Mixed High and Low Grade Bladder Tumors—Are They Clinically High or Low Grade?

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Purpose: The pathological grade of bladder cancer has an immense impact on patient treatment and prognosis. While most bladder tumors show pure high or low grade patterns, some show a mixed pattern. We explored the incidence and clinical significance of this phenomenon.

Materials and Methods: A total of 642 patients with a mean age of 67.5 years underwent transurethral resection of nonmuscle invasive bladder tumors between June 1998 and December 2008, including 156 and 454 with low and high grade lesions, respectively. In 32 patients (5%) mixed grade tumors were found, defined as low grade tumors with 10% or less of a high grade component. All patients were followed a median of 60 months postoperatively.

Results: Mean age, the proportion of men and the proportion of stages Ta/T1 in patients with mixed grade tumors were between those of the high and low grade groups. Five-year recurrence-free survival was similar for high, low and mixed grade tumor types (56.9%, 63.8% and 66.4%, respectively, $p = 0.252$). Five-year progression-free survival was significantly lower in patients with high grade disease (73.9%, $p < 0.0001$) but similar in those with high and mixed grade tumors (99% and 96.9%, respectively, $p = 0.167$). Similarly, disease specific survival was significantly worse in patients with high grade tumors ($p < 0.0001$) but similar in those with high and mixed grade lesions ($p = 0.679$).

Conclusions: Mixed grade is found in about 5% of nonmuscle invasive tumors, representing a patient group with unique clinical features. The clinical course of patients with mixed grade tumors parallels that of patients with low grade tumors.

Key Words: urinary bladder, urothelium, carcinoma, neoplasm grading, mortality

Abbreviations and Acronyms

BCG = bacillus Calmette-Güerin
HG = high grade
LG = low grade
MG = mixed grade

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Bladder cancer grade is determined by studying tumor histology and cytology. Tumor grade has an immense impact on management.[1] While most urothelial carcinomas show pure LG or HG histology, some show a mixed LG/HG pattern (MG). Standard pathology textbooks state that a tumor should be graded according to the highest grade even if it is present only in a small focus of the lesion.[2,3] Therefore, most patients with MG tumors are treated as though they have a HG tumor. To our knowledge the frequency, clinical features and prognostic significance of MG tumors are unknown.

We investigated the phenomenon of MG tumors in patients with nonmuscle invasive urothelial carcinoma.

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We determined whether they represent a different group of patients and whether tumor clinical behavior is closer to that of HG or to LG lesions.

PATIENTS AND METHODS

Patients

Population. We surveyed a prospectively maintained database that holds data on 642 patients who underwent transurethral resection of initial nonmuscle invasive bladder tumors between June 1998 and December 2008. The pathological diagnosis of bladder cancer was made using histological specimens from transurethral resection of bladder tumor by a dedicated uropathologist (GP) who reviewed all cases. Pathological staging was performed according to the 1997 TNM system and grading was done according to the 1998 International Society of Urological Pathology classifications. A tumor was designated as MG when LG as well as HG elements were present in the same lesion but less than 10% of it was HG (fig. 1). When more than 10% of the tumor was HG, the tumor was considered HG. The study was approved by the institutional review board committee (Institutional Helsinki committee).

Treatment. Patients with HG tumors, including those with MG neoplasms, underwent second look resection. Patients with HG, MG or stage T1 tumors, or bladder Tis received an induction course of 6 weekly intravesical instillations of 81 mg Connaught BCG in 50 cc normal saline, which was initiated 10 to 20 days postoperatively. Patients in whom LG disease recurred sooner than 24 months after initial resection also received an induction course of BCG. Maintenance therapy (2 or 3 instillations every 3 months for 1 year and then every 6 months for an additional 2 years) was given to patients with HG cancer. The followup protocol included cystoscopy and urinary cytology every 3 months for 2 years and then every 6 months for an additional 3 years. Bladder biopsies were done to monitor the response to BCG in patients with HG disease.

