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Non-muscle invasive micropapillary urothelial carcinoma of the bladder: Variable use of initial cystectomy versus intravesical bacillus calmette-guérin

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Abstract

Introduction and Objective Micropapillary urothelial carcinoma (MPUC) is a rare and aggressive histologic variant of bladder cancer. Treatment guidelines recommend forgoing Bacillus Calmette-Guérin (BCG) therapy in favor of early radical cystectomy for non-muscle invasive (NMI)-MPUC due to high rates of disease progression. We aimed to evaluate its management in patients with immediate cystectomy and BCG across various centers.

Methods Patients with MPUC were identified from the National Cancer Database (2004-2017). Treatment trends and rates of pathological upstaging were identified. Bivariate and multivariate analyses were performed to assess differences in outcomes by treatment approach.

Results 1,685 patients were diagnosed with MPUC during the study period with 531 identified with localized Ta, T1, or Tis disease. BCG was administered as an initial therapy in 24.1% of NMI-MPBC patients and in 16.3% of NMI-non-MPUC patients (p<0.001). Cystectomy was performed as primary therapy for NMI disease in 29.9% of MPUC and in 2.7% of non-MPUC patients (p<0.001). Of the patients who underwent primary cystectomy, upstaging from NMI-MPUC to T2-T4 disease was seen in 46.5% of the MPUC patients compared to 37.3% in patients with non-MPUC (p=0.025). Upstaging to pathologic N1-3 disease was observed in 33.1% of MPUC patients compared to 11.9% non-MPUC patients (p<0.001). Cox regression analysis, adjusting for patient age, sex, race, comorbidities, and disease stage, care at academic cancer centers were associated with increased odds of having cystectomy as primary therapy compared to community cancer centers (OR = 4.29, 95% CI 2.73-6.76).

Conclusion The current study lends evidence to current practice guidelines by reporting treatment patterns for patients with micropapillary bladder cancer across a broad spectrum of clinical practice. NMI-MPUC patients treated at academic cancer centers were more likely to receive radical surgery as primary treatment compared to patients at the community cancer centers.

Key words Bladder Cancer, Radical Cystoprostatectomy, Surgical Outcomes

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Introduction

Bladder cancer is the sixth most diagnosed cancer in the United States with urothelial carcinoma (UC) of the bladder accounting for over 90% of all bladder cancer diagnosed [1, 2]. Micropapillary urothelial cancer (MPUC) is an aggressive histologic variant that comprises 0.7 to 2.2% of UC malignancies [3, 4]. MPUC typically presents at a more advanced stage and has been associated with a worse prognosis compared to conventional UC [5–8]. High rates of disease progression and mortality have been reported in muscle invasive and non-muscle invasive micropapillary bladder cancer (NMI-MPBC) patients alike, leading some experts to advocate for early radical cystectomy independent of disease stage [9].

Currently, there are no standardized treatment guidelines for this rare and aggressive form of malignancy. The recommendations in literature are primarily from small institutional-based reports. Bladder preserving treatments such as intravesical Bacillus Calmette-Buérin (BCG) is generally preferred for NMI-MPUC. Several studies, however, have shown that BCG treatment has a high rate of disease progression and is an ineffective option for NMI-MPUC when compared to radical cystectomy, with many urologists advocating for surgery as a first line of treatment [2, 9-11].

The rarity of the condition and paucity of evidence for treatment guidelines on NMI-MPUC has led to great variation in its management. A survey-based study from physicians in the Society of Urologic Oncology found that 89% of responders preferred to treat cT1 MPUC with radical cystectomy, while only 36% would offer this treatment for cTa MPUC [12]. The results from small studies lack the evidence to make generalized treatment guidelines. Specifically, a recent study found that their cohort identified using the Surveillance, Epidemiology, and End Results (SEER) database had significantly different demographic information, cystectomy treatment, and survival outcomes from the single institution reports [13]. We plan to use a national database to investigate treatment patterns and variability of NMI-MPUC.

Materials and Methods

Retrospective data was collected from the National Cancer Database and patients diagnosed with NMI-UC defined as clinical Ta, T1, or Tis disease, between 2003-2017 were selected. Patients with clinical evidence of metastatic disease or lymph node involvement were excluded. Management of NMI-MPUC patients were compared to the management of NMI, non-MPUC patients during the same study period in the database.

