Published in final edited form as:

J Urol. 2015 April ; 193(4): 1129–1134. doi:10.1016/j.juro.2014.09.092.

Clinical Outcomes in cT1 Micropapillary Bladder Cancer

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Abstract

Purpose—While many urologists recommend radical cystectomy for patient with micropapillary bladder cancer (MPBC) invading the lamina propria (cT1), contradictory small reports exist regarding the efficacy of conservative management with intravesical BCG for this disease. Herein we report our updated experience with largest series of patients with cT1 MPBC.

Materials and Methods—An IRB approved review of our cancer database identified 283 patients with MPBC, including 72 staged as cT1N0M0 at diagnosis and initiation of therapy. Survival analysis was performed using Kaplan-Meier estimator and compared using the log-rank test.

Results—Within this 72 patient cohort, 40 received primary intravesical BCG and 26 underwent upfront radical cystectomy. Patients receiving BCG experienced high rates of disease recurrence (75%) and progression (45%); 35% developed lymph node metastasis. Patients treated with upfront cystectomy had improved survival compared to patients treated with primary BCG (5 year disease specific survival (DSS) of 100% vs. 60% respectively, $p=0.006$) or patients undergoing delayed cystectomy after recurrence (5 yr. DSS: 62%, $p=0.015$). Prognosis was especially poor in patients who waited for progression prior to undergoing radical cystectomy, with an estimated 5-year DSS of only 24% and a median survival of 35 months. In patients treated with upfront cystectomy, pathologic upstaging occurred in 27%, including 20% with lymph node metastasis.

Conclusions—While certain patients with T1 MPBC may respond to intravesical BCG, improved survival is seen in those patients who undergo early radical cystectomy. Further molecular studies are needed to identify subsets of patients able to spare their bladders safely.

Keywords

micropapillary bladder cancer; non-muscle invasive; T1; management; clinical outcomes

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Introduction

Micropapillary bladder cancer (MPBC) is a rare variant of urothelial carcinoma first reported in 1994.¹ While the biology of MPBC is still poorly understood, even small amounts of micropapillary histology in a tumor has been reported to be clinically significant.² In our earlier report on 100 patients with MPBC,³ we confirmed earlier findings that this histology conferred a predisposition to advanced local stage and metastatic disease.^{1, 2, 4, 5} Some series have suggested that when controlling for stage, MPBC and pure urothelial carcinoma have similar survival outcomes.^{6, 7}

In a SEER study comparing MPBC to conventional UC, patients with stage controlled MPBC had similar survival rates to conventional UC but not in the non-muscle invasive (NMI) disease cohort where NMI-MPBC was associated with worse survival.⁸ NMI-MPBC represents a potentially treatable form of the disease and may warrant a more aggressive management strategy. In 2006, we first advocated early cystectomy for NMI-MPBC,⁹ others have suggested that intravesical BCG therapy may be appropriate as primary treatment.^{10, 11} At present, no guidelines exist for the management of NMI-MPBC and thus, herein, we present our updated experience with an emphasis on cT1 MPBC.

Materials and Methods

An IRB approved search of all patients diagnosed with MPBC at our institution between 1990 and 2012 was performed; patient records were used to extract data points. We identified 283 patients with MPBC diagnosed at the time of transurethral resection (TUR) (by our dedicated GU pathologists) of which 83 patients had cT1 MPBC within an adequate TUR specimen containing muscularis propria. Of these, 5 were excluded for concurrent variant histology (such as small cell carcinoma, signet ring carcinoma). Of the remaining 78 patients, 6 were excluded due to metastatic disease (3 lymph node metastasis, 2 with pulmonary metastasis and 1 with bony metastasis). Thus, 72 patients with cT1N0M0 MPBC were included for the primary analysis. Micropapillary component <25% of total tumor architecture was considered "focal." Median follow up time was 55.5 months.

