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CLINICAL OUTCOME OF PATIENTS WITH T1 MICROPAPILLARY UROTHELIAL CARCINOMA OF THE BLADDER

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Abstract

Purpose—To report cancer-specific outcomes of micropapillary NMIBC.

Materials and Methods—The records of 36 patients restaged within three months of initial micropapillary NMIBC diagnosis were retrospectively reviewed. Early radical cystectomy (RC) within a three-month landmark after restaging transurethral resection of bladder tumor (TURBT), or conservative management (intravesical Bacillus Calmette-Guérin, surveillance, or deferred RC) was offered according to surgeon and patient preference. Cumulative incidence of cancer-specific mortality (CSM) and metastasis was estimated using Kaplan-Meier methods. Differences in cumulative incidence of CSM and metastasis between groups were tested using the log rank test.

Results—Median patient age was 68 (interquartile range [IQR] 63, 77) years. Male-to-female ratio was 3:1. At restaging, all patients had cT1 disease. Fifteen (42%) patients underwent early RC; 21 (58%) conservative management. Median follow-up time from landmark for cancer-specific survivors was 3.1 years (IQR 1.1, 5.9). Five-year cumulative incidence of CSM was 17% in the early RC group and 25% in the conservative management group, with an absolute difference of 7% (95% confidence interval [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 CSM ($p = 0.4$) or metastasis ($p = 0.9$).

Conclusions—Using proper selection criteria, including patient and pathologic factors, certain patients with cT1 micropapillary UC managed conservatively were not found to have significantly worse outcomes compared to patients undergoing early radical cystectomy.

Keywords

Bladder Cancer; Micropapillary; T1; Conservative Treatment; Outcomes

INTRODUCTION

Micropapillary carcinoma of the bladder, a variant of urothelial carcinoma (UC) reportedly representing 0.7% to 8% of all UC, has an aggressive course and may present at advanced stage. In most cases, it is associated with conventional urothelial carcinoma and possibly other variant histologies.^{1, 2} The micropapillary pattern may also be retained in metastases. Some studies showed relatively poor response to intravesical therapy, external beam radiotherapy, and chemotherapy hence the choice of such modalities as initial treatment may potentially delay definitive surgical therapy.³⁻⁶

The management of micropapillary UC limited to the lamina propria (cT1) at initial and restaging transurethral resection of the bladder tumor (TURBT) represents a clinical dilemma. In fact, the optimal management of micropapillary non-muscle-invasive bladder cancer (NMIBC) is still not defined and it remains controversial whether these patients can be safely managed following current guidelines for conventional NMIBC or if immediate radical cystectomy (RC) is required.^{3, 7} Current studies regarding micropapillary NMIBC are inconclusive for several reasons, including: 1) small patient numbers; 2) possible incomplete resection or understaging due to lack of restaging TURBT;^{8, 9} 3) no stratification based on percentage of micropapillary component (MPC) in the specimen; 4) lack of interobserver reproducibility of MPC diagnosis;¹⁰ and 5) combined patient cohorts, including different stages and grades of disease and treatment modalities, when assessing prognosis and survival rates.

To better delineate treatment options, we retrospectively reviewed our clinical experience and analyzed the outcomes in patients with restaged cT1 micropapillary UC treated with early RC or initially conservative management.

PATIENTS AND METHODS

Following Institutional Review Board approval, we queried the prospectively-maintained MSKCC bladder cancer database for the term “micropapillary” between 1994 and 2012. Patients newly diagnosed with cT1 NMIBC with MPC identified at initial or restaging TURBT; undergone restaging TURBT within three months of initial diagnosis; not previously treated for bladder cancer; managed at our institution; and with a minimum follow-up of six months were included in this study. Thirty-six patients met these strict criteria between September 2000 and February 2012. Available pathology slides, including those from outside facilities, were reevaluated by three genitourinary pathologist (HAA, HH, VER) for diagnosis confirmation, semiquantitative (visual) estimation of MPC percentage on initial or restaging TURBT specimens; tumor multifocality; associated CIS; lymphovascular invasion (LVI); lymph node involvement; and surgical margin status. Grading and staging followed the 2004 World Health Organization classification and the TNM staging manual.^{11, 12} Management options included early RC or conservative

management offered according to surgeon and patient preference, also considering surgical risk and previously reported prognostic indicators including tumor grade, LVI, associated CIS, and multifocality.¹³ Early RC was defined as one performed within three months after restaging TURBT. Intravesical bacillus Calmette-Guérin (BCG), TURBT alone, or RC after the three-month landmark was considered conservative management. We defined recurrence as <cT2 UC found on TURBT performed after the landmark; progression as cT2 recurrent UC after the landmark; and metastasis as presence of disease at non-adjacent organs or in lymph nodes after the landmark. Time to each event was measured from the landmark to the date of repeat TURBT or procedure, e.g. lymph node biopsy or small bowel resection.