Primary Outcomes and Clinicopathologic Covariates

The primary outcome of this study was the initial therapy choice with BCG or radical cystectomy for NMI-MPUC at academic or community cancer care centers. Patient variables and initial therapy received for MPUC were compared with patients with non-MPUC patients. Secondary outcomes include the degree of upstaging in terms of pathologic T-stage or node positive disease in patients who undergo radical cystectomy as primary therapy. Covariates used to test for odds of having cystectomy as primary therapy at an academic cancer centers compared to community cancer centers includes age, sex, race, Charlson-Deyo comorbidity index, disease grade, and disease stage.

Classification of the treatment center was based on the Commissioner on Cancer designation through the National Cancer Database. Hospitals were classified as academic cancer centers or community cancer centers. Designated academic cancer centers were those who provide postgraduate medical education in at least four specialties, including general surgery, and receive more than 500 newly diagnosed cancer cases each year. Charlson-Deyo comorbidity score was assigned using the International Classification of Diseases, 9th edition or 10th edition, clinical modification, and secondary diagnosis codes, with scores being 0 (no comorbidities), 1, or >1.

Statistical Analysis

Patients were categorized into two groups for comparison of variables including presence of micropapillary disease, treatment of NMI-MPUC at the academic cancer centers versus community cancer centers, and use of BCG or radical cystectomy for NMI-MPUC patients. Univariate variables including primary therapy choice, type of cancer care center, and disease stage were assessed using the Pearson chi-square and the two-sided t-test as appropriate. Logistic regression was used to determine the odds of receiving radical cystectomy as primary therapy at academic and community cancer care centers. Cox proportional hazards model was performed to determine associations with overall survival based on treatment modality adjusting for patient age, sex, race, comorbidities, and disease stage. Stata SE, version 16.0 (StataCorp, College Station, TX) was used to perform all statistical analyses.

Results

1,685 patients were diagnosed with MPUC during the study period, out of which 531 patients were identified with localized Ta, T1, or Tis disease on presentation. As seen in **Table 1A**, MPUC patients were more likely to present with high-grade disease (93.1% versus 55%, $p<0.001$) and T1 disease (91% versus 31.4%, $p<0.001$) compared to urothelial carcinoma patients. BCG was administered as initial therapy in 24.1% of NMI-MPUC patients and in 14.3% of non-MPUC patients ($p<0.001$) (**Table 1B**). When controlling for disease grade and stage, micropapillary histology did not significantly predict overall survival in a Cox proportional hazards model (HR 1.28, 95% CI 1.20-1.22) (**Table 2**).

NMI-MPUC patients treated at the academic cancer centers have undertaken radical cystectomy as primary treatment (45.5% versus 15.6%, $p<0.001$) (**Table 3A**). NMI-MPUC patients who received BCG were no more likely to have more comorbidities or more advanced stage disease than the patients who did not receive BCG therapy (**Table 3B**). There were no statistically significant differences between utilization of primary BCG therapy between academic (20.7%) and community cancer centers (27.1%) ($p = 0.09$). Radical cystectomy was performed in 39.2% of NMI-MPUC patients who did not receive BCG compared to those (2.5%) who did receive BCG ($p<0.001$).

Radical cystectomy was performed as primary therapy for NMI-UC in 29.9% of MPUC and in 2.7% of non-MPUC patients ($p<0.001$), which remains consistent when comparing patients with T1 disease only (97.4% versus 80.1%, $p<0.001$). Of the patients who underwent primary cystectomy, upstaging to pT2-T4 disease was observed in 46.5% of the MPUC patients compared to 37.3% in patients with typical UC disease ($p = 0.017$) (**Table 4**). Upstaging to pathologic N1-3 disease was observed in 33.1% of MPUC patients compared to 11.9% of typical UC patients ($p<0.001$).

Cystectomy as primary therapy for NMI-MPUC was more likely to be performed at academic centers (45.5%) compared to community cancer centers (15.6%) ($p<0.001$). On logistic regression adjusting for patient age, sex, race, comorbidities, and disease stage, care at academic cancer centers was associated with increased odds of having radical cystectomy as primary therapy compared to community cancer centers (OR = 4.29, 95% CI 2.73-6.76) (**Table 5A**). No association with overall survival was identified with use of radical cystectomy (HR 0.83, 95% CI 0.58-

Table 1A. Characteristics of Urothelial and Micropapillary Bladder Cancer Patients.