As is our standard practice, all patient data were independently re-reviewed and patients underwent repeat staging TUR and EUA before therapy. In cases when MPBC was present on review of outside TUR slides by our pathologists the original TUR date was used as the time of diagnosis. When radical cystectomy was performed it included bilateral pelvic lymph node dissection. Tumor staging was based on the AJCC Cancer Staging Manual.¹²

Statistical analysis was performed using IBM SPSS version 21 statistical software and Stata/SE version 12.1 statistical software (Stata Corp. LP, College Station, TX). Test used included Pearson chi square analysis, student T-tests, survival via the Kaplan-Meier method and univariate log rank tests and multivariate survival analysis using a Cox proportional-hazards regression model. Survival times were measured from the date of 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

The 5-year disease-specific survival (DSS) for the cT1N0M0 cohort was 73.6%. Primary treatment strategies included primary BCG (induction and maintenance): 40 patients (55%), upfront radical cystectomy: 26 (36%), primary chemoradiation: 2 (3%), primary chemotherapy: 1 (1%), and only TUR: 3 (4%). The remainder of the discussion will focus on the primary BCG and upfront radical cystectomy cohorts. As noted in Table 1, there were no differences in patient or tumor characteristics between groups including lymphovascular invasion, CIS, hydronephrosis, or extent of MPBC. In a multivariate model that included tumor characteristics, treatment strategies (i.e. neoadjuvant chemotherapy), and outcomes (i.e. progression on BCG) there was no single predictor of survival.

Primary BCG

The 5-year DSS for the 40 patients receiving primary BCG was 60% (Figure 1). 38% of the patients in the primary BCG cohort underwent re-resection prior to initiation of BCG therapy. However, there were no differences in survival, recurrence, or progression rates between these patients and those that did not. Among patients treated with primary BCG, 30 (75%) developed a tumor recurrence and 18 (45%) progressed with cT2 disease or distant metastatic disease; a total of 20 (50%) patients underwent delayed radical cystectomy, and 10 are alive with an intact bladder (median follow up of 67.5 months). As seen in Figure 2 the median time to progression was 8 months. Of the 18 patients that progressed, 9 (50%) presented with cT2 disease in the bladder, including 3 (17%) with concurrent lymph node metastasis. 10 (25%) patients developed metastatic disease during primary BCG therapy, including 8 with nodal disease and 2 patients with cM+ disease (lung and pelvic metastasis) (Table 2). Of these 18 patients 14 (78%) received subsequent chemotherapy and 11 (61%) underwent radical cystectomy, though one was aborted for carcinomatosis. Survival after progression was poor with a 5-y DSS of 24% and a median survival of 35 months. Patients undergoing cystectomy after progression on BCG therapy had a median DSS of 43 months compared to 35 months median DSS for patients who progressed but did not undergo radical cystectomy ($p=0.051$).

To evaluate the effect of the extent of MPBC on response to BCG, specimens were categorized as focal (<25%) or extensive MPBC. Patients with extensive MPBC were more likely to progress during BCG therapy (69.2%) when compared to those with focal MPBC (30.8%, $p=0.022$) and to develop nodal metastasis (54% vs 23%, $p = 0.055$). This correlated with a DSS advantage for patients with focal MPBC (Figure 3). While most patients received induction and maintenance BCG fashioned after the SWOG protocol, subgroup analysis based on duration of BCG therapy was not possible from the records.

Upfront Cystectomy

26 patients were treated with upfront radical cystectomy of whom 6 patients (23%) who received neoadjuvant chemotherapy (NAC). Only one death occurred in this cohort, 8.5 years after diagnosis and cystectomy. Of the 6 patients receiving NAC, 3 were downstaged to pT0N0 and 3 to pTisN0. In contrast, of the 20 remaining upfront cystectomy patients,

only 3 patients were downstaged to pT0 and 3 to pTis by TUR alone. With a limited sample size and low death rate, statistical analysis for NAC was inadequate.

