57 patients. These 57 patients comprise the study group.

Precystectomy characteristics of patients with node-positive disease are demonstrated in Table 1. Although all 3 patients with SmC disease had their variant histology noted at transurethral resection (TUR), the remaining histologies were identified at TUR in approximately 30% to 50% of cases. Only 8 patients received preoperative chemotherapy including 2 patients with MP, 3 with PC, 2 with SC, and 1 with CC variant. Only 10 patients (17.5%) had enlarged nodal metastases or biopsy-proven nodal metastases or both before cystectomy.

Pathologic findings at radical cystectomy are listed in Table 2. Primary tumors were predominantly locally advanced, with 82.4% of patients demonstrating pT3-4 disease and nearly a third having positive surgical margins.

Table 3 provides histologic characteristics of nodal metastases and surgical margins broken down by variant. Patients with multiple variants in the bladder specimen are included in the analysis of each variant. MP, PC, and CC

Table 1
Precystectomy characteristics

| | |
|---------------------------------------|------------|
| Number of patients | 57 |
| Median age (range) | 65 (44–92) |
| Sex | |
| Male | 43 (75.4%) |
| Female | 14 (24.6%) |
| Clinical stage | |
| CIS | 1 (1.8%) |
| I | 8 (14%) |
| II | 31 (54.4%) |
| III | 4 (7%) |
| IV | 13 (22.8%) |
| Clinical node status | |
| Negative | 47 (82.5%) |
| Positive | 10 (17.5%) |
| Variant histology identified at TURBT | |
| Micropapillary | 12 (48%) |
| Plasmactyoid | 8 (47%) |
| Sarcomatoid | 3 (37.5%) |
| Small cell | 3 (100%) |
| Glandular | 3 (50%) |
| Nested | 2 (50%) |
| Clear cell | 1 (33.3%) |
| Lymphoepitheliomalike | 0 |
| Preoperative chemotherapy | |
| None | 49 (86%) |
| Neoadjuvant | 2 (3.5%) |
| Metastatic disease | 6 (10.5%) |

CIS = carcinoma in situ, TURBT = transurethral resection of bladder tumor.

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