Characteristic		UCB (n=592,692)	MPBC (n=1,685)	p-Value
Age (years)	Median (IQR)	72 (64-80)	71 (64-78)	0.0021
Sex, n (%)	Male	447,828 (75.55)	1,323 (78.52)	<0.001
	Female	144,864 (24.44)	362 (21.48)	NS
CCI, n (%)	0	418,226 (70.56)	1,135 (67.36)	<0.001
	1	119,846 (20.22)	353 (20.95)	NS
	2	37,475 (6.32)	126 (7.48)	NS
	3	17,145 (2.89)	71 (4.21)	NS
Race, n (%)	White	501,212 (84.57)	1,463 (86.82)	<0.001
	Non-white	84,803 (14.31)	206 (12.23)	NS
	Unknown	6,677 (1.13)	16 (0.95)	NS
Academic Facility, n (%)	CCC	416,169 (70.81)	763 (45.53)	<0.001
	ACC	171,539 (29.19)	913 (54.47)	NS
Clinical T-Stage, n (%)	Ta	238,754 (40.28)	39 (2.31)	<0.001
	Tis	23,243 (3.92)	7 (0.42)	NS
	T1	122,470 (20.66)	485 (28.78)	NS
Grade, n (%)	Low	212,186 (35.80)	63 (3.74)	<0.001
	High	380,506 (64.20)	1622 (96.26)	NS
BCG Use	No BCG	510,480 (87.56)	1,473 (89.00)	<0.001
	BCG administered	72,529 (12.44)	182 (10.99)	NS
Surgery	TURBT	489,069 (82.84)	753 (44.69)	<0.001
	Partial cystectomy	6,942 (1.18)	23 (1.36)	NS
	Radical cystectomy	64,750 (10.97)	854 (50.68)	NS
	No surgery	29,613 (5.02)	55 (3.26)	NS
Follow-up (months)	Median (IQR)	45.21 (20.07-81.64)	27.79 (12.65-52)	<0.001
Vital Status, n (%)	Alive	294,133 (53.99)	599 (40.67)	<0.001
	Deceased	250,699 (46.01)	874 (59.33)	NS
Neo-adjuvant chemo	No	457,552 (96.67)	1,265 (86.23)	<0.001
	Yes	15,798 (3.34)	202 (13.77)	NS

NS: No significance.

1.35) or BCG (HR 0.62, 95% CI 0.40-0.96) on Cox proportional hazard model (**Table 5B**).

Discussion

Micropapillary urothelial carcinoma is a rare histologic subtype of bladder cancer typically associated with worse prognosis when compared to conventional UC [8, 9]. There are conflicting

Table 1B. Characteristics of Non-Muscle Invasive Urothelial and Micropapillary Bladder Cancer Patients.

Characteristic		UCB (n=380,443)	MPBC (n=509)	p-Value
Age (years)	Median (IQR)	72 (63-80)	71 (65-79)	0.600
Sex, n (%)	Male	290,358 (76.32)	406 (879.76)	0.068
	Female	90,085 (23.68)	103 (20.24)	NS
CCI, n (%)	0	271,429 (71.35)	348 (68.37)	0.428
	1	75,654 (19.89)	110 (21.61)	NS
	2	22,984 (6.04)	33 (6.48)	NS
	3	10,376 (2.73)	18 (3.54)	NS
Race, n (%)	White	324,509 (85.30)	437 (85.85)	0.771
	Non-white	51,623 (13.57)	65 (12.77)	NS
	Unknown	4,311 (1.13)	7 (1.38)	NS
Academic Facility, n (%)	CCC	276,110 (73.29)	263 (52.08)	<0.001
	ACC	100,620 (26.71)	242 (47.92)	NS
Clinical T-Stage, n (%)	Ta	237,916 (62.54)	39 (7.66)	<0.001
	Tis	23,131 (6.08)	7 (1.38)	NS
	T1	119,396 (31.38)	463 (90.96)	NS
Grade, n (%)	Low	171,194 (45.00)	35 (6.88)	<0.001
	High	209,249 (55.00)	474 (93.12)	NS
BCG Use	No BCG	313,393 (83.73)	378 (75.90)	<0.001
	BCG administered	60,904 (16.27)	120 (24.10)	NS
Surgery	TURBT	352,295 (92.96)	341 (66.99)	<0.001
	Partial cystectomy	2,700 (0.71)	6 (1.18)	NS
	Radical cystectomy	10,236 (2.70)	152 (29.86)	NS
	No surgery	13,763 (3.63)	10 (1.96)	NS
Follow-up (months)	Median (IQR)	52.21 (28.09-85.75)	38.46 (20.93-73.3)	<0.001
Vital Status, n (%)	Alive	222,281 (63.96)	247 (57.44)	0.005
	Deceased	124,678 (36.04)	183 (42.56)	NS
Neo-adjuvant chemo	No	303,618 (99.20)	400 (96.15)	<0.001
	Yes	2,461 (0.80)	16 (2.85)	NS