Cumulative incidence of cancer-specific mortality (CSM) and metastasis was estimated using Kaplan-Meier methods. Differences in cumulative incidence of CSM and metastasis between groups were tested using the log rank test. The impact of MPC percentage on CSM and metastasis was evaluated using Cox proportional hazards regression. Survival times in all time-to-event analyses began at the landmark time. All statistical analyses were performed in Stata 12.0 (StataCorp, College Station, TX).

RESULTS

Baseline demographic and pathologic characteristics of initial and restaging TURBT are summarized in Table 1. All patients underwent restaging TURBT at MSKCC within three months of initial diagnosis and no deaths occurred in this interval. All tumors were high grade.

Fifteen patients underwent early RC; 21 were managed conservatively. The majority of patients in the conservative management group was male (90% vs. 53%, $p = 0.019$). Rates of T0 stage upon restaging TURBT were not significantly different (33% vs. 28.5%, $p = 0.8$). Median follow-up time from landmark was 3.2 (interquartile range [IQR] 1.1, 6.1) years for overall survivors. Outcomes of patients treated with early RC are shown in Table 2. Upstaging at RC occurred in five patients (Table 3). The morphology of metastatic tumor in positive lymph nodes at RC was conventional UC in two patients, micropapillary in one, and both patterns in one. Management and outcomes of patients treated conservatively are shown in Table 3. Median time from restaging TURBT to initiation of BCG treatment was 23.5 (IQR 19, 29) days. Among patients managed conservatively, two progressed to cT2 at 1 month and 1.2 year after landmark and four developed pelvic metastases at median 2.6 (IQR 1.0, 4.2) years after landmark.

Cumulative incidence of CSM (Fig. 1, Table 4) at five years after restaging TURBT was 17% in the early RC group and 25% in the conservative management group, with an absolute difference of 7% (95% CI: -26%, 41%). The log rank test did not show evidence of difference between the groups in cumulative incidence of CSM throughout follow-up ($p = 0.8$). Five-year cumulative incidence of metastasis (Fig. 2, Table 4) was 21% and 34% in the early RC and conservative management group, respectively, with an absolute difference of -13% (95% CI: -23%, 49%). The log rank test did not show evidence of difference between the groups in cumulative incidence of metastasis throughout follow-up ($p = 0.9$).

The amount of MPC was moderate (10%–50%) in 22 patients; extensive (>50%) in eight; and was limited to the non-invasive component of the tumor in two. Among the 22 patients with moderate MPC, four cancer-related deaths at median 2.7 (IQR 1.3, 6.0) years after landmark and one nodal (pN1) disease were observed. Pathology slides from referring institutions were not available for review in four patients. The percent extent of the MPC was not significantly associated with CSM ($p = 0.4$) or metastasis ($p = 0.9$).

DISCUSSION

Micropapillary UC of the bladder has been concerning for aggressive nature since its initial description by Amin et al. in 1994.¹ In their study, seven patients died of disease, four were alive with disease, and seven had no evidence of disease (NED) at a mean follow-up of 44 months. Johansson et al. observed poor prognosis with limited-to-absent response to radiation therapy or cisplatin-based chemotherapy in 20 patients with micropapillary UC of the bladder.³ Of note, three of the four long-term survivors in their cohort had cT1 disease. In some cases micropapillary NMIBC were reported locally advanced despite having normal-appearing overlying urothelium on cystoscopy.⁴

Current treatment options for cT1 conventional UC include restaging TURBT followed by either intravesical BCG or early RC, which is indicated for younger patients with unfavorable prognostic factors (high-grade disease, tumor size >3 cm, or presence of CIS), or recurrent/persistent T1 disease after BCG.^{14, 15} However, due to the limitations of reported data and the associated lack of an optimal management strategy, it is unknown whether cT1 micropapillary UC of the bladder may safely be managed according to these guidelines. In this study, we attempted to delineate whether conservative management could be suitable for these patients. In an effort to restrict our analysis to a homogeneous group of true micropapillary NMIBC, we included only patients with cT1 disease confirmed by restaging TURBT.

