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Original article

Does presence of squamous and glandular differentiation in urothelial carcinoma of the bladder at cystectomy portend poor prognosis? An intensive case-control analysis

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Abstract

Objective: The prognostic significance of squamous and glandular elements, the most common histologic variants of urothelial carcinoma of the bladder (UCB), is unclear. This study aimed to examine the sole influence of squamous or glandular or both differentiation on UCB outcome following cystectomy and to identify factors that explain the relatively poor prognosis observed in UCB patients with these differentiation elements.

Materials and methods: A total of 2,444 patients who underwent radical cystectomy with extended lymph node dissection at a single referral center between 1976 and 2008 were considered. We identified 141, 97, and 21 patients with squamous, glandular, and squamous + glandular differentiation elements, respectively ("cases"). Pure UCB patients without differentiation were matched 1:1 to these cases for demographic, tumor, and treatment characteristics ("controls"). Cases were also compared with an independent cohort of 1,244 pure UCB controls. Recurrence-free and overall survivals were compared between cohorts using univariable and multivariable Cox proportional hazards analyses.

Results: Median follow-up for cases, controls, and independent control cohort was 15.2, 11.0, and 12.2 years, respectively. Cases were matched to controls for pathologic stage (chi-square $P = 1.00$) and administration of intravesical agents ($P \geq 0.85$), neoadjuvant ($P \geq 0.31$), and adjuvant ($P \geq 0.96$) chemotherapy. Cases were also balanced with controls for age, gender, and race ($P \geq 0.30$). Following this intensive matching, no differences in outcomes between cases and controls were observed (log-rank $P \geq 0.12$). Pathologic stage was predictive of outcome in cases with differentiation by multivariable analysis ($P \leq 0.004$). When compared to an independent control cohort, cases with differentiation were observed to present with higher pathologic stage at cystectomy (chi-square $P \leq 0.005$).

Conclusions: Outcomes of UCB patients with squamous or glandular or both differentiation are similar to those of patients with pure UCB, given comparable demographic, clinicopathologic, and management characteristics. However, UCB with differentiation present with higher pathologic stage, thus explaining the aggressive clinical course in these patients.

Keywords: Case-control studies; Pathology; Prognosis; Transitional cell carcinoma; Urinary bladder neoplasms

1. Introduction

Urothelial carcinoma of the bladder (UCB) demonstrates a wide range of clinical behavior and morphology, including a peculiar capacity for divergent histologic differentiation [1]. In the United States, nearly 5% to 10% of bladder tumors consist of urothelial carcinoma with aberrant differentiation or non-UCB [2]. The incidence of squamous differentiation, defined by the presence of intracellular keratin, intercellular bridges, or keratin pearls, ranges from 11% to 60% of all UCBs [3,4]. Glandular elements, characterized by intratumoral tubular or enteric gland-like spaces, are less common than squamous differentiation, although these histologic subtypes often coexist within the same tumor [1,5,6].

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Although these UCB variants often receive limited consideration, they pose a controversial clinical challenge. Some report a more aggressive behavior than pure UCBs [3,4,7–13], whereas others claim that their clinical course is not different from tumors without differentiation [14–18]. These contrasting observations have led to 2 schools of thought regarding their management: some argue for maintaining a high index of suspicion for aggressive disease in UCB patients with divergent histology and planning aggressive therapies in this subpopulation [16,19], whereas others suggest similar clinical management as that of pure UCB [20]. However, all prior studies examining outcomes in UCB patients with differentiation have done so by comparing them with unmatched and disproportionately balanced cohorts of patients with pure UCB, which is largely culpable for these discrepant observations. This study was therefore designed to compare outcome differences between bladder cancer patients with squamous or glandular or both differentiation and their pure UCB counterparts following cystectomy using an intensive case-control approach after matching for demographic, tumor, and treatment characteristics. The aims were to examine the effect of variant histology on UCB clinical outcome after cystectomy provided all other factors were equal and to investigate potential reasons for discrepant results in the literature.

2. Materials and methods

2.1. Patient population

Between 1976 and 2008, a total of 2,444 patients underwent radical cystectomy for bladder cancer at the University of Southern California. Patient characteristics were entered into an institutional review board–approved database. Study inclusion criteria were (a) primary UCB treated with open radical cystectomy with intent to cure and (b) availability of detailed assessment of primary tumor histology. Exclusion criteria were (a) absence of urothelial carcinoma histology in the cystectomy specimen, (b) perioperative complications leading to death, and (c) presence of urethral or upper tract primaries, or distant metastasis at diagnosis.

All patients underwent extended pelvic lymphadenectomy and urinary diversion [21]. Postoperative follow-up was at 4-month intervals in year 1, 6-month intervals in year 2, and annually thereafter with laboratory and imaging studies unless otherwise clinically indicated.

2.2. Patient-related variables and study design

Surgical specimens were examined by at least 1 of 3 genitourinary pathologists under a standardized reporting protocol [1]. Tumor staging and grading were standardized to the American Joint Committee on Cancer and World Health Organization recommendations, respectively [22,23]. Pathologic stages were defined as organ confined (Ta/TIS/T1/T2, N0), extravesical (T3/T4, N0), and node positive (any T, N1-3).

Presence of differentiation was defined by evidence of squamous or glandular or both histology against a background of urothelial elements in cystectomy specimens; tumors with squamous or glandular histology with no identifiable urothelial elements were classified as squamous cell carcinoma and adenocarcinoma of the bladder, respectively, and excluded from analysis [1,24]. Tumors of 259 patients had squamous or glandular or both differentiation elements; 141 (54.4%), 97 (37.5%), and 21 (8.1%) patients had squamous, glandular, and squamous + glandular differentiation, respectively. These patients were labeled as "cases." Of these, 23 (16.3%), 1 (1.0%), and 2 (9.5%) cases, respectively, had widespread differentiation as defined previously by differentiated areas comprising $\geq$50% of the neoplastic surface; remaining cases were defined as having focal areas of differentiation [12].

Of the remaining patients in the population who met the study criteria, those with pure urothelial carcinoma devoid of any variant histologic patterns, including micropapillary, sarcomatoid, neuroendocrine, nested, microcystic, giant cell-like, lymphoepithelioma-like, and plasmacytoid, were identified (n = 1,503). An intensive selection was performed using this subpopulation to identify a "control" patient for each "case": a control with pure UCB histology was matched to a corresponding case with respect to pathologic stage and administration of intravesical agents, neoadjuvant, and adjuvant chemotherapy. Thus, 141, 97, and 21 pure UCB controls were identified and matched to cases with squamous, glandular, and squamous + glandular differentiation, respectively. The balance subpopulation of patients with pure UCB following this matching (n = 1,244) served as an independent control cohort. Thus, a total of 1,762 patients were included in this study.

Between 1976 to 1992 and 1993 to 2008, 115 (44.4%) and 144 (55.6%) cases with squamous or glandular or both differentiation, and 100 (38.6%) and 159 (61.4%) pure UCB controls were diagnosed, respectively; proportion of patients with or without differentiation diagnosed in both eras did not differ (chi-square $P = 0.21$). In these respective eras, 472 (37.9%) and 772 (62.1%) independent control cohort patients were also diagnosed.

2.3. Clinical outcomes and statistical analysis

Outcomes of interest were recurrence-free survival (RFS) and overall survival (OS). RFS duration was calculated from date of cystectomy to date of first clinical recurrence; patients who were recurrence free at the end of the study were censored at death or last follow-up. OS duration was calculated from date of cystectomy to death due to any cause; surviving patients were censored at last follow-up.