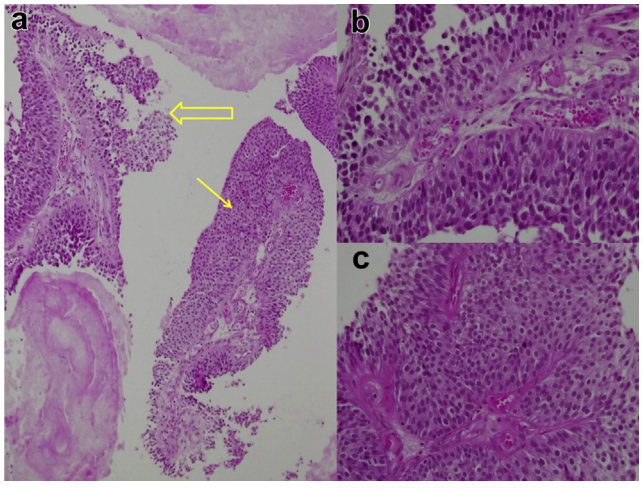

Figure 1. *a*, tumor composed of LG (thin arrow) and HG (open arrow) elements. H&E, reduced from ×20. *b*, higher magnification of HG element. H&E, reduced from ×40. *c*, higher magnification of LG element. H&E, reduced from ×40.

Statistical Analysis

We evaluated the incidence and clinical features of patients with HG, LG and MG disease. Continuous variables were compared using the t-test and categorical variables were compared using the Fisher exact and chi-square tests, as appropriate. All statistical tests were 2-tailed with $p < 0.05$ considered significant. Recurrence-free survival, progression-free survival to T2 or greater and disease specific mortality were analyzed using the Kaplan-Meier method. SPSS® was used for data processing.

RESULTS

The study cohort included 454 patients (70.7%) with LG, 156 (24.3%) with HG and 32 (5%) with MG tumors. Mean ± SD patient age was 66.5 ± 12.7 years. Patients with HG tumors were significantly older than patients with LG tumors (mean age 70 ± 10.55 vs 65 ± 13.3 years, $p < 0.0001$). The age of patients with MG tumors was between that of the other groups (mean 68 ± 10.8 years) and it did not statistically differ from that in the single grade groups. The cohort included 531 men (82.7%) and 111 women (17.3%). The proportion of males was significantly higher in the HG group than in the LG group (88% vs 80%, $p = 0.01$). The proportion of males in the MG group (90%) was closer to that of the HG group and it differed marginally from the LG group ($p = 0.07$).

Tumors were stage Ta in 488 patients (76%), stage T1 in 143 (22.2%) and pure Tis in 13 (2%). As expected, the incidence of stage T1 in patients with HG tumors was significantly higher than in those with LG tumors (72.4% vs 4.8%, $p < 0.0001$). The incidence of stage T1 in patients with MG tumors was marginally higher than in the LG group (59.4%, $p = 0.057$). Tis was present in 72 patients with HG while significantly fewer patients with MG tumors had Tis (46% vs 28%, $p = 0.045$).

Figure 2 shows followup results. By a median followup of 60 months 230 patients (35.8%) had experienced tumor recurrence, 41 (6.4%) had progressed to stage 2 or greater and 23 (3.6%) had died of bladder cancer. Five-year recurrence-free survival was statistically similar in patients with HG, LG and MG tumors (56.9%, 63.8% and 66.4%, respectively, $p = 0.252$). Five-year progression-free (to T2 or greater) survival of patients with HG, LG and MG tumors was 73.9%, 99% and 96.9%, respectively, significantly lower for HG ($p < 0.0001$) but similar for LG and MG ($p = 0.167$). Five-year disease specific survival in patients with HG, LG and MG tumors was 87.6%, 99.5% and 100%, respectively. This was significantly lower for HG