Kamat et al. reported the largest experience with micropapillary NMIBC in 44 patients.^{5, 7} Median cancer-specific survival (CSS) was 81 (range, 1.7–181.2) months. Of 27 patients initially managed with intravesical BCG, 18 reportedly progressed and underwent cystectomy, including two patients who received neoadjuvant therapy for nodal metastases; five patients were NED at a median follow-up of 30 months; and four developed inoperable metastatic disease. Five-year CSS was 60% for patients who underwent salvage cystectomy and 72% for those treated with initial cystectomy. Higher, yet not statistically significant ($p = 0.23$) incidence of cancer-related deaths (8 of 18 vs. 2 of 12, respectively) was noted in the intravesical therapy group when compared to the initial cystectomy group. Reportedly, overall incidence of pathological upstaging and nodal disease detection was 57% and 33%, respectively, in the 30 patients who underwent initial or salvage cystectomy. The authors advocated immediate radical cystectomy before progression as the treatment of choice for patients with micropapillary NMIBC.

In our study, rates of pT2 disease in the bladder (13%) was similar to that (17%) reported by Kamat et al.⁷ Patients who underwent early RC in our cohort had a surprisingly high rate (27%) of nodal disease, which corroborated the 25% rate of nodal disease in Kamat's early

RC group. This is somewhat worrisome and should be considered when evaluating a patient with micropapillary NMIBC. Based on these findings, the presence of MPC should be used in conjunction with other recognized high-risk criteria, which include multifocal cT1, multifocal or diffuse CIS, LVI, residual cT1 disease at restaging TURBT, multiple cT1 recurrences, or BCG failure,¹⁶ in counseling patients for RC. Furthermore, tumor size greater than 3 cm and presence of CIS has also been confirmed as a high-risk feature in a recent multicenter study.¹⁷

Five-year CSS of 83% in our early RC group was higher than that of 72% observed in their cohort.⁷ Compared to their findings, our subgroup of patients initially treated with BCG or TURBT alone followed with or without RC had lower rates of cT2 progression within the bladder (2 of 21 vs. 18 of 27) and metastasis development (4 of 21 vs. 6 of 27), and higher rate of NED patients (17 of 21 vs. 5 of 27) at a median 3.0 (IQR 1.2, 6.9) years after landmark. Five-year CSS of 75% in our patients managed conservatively was higher than their five-year CSS of 41.5% once a 40% CSM after salvage cystectomy and the presumed additional mortality associated with metastatic disease not amenable to surgical treatment is taken into account. Finally, no significant differences in cumulative incidence of CSM and metastasis were detected between our patients managed conservatively and those treated with early RC.

Consistent with prior reports on conservative management of cT1 tumors,^{16, 18} our micropapillary NMIBC patients managed conservatively had recurrence and progression rates of 38% and 10%, respectively (after a median follow-up of 3.2 years for overall survivors). Four of these patients developed metastases at median 2.6 (IQR 1.0, 4.2) years after landmark and died of their disease. Nevertheless, the potential aggressive nature of micropapillary NMIBC should not be underestimated: all the patients who developed metastases and died of disease in our conservative management group were confirmed having true cT1 at restaging TURBT. Our patient who developed metastatic disease in the absence of local recurrence (pT0N3 at cystectomy) 4.3 years after having been initially treated with BCG and died of disease at 7.6 years from landmark is a worrisome example. A significant limitation of our study was our inability to accurately assess the prognosis and to compare CSS between patients undergoing early versus post-BCG-failure cystectomy. In fact, only one of the two patients who progressed to cT2 disease after initial BCG underwent cystectomy but died of unrelated malignancy while the other declined cystectomy and remained NED.

Although limited by the small patient number, we did not find an association between the proportion of MPC in the specimen and patient outcomes similar to that found by Samaratunga and colleagues.¹⁹ In their cohort of 20 micropapillary UC patients treated with RC, the majority of cases with focal (<10%) MPC were low stage (pT1) whereas the majority of cases with moderate (10%-50%) and extensive (>50%) MPC were high stage (pT3). Four patients with pT1 disease had focal MPC and were all NED at a median follow-up of 23 months. In our cohort of patients with cT1 tumors confirmed by restaging, none of the eight patients with extensive MPC died of disease irrespective of treatment at a median 3.1 (IQR 1.3, 6.0) years of follow up after the landmark. Nodal disease (pN3) was found in three patients treated with early cystectomy, although the presence of both the

conventional UC and micropapillary components in the lymph node metastases of these patients seems to argue against MPC as the sole feature responsible for the aggressiveness or the metastatic potential of micropapillary UC.

