Clinical Outcome of Patients with T1 Micropapillary Urothelial Carcinoma of the Bladder

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Abbreviations and Acronyms

BCG = bacillus Calmette-Guérin
CIS = carcinoma in situ
CSM = cancer specific mortality
CSS = cancer specific survival
LVI = lymphovascular invasion
MPC = micropapillary component
NED = no disease evidence
NMIBC = nonmuscle invasive bladder cancer
RC = radical cystectomy
TURBT = transurethral bladder tumor resection
UC = urothelial carcinoma

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Purpose: We report cancer specific outcomes of micropapillary nonmuscle invasive bladder cancer.

Materials and Methods: We retrospectively reviewed the records of 36 cases restaged within 3 months of the initial diagnosis of micropapillary nonmuscle invasive bladder cancer. Early radical cystectomy within a 3-month landmark after restaging transurethral bladder tumor resection or conservative treatment with intravesical bacillus Calmette-Guérin, surveillance or deferred radical cystectomy was offered according to surgeon and patient preference. The cumulative incidence of cancer specific mortality and metastasis was estimated using the Kaplan-Meier method. Differences in the cumulative incidence of cancer specific mortality and metastasis between the groups were tested using the log rank test.

Results: Median patient age was 68 years (IQR 63–77). The male-to-female ratio was 3:1. At restaging all patients had cT1 disease or less. Early radical cystectomy was performed in 15 patients (42%) while 21 (58%) underwent conservative treatment. Median followup after landmark in cancer specific survivors was 3.1 years (IQR 1.1–5.9). The 5-year cumulative incidence of cancer specific mortality was 17% in the early radical cystectomy group and 25% in the conservative management group for an absolute difference of 7% (95% CI −26–41, $p = 0.8$). The 5-year cumulative incidence of metastasis was 21% and 34%, respectively, with an absolute difference of 13% (95% CI −23–49, $p = 0.9$). The extent of the micropapillary component was not significantly associated with cancer specific mortality ($p = 0.4$) or metastasis ($p = 0.9$).

Conclusions: Using proper selection criteria, including patient and pathological factors, certain patients in whom cT1 micropapillary urothelial carcinoma was managed conservatively did not have significantly worse outcomes than patients treated with early radical cystectomy.

Key Words: urinary bladder neoplasms, BCG vaccine, cystectomy, treatment outcome

Micropapillary carcinoma of the bladder, a variant of UC reportedly representing 0.7% to 8% of all UC cases, has an aggressive course and may present at advanced stage. In most cases it is associated with

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conventional UC and possibly other variant histologies.[1,2] The micropapillary pattern may also be retained in metastases. Because some studies showed a relatively poor response to intravesical therapy, external beam radiotherapy and chemotherapy, the choice of such modalities as initial treatment may potentially delay definitive surgical therapy.[3–6]

Management of micropapillary UC limited to the lamina propria (cT1 or less) at initial and restaging TURBT represents a clinical dilemma. In fact, optimal management of micropapillary NMIBC is still not defined. It remains controversial whether these patients can be safely treated according to current guidelines for conventional NMIBC or whether immediate RC is required.[3,7] Current studies of micropapillary NMIBC are inconclusive for several reasons, including 1) small patient numbers, 2) possibly incomplete resection or under staging due to lack of restaging TURBT,[8,9] 3) no stratification based on the percent of MPC in the specimen, 4) lack of interobserver reproducibility of the MPC diagnosis[10] and 5) combined patient cohorts including different disease stages and grades, and different treatment modalities when assessing prognosis and survival rates.

To better delineate treatment options we retrospectively reviewed our clinical experience. We analyzed the outcomes in patients with restaged cT1 micropapillary UC treated with early RC or initially managed conservatively.

PATIENTS AND METHODS

After receiving institutional review board approval we queried our institutional, prospectively maintained bladder cancer database for the term micropapillary between 1994 and 2012. Included in study were patients newly diagnosed with cT1 or less NMIBC with MPC identified at initial or restaging TURBT, restaging TURBT within 3 months of initial diagnosis, no previous treatment for bladder cancer, treatment at our institution and a minimum 6-month followup. A total of 36 patients met these strict criteria between September 2000 and February 2012.

Available pathology slides, including those from elsewhere, were reevaluated by 3 genitourinary pathologists (HAA-A, HH and VER) for diagnosis confirmation, semiquantitative (visual) estimation of the percent MPC on initial or restaging TURBT specimens, tumor multifocality, associated CIS, LVI, lymph node involvement and surgical margin status. Grading and staging were done according to the 2004 WHO classification and the TNM staging manual.[11,12]

Management options included early RC or conservative treatment offered according to surgeon and patient preference, and considering surgical risk and previously reported prognostic indicators such as tumor grade, LVI, associated CIS and multifocality.[13] Early RC was defined as RC performed within 3 months after restaging TURBT. Intravesical BCG, TURBT alone or RC after the 3-month landmark was considered conservative management. We defined recurrence as less than cT2 UC found on TURBT performed after the landmark. Progression was defined as cT2 or greater recurrent UC after landmark. Metastasis was defined as disease at nonadjacent organs or in lymph nodes after the landmark. Time to each event was measured from the landmark to the date of repeat TURBT or the procedure, eg lymph node biopsy or small bowel resection.

The cumulative incidence of CSM and metastasis was estimated using the Kaplan-Meier method. Differences in the cumulative incidence of CSM and metastasis between groups were tested using the log rank test. The impact of the percent MPC on CSM and metastasis was evaluated using Cox proportional hazards regression. Survival time in all time to event analyses began at the landmark time. All statistical analysis was done with Stata® 12.0.

RESULTS

Table 1 lists baseline demographic and pathological characteristics of initial and restaging TURBT. All patients underwent restaging TURBT at our institution within 3 months of initial diagnosis. No deaths occurred in this interval. All tumors were high grade.

Early RC was performed in 15 patients and 21 were treated conservatively. Most patients in the conservative management group were male (90% vs 53%, $p = 0.019$). On restaging TURBT the rates of stage T0 did not significantly differ (33% vs 28.5%, $p = 0.8$). In overall survivors median post-landmark followup was 3.2 years (IQR 1.1–6.1). Table 2 shows the outcomes of early RC. Up-staging at RC was done in 5 patients. Metastatic tumor morphology in positive lymph nodes at RC was conventional UC in 2 patients, micropapillary in 1 and the 2 patterns in 1. Table 3 lists treatments and outcomes in cases managed conservatively. Median time from restaging TURBT to the initiation of BCG treatment was 23.5 days (IQR 19–29). Two patients treated conservatively showed progression to cT2 at 1 month and 1.2 years after landmark, respectively, and 4 showed pelvic metastasis a median of 2.6 years (IQR 1.0–4.2) after landmark.

The cumulative incidence of CSM 5 years after restaging TURBT was 17% in the early RC group and 25% in the conservative management group for an absolute difference of 7% (95% CI −26–41, table 4 and fig. 1). The log rank test showed no difference between the groups in the cumulative incidence of CSM throughout followup ($p = 0.8$). The 5-year cumulative incidence of metastasis was 21% and 34% in the early RC and conservative management groups, respectively, for an absolute difference of −13% (95% CI −23–49, table 4 and

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