In the upfront cystectomy cohort, 5-year DSS was 100% with a mean follow up of 72 months (range 31–148 months). Pathologic upstaging occurred in 6 - 3 (12%) with pT2 disease, 1 (4%) with concurrent nodal disease, and 3 (12%) with positive nodal disease without muscle invasive disease in the bladder. Thus the rate of occult nodal disease in the upfront cystectomy cohort was 15%. The extent of MPBC (focal vs. extensive, in 12 quantified cases) did not affect DSS in the cystectomy cohort. For those with pathologic lymph node metastasis, adjuvant chemotherapy was selected by 2.

Among the primary BCG cohort, 20 (50%) patients underwent delayed radical cystectomy (Table 2); patients in the delayed cystectomy group had a higher rate of pT3 disease (25% vs. 0%, $p = 0.04$). Overall, the rate of pathologic disease progression among the delayed cystectomy group (pT2 or nodal disease) was 40% with 2 patients presenting with node positive disease despite being pT0 in the primary site. The 5-year DSS for the delayed cystectomy group was 62% vs. 100% in the upfront cystectomy group ($p=0.015$) as depicted in Figure 4.

Discussion

This study represents the largest series of patients with cT1 MPBC. In our cohort, intravesical BCG therapy was associated with high rates of recurrence and progression and a relatively poor DSS compared to upfront radical cystectomy. Several factors may explain the poor response to intravesical BCG therapy. The first is the relatively high rate of lymph node metastasis found within the cohort of 35%: 10 (25%) patients developed lymph node disease during the course of BCG therapy, and 4 patients had occult lymph node disease detected at delayed cystectomy. Adding to this the 2 patients with non-nodal distant disease, 40% of patients who received primary BCG cohort developed metastatic disease. To this, if we add the 15% of patients in the upfront radical cystectomy group with occult lymph node positive disease and the 6 patients who presented with cT1N+M+ disease (excluded from the comparative analysis) it is apparent that cT1 MPBC is associated with an alarmingly high rate of metastatic disease at presentation. This suggests that cT1 MPBC is more aggressive than would be expected for conventional cT1 UC and warrants a more aggressive management strategy.

A second factor is understaging of the primary MPBC tumor itself. The largest series of MPBC reported to date contained 67% NMI-MPBC³. In that study, 75% of patients receiving upfront cystectomy were upstaged to MIBC and 38% were reported to have N+ disease. Similarly, we reported a 57% rate of upstaging in the first NMI-MPBC series published.⁹ A lower rate of upstaging (23%) was noted in our study at the time of upfront cystectomy, but still represents a concerning attribute of MPBC.

A third factor may be that BCG is ineffective against MPBC due to as yet undetermined mechanistic reasons. Patients with focal MPBC showed lower rates of disease progression and increased survival and were less likely to develop N+ disease compared to extensive

MPBC. Regardless, even focal MPBC is associated with N+ disease in 23% of cases and has a 5-year DSS of 73%, which is still inferior to the survival rates achieved with upfront radical cystectomy.

The initial recommendation for upfront radical cystectomy for NMI-MPBC came in 2006 from the MD Anderson NMI-MPBC series by Kamat et al.⁹ In that report of 44 patients, among those treated with primary BCG therapy, 67% progressed including 22% who developed metastases. Only 19% of the primary BCG cohort remained disease-free with an intact bladder after a median follow-up of 30 months. Among those undergoing delayed cystectomy after progression, median DSS was 61.7 months with no patients surviving at 10 years. In contrast, patients receiving upfront cystectomy had a 10-year DSS rate of 72% (median survival not reached).

