Clinical Outcomes of cT1 Micropapillary Bladder Cancer

Daniel L. Willis, Mario I. Fernandez, Rian J. Dickstein, Sahil Parikh, Jay B. Shah, Louis L. Pisters, Charles C. Guo, Samuel Henderson, Bogdan A. Czerniak,* H. Barton Grossman, Colin P. Dinney and Ashish M. Kamat†

From the Departments of Urology and Pathology (CCG, SH, BAC), University of Texas M.D. Anderson Cancer Center, Houston, Texas

Purpose: While many urologists recommend radical cystectomy for micropapillary bladder cancer invading the lamina propria (cT1), contradictory small reports exist on the efficacy of conservative management with intravesical bacillus Calmette-Guérin for this disease. We report our updated experience in what to our knowledge is the largest series of patients with cT1 micropapillary bladder cancer.

Materials and Methods: An institutional review board approved review of our cancer database identified 283 patients with micropapillary bladder cancer, including 72 staged with cT1N0M0 disease at diagnosis and initiation of therapy. Survival analysis was performed using the Kaplan-Meier estimator and compared using the log rank test.

Results: In this cohort of 72 patients 40 received primary intravesical bacillus Calmette-Guérin and 26 underwent up-front radical cystectomy. Of patients who received bacillus Calmette-Guérin 75%, 45% and 35% experienced disease recurrence, progression and lymph node metastasis, respectively. Patients treated with up-front cystectomy had improved survival compared to patients treated with primary bacillus Calmette-Guérin (5-year disease specific survival 100% vs 60% $p = 0.006$) and patients who underwent delayed cystectomy after recurrence (5-year disease specific survival 62%, $p = 0.015$). Prognosis was especially poor in patients who waited for progression before undergoing radical cystectomy with an estimated 5-year disease specific survival of only 24% and a median survival of 35 months. In patients treated with up-front cystectomy pathological up-staging was found in 27%, including 20% with lymph node metastasis.

Conclusions: While certain patients with T1 micropapillary bladder cancer may respond to intravesical bacillus Calmette-Guérin, survival is improved in those who undergo early radical cystectomy. Further molecular studies are needed to identify subsets of patients in whom the bladder can be safely spared.

Key Words: urinary bladder, BCG vaccine, cystectomy, neoplasm invasiveness, mortality

Abbreviations and Acronyms

BCG = bacillus Calmette-Guérin
DSS = disease specific survival
MPBC = micropapillary bladder cancer
NAC = neoadjuvant chemotherapy
NMI = nonmuscle invasive
TUR = transurethral resection
UC = urothelial carcinoma

Accepted for publication September 15, 2014.
Study received institutional review board approval.

* Financial interest and/or other relationship with Abbott Molecular.

† Correspondence: Department of Urology, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Unit 1373, Houston, Texas 77030 (telephone: 713-792-3250; FAX: 713-794-4824; e-mail: akamat@mdanderson.org).

MICROPAPILLARY bladder cancer is a rare variant of urothelial carcinoma that was first reported in 1994.[1] While the biology of MPBC is still poorly understood, even a small amount of micropapillary histology in a tumor can be clinically significant.[2] In our earlier report of 100 patients with

0022-5347/15/1934-1129/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2014.09.092
Vol. 193, 1129-1134, April 2015
Printed in U.S.A.

MPBC[3] we confirmed previous findings that this histology conferred a predisposition to advanced local stage and metastatic disease.[1,2,4,5] Some groups suggested that when controlling for stage, MPBC and pure urothelial carcinoma have similar survival outcomes.[6,7]

In a SEER (Surveillance, Epidemiology and End Results) study comparing MPBC to conventional UC the patients with stage controlled MPBC had a survival rate similar to that of patients with conventional UC but not in the NMI disease cohort.[8] NMI-MPBC was associated with worse survival. NMI-MPBC represents a potentially treatable form of the disease that may warrant a more aggressive management strategy. In 2006 we first advocated early cystectomy for NMI-MPBC.[9] Others suggested that intravesical BCG therapy may be appropriate as primary treatment.[10,11]

Currently to our knowledge no guidelines exist for NMI-MPBC management. Thus, we present our updated experience with an emphasis on cT1 MPBC.