To our knowledge, we report the largest experience in patients with micropapillary NMIBC having cT1 as the highest stage at initial and restaging TURBT. The small sample size of each treatment group may have been insufficient to detect small differences between groups. Our results may also have been affected by biases in the selection of patients for early RC versus intravesical therapy due to and the absence of definitive criteria to adequately quantify risk of recurrence and progression in patients with cT1 bladder UC and the lack of optimal management strategy. However, although unable to rule out large differences in survival between the groups, we did not find evidence that our patients managed conservatively had worse survival outcomes compared to the early cystectomy group. Our data seem to suggest that in properly selected patients with restaged cT1 micropapillary UC, clinical outcomes associated with initially conservative management may be not as unfavorable as currently believed.

We acknowledge that definitive criteria for the selection of patients eligible for conservative management could not be identified from our retrospective study. However, we believe that before aggressive treatment paradigms are established, prospective cohort studies are needed in cT1 micropapillary UC to further elucidate the impact of the presence of a MPC on cancer-specific outcomes, including recurrence, progression, and metastasis rates after conservative treatment compared to similarly-treated conventional high-grade cT1 tumors.

CONCLUSIONS

Risk assessment is critical for proper treatment assignment in patients with cT1 NMIBC, which is a heterogeneous disease with significant potential for metastasis and systemic involvement. In our cohort of select patients with restaged cT1 micropapillary UC treated conservatively, no evidence of significantly higher incidence of cancer-specific mortality or metastasis was detected compared to patients undergoing early cystectomy.

However, despite rigorous restaging there was a high proportion of patients with nodal disease at cystectomy compared to conventional cT1 NMIBC and thus the presence of the micropapillary growth pattern in cT1 micropapillary UC should be considered as one of the high-risk features in the management decision process.

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ABBREVIATIONS

BCG Bacillus Calmette-Guerin

CI	Confidence Interval
CIS	Carcinoma In Situ
CSS	Cancer-Specific Survival
cT1	Clinical Stage T1
cT2	Clinical Stage T2
cT3	Clinical Stage T3
CSM	Cancer-Specific Mortality
IQR	Interquartile Range
LVI	Lymphovascular Invasion
MPC	Micropapillary Component
MSKCC	Memorial Sloan-Kettering Cancer Center
NED	No Evidence of Disease
NMIBC	Non-Muscle-Invasive Bladder Cancer
RC	Radical Cystectomy
TURBT	Transurethral Resection of Bladder Tumor
UC	Urothelial Carcinoma

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Figure 1.

Kaplan-Meier estimate of cumulative incidence of cancer-specific mortality for patients treated with early cystectomy (dashed line) and conservative treatment (solid line).

Figure 2.

Kaplan-Meier estimate of cumulative incidence of metastasis for patients treated with early cystectomy (dashed line) and conservative treatment (solid line).

Table 1

Baseline patient characteristics by treatment group.

Characteristics	Early Radical Cystectomy n = 15	Conservative Management n = 21	p value
Age at diagnosis, yr, median (IQR)	68 (62, 75)	69 (64, 79)	0.7
Sex, male, no. (%)	8 (53)	19 (90)	0.019
Clinical and pathologic features at initial TURBT			
Multifocal T1, n = 28, no. (%)	5 (33)	6 (29)	1
CIS, no. (%)	8 (53)	7 (33)	0.3
LVI, n = 32, no. (%)	6 (43)	5 (28)	0.5
Difficult staging (dome, anterior wall), no. (%)	7 (47)	6 (29)	0.3
Clinical stage at restaging TURBT			
cT0, no. (%)	5 (33)	6 (28.5)	
cTa, no. (%)	0	2 (9.5)	
cTis, no. (%)	4 (27)	5 (24)	
cT1, no. (%)	6 (40)	8 (38)	
Percent MPC, n = 32, median (IQR)	40 (20-50)	38(20-55)	1
Extent of MPC, n = 32, no.			0.9
In Non-Invasive Component only	1	1	
<10% (Focal)	0	0	
10-50% (Moderate)	9	13	
>50% (Extensive)	4	4	

Abbreviations: IQR = interquartile range; TURBT = transurethral resection of bladder tumor; CIS = carcinoma in situ; LVI = lymphovascular involvement; MPC = micropapillary component. Data presented as medians with interquartile ranges in parentheses using Fisher's exact test or number of instances with percentages in parentheses using Wilcoxon rank sum test.