Other retrospective series with NMI-MPBC have been reported with smaller sample sizes. Ghoneim et al reported 10 patients diagnosed with cTis-cT1 disease.¹³ All 7 patients treated with BCG recurred and underwent delayed radical cystectomy for pT3 disease. Positive lymph nodes were reported in 6 (86%). Comperat et al reported on a 72 patient cohort of MPBC including 33 with cT1 and 12 cTa disease. 8 of the pTa patients were treated with radical cystectomy and all were upstaged at the time of surgery (63% with pT2-pT4 disease).¹⁴ In a more recent SEER 17-based study, after controlling for TNM staging, no difference between MPBC and conventional UC was noted. However patients with NMI-MPBC had an inferior mean DSS of 47 months vs. 57 months for conventional UC ($p<0.001$).⁸

Other authors have presented alternative views on NMI-MPBC. In a recent publication from the Memorial Sloan Kettering (MSK) group, survival outcomes comparing primary BCG and upfront radical cystectomy were reported.¹⁵ The premise of the study was that outcomes for BCG might be more favorable if a restaging TUR was universally applied. However, this study was limited by its sample size ($n = 36$), selection bias, and relatively short follow up of 3 years (less than our median survival rates). Interestingly, even after selecting for the most ideal candidates with NMI-MPBC, a high incidence of metastasis was still observed with an estimated 5-year rate of 21%. Just as concerning was the high rate of occult metastatic disease in the upfront cystectomy cohort of 27% with a 5 year cancer specific metastasis rate of 34%. These data continue to demonstrate the predisposition of cT1 MPBC for distant disease. Furthermore, because of the restaging TUR, a selection bias was likely inevitable as patients could be dichotomized to a 'high risk' and 'low risk' cohort with patients with more favorable pathology proceeding with BCG. Thus, in addition to the overall low sample size and relatively short follow up of the study, the two comparison arms may also have been inherently dissimilar at baseline, further contributing to the lack of statistical significance seen in comparing outcomes – namely the reported a 5-year cancer specific mortality of 25% vs. 17% ($p=0.8$) and a 5-year rate of metastasis of 34% and 21% for primary BCG and upfront cystectomy, respectively ($p=0.9$) which was listed as 'non-significant'. Thus, while the authors should be commended in including only patients with a repeat TUR to improve BCG outcomes, no clinical factors could be identified to predict which patients with cT1 MPBC might progress on intravesical therapy. **In our study, 38% of the BCG cohort and 50% of the upfront cystectomy cohort underwent re-resection after the diagnosis of**

MPBC. Statistical analysis comparing outcomes between those that had a re-TUR and those that did not, showed no difference in pathological or survival outcomes.

Amin et al reported on 13 patients with NMI-MPBC in whom 7 underwent primary intravesical therapy, 5 underwent surveillance only, and 1 underwent primary surgery. Three patients progressed to muscle invasion (pT2, pT3, pT3N2), 1 patient died of bladder cancer, 1 died of other causes, and 64% are alive with an intact bladder after a median follow up of 14 months.¹¹ Gaya et al have reported outcomes in an 8 patient cohort of NMI-MPBC.¹⁰ 6 patients with a small percentage of micropapillary component in the tumor specimen were reported to be disease free after BCG therapy with a 5-year DSS of 87.5%. Despite limited sample size, these reports have been cited to suggest that BCG may be appropriate for NMI-MPBC.¹⁰

More recently, a survey developed by the Translational Science Working Group of the Bladder Cancer Advocacy Network-sponsored Think Tank meeting was distributed to members of the Society of Urologic Oncology (SUO). The results from 118 respondents, including 80% considering bladder cancer their primary area of interest, revealed that 78% would treat MPBC differently than conventional urothelial carcinoma, with 81% reporting that they would treat cT1 MPBC with upfront radical cystectomy.¹⁶

Limitations to our study include its retrospective nature and potential bias in patient selection for primary BCG vs. upfront cystectomy. While BCG schedules and dosing could not be controlled in this study and were subject to physician variation, this reflects real world data and is similar to the aforementioned report. Nonetheless, it is unlikely that maintenance BCG would affect the striking findings of high rates of occult metastatic disease associated with cT1 MPBC. While pathologic confirmation of MPBC was performed only within our institution by GU pathologists, and did not incorporate a centralized pathologic review, we respectfully submit that since our institution reported on the existence of MPBC (in 1994)¹ our pathologists are well qualified to make the diagnosis.