MATERIALS AND METHODS

We performed an institutional review board approved search of the records of all patients diagnosed with MPBC at our institution between 1990 and 2012. Patient records were used to extract data points. We identified 283 patients with MPBC diagnosed at TUR by our dedicated genitourinary pathologists. A total of 83 patients had cT1 MPBC in an adequate TUR specimen containing muscularis propria, of whom 5 were excluded from study due to concurrent variant histology such as small cell carcinoma or signet ring carcinoma. Six of the remaining 78 patients were excluded due to metastatic disease, including lymph node metastasis in 3, pulmonary metastasis in 2 and bony metastasis in 1. Thus, 72 patients with a mean ± SD age of 65.4 ± 10.2 years who had cT1N0M0 MPBC were included in the primary analysis. A micropapillary component of less than 25% of the total tumor architecture was considered focal. Median followup was 55.5 months.

As is our standard practice, all patient data were independently re-reviewed and patients underwent repeat staging TUR and examination under anesthesia before therapy. When MPBC was present upon review by our pathologists of TUR slides from elsewhere, the original TUR date served as the time of diagnosis. When radical cystectomy was performed, it included bilateral pelvic lymph node dissection. Tumor staging was based on the AJCC (American Joint Committee on Cancer) Cancer Staging Manual.[12]

Statistical analysis was done with IBM® SPSS®, version 21 and Stata/SE™, version 12.1. Tests included Pearson chi-square analysis, the Student t-test, survival via the Kaplan-Meier method and univariate log rank tests, and multivariate survival analysis using a Cox proportional hazards regression model. Survival time was measured from the date of the cT1 MPBC TUR diagnosis to the date of last follow up or death. All p values are 2-sided and statistical significance was set at $p < 0.05$.

RESULTS

Five-year DSS in the cT1N0M0 cohort was 73.6%. Primary treatment strategies were primary BCG (induction and maintenance) in 40 patients (55%), up-front radical cystectomy in 26 (36%), primary chemoradiation in 2 (3%), primary chemotherapy in 1 (1%) and only TUR in 3 (4%). Mean age of the patients who underwent primary BCG and cystectomy was 65.1 ± 8.3 and 64.3 ± 12.2 years, respectively ($p = 0.770$).

The primary BCG and up-front radical cystectomy cohorts were the focus of the current series. There was no difference in patient or tumor characteristics between the groups, including lymphovascular invasion, carcinoma in situ, hydronephrosis or MPBC extent (table 1). In a multivariate model including tumor characteristics, treatment strategies (ie neoadjuvant chemotherapy) and outcomes (ie progression on BCG) there was no single predictor of survival.

Primary BCG

Five-year DSS was 60% in the 40 patients who received primary BCG (fig. 1, *A*). Of patients in the primary BCG cohort 38% underwent repeat resection before the initiation of BCG therapy. However, there was no difference in the survival, recurrence or progression rates between these patients and those without repeat resection. Tumor recurred in 30 patients (75%) treated with primary BCG and 18 (45%) progressed to cT2 or greater disease, or distant metastatic disease. Of the 20 patients (50%) who underwent delayed radical cystectomy 10 were alive with an intact bladder at the time of analysis. Median followup was 67.5 months and median time to progression was 8 months (fig. 1, *B*). Nine of the 18 patients (50%) with progression presented with cT2 or greater disease in the bladder, including 3 (17%) with concurrent lymph node metastasis.

Table 1. *Patient characteristics*

	No. Pts (%)	No. Upfront Cystectomy (%)	No. Primary BCG (%)	p Value
Overall	72 (100)	26 (100)	40 (100)	
Female	12 (17)	3 (12)	8 (20)	0.367
Male	60 (83)	23 (89)	32 (80)	
Repeat resection	28 (39)	11 (42)	15 (38)	0.696
MPBC extent:				
Focal	47 (65)	17 (65)	26 (65)	0.107
Extensive	19 (26)	5 (19)	13 (33)	
Unknown	6 (8)	4 (15)	1 (3)	
Lymphovascular invasion	12 (17)	6 (23)	5 (13)	0.527
Ca in situ	11 (15)	4 (15)	6 (15)	0.966
Hydronephrosis	3 (5)	0	3 (8)	0.144