Table 2
Early cystectomy for patients with non-muscle-invasive micropapillary urothelial carcinoma of the bladder. (n = 15)

Initial TURBT Stage	Restaging TURBT Stage	Percent MPC	Cystectomy Stage	Adjuvant Chemotherapy	Metastasis	Site of Metastasis	Follow-up from Landmark, yr	Status
T1	T0	10	T0 Nx (Partial)				5.9	NED
T1	T1	50	T0 Nx		1	Lung; Pelvic and Retroperitoneal LN	1.2	DOD
T1	T0	25	T0 N0				0.8	NED
T1	Tis	10	T0 N0				6.1	NED
T1	Tis	N/A	T0 N0		1	Small Bowel	1.9	DOD
T1	T0	55	T0 N3	1			3.8	NED
T1	T0	85	T0N3	1			1.5	NED
T1	T0	40	Tis N0				5.0	NED
T1	Tis	90	Tis N0				8.3	NED
T1	Tis	NIC	TisN0				2.5	NED
T1	T1	20	T1 N0				3.2	NED
T1	T1	35	T1 N0				0.8	NED
T1	T1	70	T1 N3		1	Lung; Pelvic LN	1.0	NED
T1	T1	50	T2a N1				2.9	DOC
T1	T1	30	T3 N0	1			5.7	NED
Total				3	3			

Abbreviations: TURBT = transurethral resection of bladder tumor; MPC = micropapillary component; LN = Lymph Nodes; NED = no evidence of disease; DOD = died of disease; N/A = not available; NIC = non-invasive component; DOC = died of other causes.

Conservative treatment of patients with non-muscle-invasive micropapillary urothelial carcinoma of the bladder. (n = 21)

Table 3

Initial TURBT Stage	Restaging TURBT Stage	Percent MPC	Treatment	Bladder Recurrence	Progression	Metastasis	Site of Metastasis	Follow-up from Landmark, yr	Status
T1	T0	20	BCG	1				8.5	NED
T1	T0	50	BCG	1				7.9	NED
T1	T0	70	BCG					1.2	NED
T1	T0	40	BCG					0.9	NED
T1	T0	N/A	BCG					0.8	NED
T1	Ta	30	BCG	1				1.6	NED
T1	Ta	N/A	BCG			1	Pelvis	1.4	DOD
T1	Tis	70	BCG	1				11.8	NED
T1	Tis	N/A	BCG					6.9	NED
T1	Tis	45	BCG					5.8	NED
T1	Tis	20	BCG	1		1	Pelvic LN	7.6	DOD
T1	T1	NIC	BCG					11.5	NED
T1	T1	70	BCG					3.0	NED
T1	T1	40	BCG		1			3.2	NED
T1	T1	50	BCG					0.3	NED
T1	T1	80	BCG		1			3.1	DOC
T1	T0	10	TURBT Alone					0.7	DOC
T1	Tis	30	TURBT Alone					1.4	NED
T1	T1	30	TURBT Alone	1		1	Pelvis; Liver	4.4	DOD
T1	T1	50	TURBT Alone	1				1.1	NED
T1	T1	10	Declined	1		1	Lung; Pelvic LN	1.5	DOD
Total				8	2	4			

Abbreviations: TURBT = transurethral resection of bladder tumor; MPC = micropapillary component; BCG = bacillus Calmette-Guérin; NED = no evidence of disease; N/A = not available; DOD = died of disease; LN = lymph nodes; NIC = non-invasive component DOC = died of other causes.

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Table 4

Cumulative incidence of cancer-specific mortality and metastasis by treatment modality.

Years from Landmark (3 months after restaging TURBT)	Treatment Modality		Difference, % (95% Confidence Interval)
	Early Cystectomy	Conservative Management	
	Cancer-Specific Mortality, %		
1	0	0	0
2 to 4	17	14	-4 (-32.1, 25)
5	17	25	7 (-26, 41)

	Metastasis, %		Difference, % (95% Confidence Interval)
	21	6	
1			-16 (-40, 8)
2 to 4	21	12	-9 (-36, 17)
5	21	34	-13 (-23, 49)

Abbreviations: TURBT = transurethral resection of bladder tumor; CI = confidence interval