Conclusion

While certain patients with T1 micropapillary bladder carcinoma may respond to intravesical BCG, the best survival appears to be in those patients who undergo early radical cystectomy. Patients who are offered a trial of intravesical BCG should be counselled that radical cystectomy after disease recurrence or, especially progression, may result in inferior outcomes. Further molecular studies are needed to identify subsets of patients able to spare their bladders safely and are currently underway in a multi-center collaboration initiated by the Bladder Cancer Think Tank.¹⁶

Abbreviations

CIS	Carcinoma in situ
RC	Radical cystectomy
STSM	Soft tissue surgical margin

UCB Urothelial carcinoma of the bladder

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Figure 1.

Disease specific survival for upfront cystectomy vs. primary BCG

Kaplan-Meier plots of recurrence-free (A) and cancer-specific survival (B) stratified by pure urothelial carcinoma of the bladder versus variant urothelial carcinoma of the bladder histology in 485 patients treated with radical cystectomy and bilateral pelvic lymphadenectomy

Figure 2.
Recurrence and progression free survival curves for intravesical BCG
Kaplan-Meier plots of recurrence-free (A) and cancer-specific survival (B) stratified by urothelial carcinoma histologies in 485 patients treated with radical cystectomy and bilateral pelvic lymphadenectomy

Figure 3.

Focal vs. extensive MPBC for intravesical BCG

Kaplan-Meier plots of recurrence-free (A) and cancer-specific survival (B) stratified by the extent of variant histology within urothelial carcinoma of the bladder in 485 patients treated with radical cystectomy and bilateral pelvic lymphadenectomy

Figure 4.
Disease specific survival by timing of cystectomy

Table 1

Patient Characteristics

	All	Upfront Cystectomy	Primary BCG	p-value
Characteristic	n (%)	n (%)	n (%)	
All patients	72 (100%)	26 (100%)	40 (100%)	
Age $\pm$ SD	65.4 $\pm$ 10.2	65.1 $\pm$ 8.3	64.3 $\pm$ 12.2	0.770
Sex				
Female	12 (17%)	3 (12%)	8 (20%)	0.367
Male	60 (83%)	23 (89%)	32 (80%)	
Re-resection	28 (39%)	11 (42%)	15 (38%)	0.696
Extent of MPBC				
Focal	47 (65%)	17 (65%)	26 (65%)	0.107
Extensive	19 (26%)	5 (19%)	13 (33%)	
Unknown	6 (8%)	4 (15%)	1 (3%)	
LVI	12 (17%)	6 (23%)	5 (13%)	0.527
CIS	11 (15%)	4 (15%)	6 (15%)	0.966
Hydronephrosis	3 (5%)	0 (0%)	3 (8%)	0.144

Table 2

Patient Outcomes

	Upfront Cystectomy	Primary BCG	p-value
Characteristic	n (%)	n (%)	
Tumor recurrence after BCG	--	30 (75%)	--
Progression	--	18 (45%)	--
Progression to cT2	--	9 (50%)	--
cT2	--	7 (39%)	--
cT3	--	2 (11%)	--
Progression to cN+	--	10 (25%)	--
Progression cM+	--	2 (5%)	--
Cystectomy	26	20	--
Preoperative Chemotherapy	6 (23%)	9 (45%)	0.116
pT stage			
pT0	6 (23%)	7 (35%)	
pTis	9 (35%)	3 (15%)	
pTa	1 (4%)	2 (10%)	
pT1	7 (27%)	2 (10%)	0.041
pT2	3 (12%)	1 (5%)	
pT3	0 (0%)	5 (25%)	
pT4	0 (0%)	0 (0%)	
pN+	5 (20%)	7 (35%)	0.258
Adjuvant Chemotherapy	2 (8%)	4 (11%)	0.678
5-year DSS	100%	60%	0.006