NS: No significance.

opinions on the appropriate treatment course of NMI-MPUC due to the lack of prospective studies of this rare form of malignancy [14-16]. American Urologic Association/Society of Urologic Oncology (AUA/SUO) Guidelines on Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer classify all cases of variant histology, including micropapillary disease, to be “high risk”

Table 2. Cox Proportional Hazards Model Evaluating Overall Survival in Non-Muscle Invasive UCB Patients Multivariate Analysis.

	Characteristic	OR	95% CI	p-Value
	Age (Continuous)	1.07	1.07-1.08	0.000
Sex	Female	0.89	0.88-0.91	0.000
	1	1.29	1.37-1.40	0.000
CCI	2	1.91	1.88-1.95	0.000
	3	2.54	2.47-2.61	0.000
Race	Non-White	1.04	1.03-1.06	0.000
Grade	High grade	1.2	1.18-1.21	0.000
	Ta	1	Referrant	NS
Clinical T-Stage	Tis	1.15	1.12-1.17	0.000
	T1	1.54	1.52-1.56	0.000
Academic Hospital Status	ACC	0.91	0.90-0.03	0.902
	BCG	0.75	0.73-0.76	0.761
Treatment	RC	0.87	1.21-1.29	1.292
	Chemo	1.25	0.86-0.88	0.884
	90-day mortality	1.28	1.20-1.22	0.000

NS: No significance.

[17]. Guidelines further provide a “Strong Recommendation” for the use of BCG in all high-risk patients. Our study observed that 341 patients (67.0%) with Ta, Tis, or T1 MPUC were treated with transurethral resection of bladder tumor alone without further intravesical therapy or radical surgery administered, indicating a large degree of under-treatment in these high-risk patients.

The AUA/SUO guidelines further provide an “Expert Opinion" that clinicians should consider initial radical cystectomy for patients with non-muscle invasive variant histology due to a high rate of associated upstaging and disease progression [17]. Kamat et al. conducted a study of 44 patients with NMI-MPUC and argued strongly in favor of early radical cyctectomy in this patient population [10]. In their report, they observed 67% of the 22 patients treated with BCG advanced to muscle-invasive disease with metastases at a median time of 8 months following therapy. Authors reported 72% 10-year cancer specific survival for patients who underwent upfront radical cystectomy compared to 100% 10 year-mortality rate in those who underwent surgery only after disease progression following initial bladder preservation. Willis et al. also advocated for early radical cystectomy for all micropapillary bladder tumors. In their study of 72 cT1N0M0 MPUC cases, 55% (n=40) received initial BCG therapy and 36% (n=26) received early radical cystectomy, resulting in a five-year disease specific survival of 62% in the delayed radical cystectomy group and 100% for the early radical cystectomy group on univariate analysis (p = 0.015) [11].

Our series of 531 MPBC patients with non-muscle-invasive disease revealed a significant hazard ratio of 1.28 (95% CI 1.20-1.22) when assessing for 90-day mortality, adjusted for patient characteristics, tumor stage, and grade (**Table 5B**). These results suggest that patients who have been adequately staged with non-muscle-invasive disease may still be at significantly increased risk. This is in contrast to Wang et. al. who found that when stage-matching 73 MPUC patients to patients with typical UC, no significant differences were noted in 10-year cancer specific survival (31% versus 40%, p=0.41) [8]. Fairey et. al. found that histologic variant was not significantly associated with overall survival (HR 0.91, 95% CI 0.55-1.49) in the 33 MPUC patients included in the Cox proportional hazard model when adjusted for disease stage, grade, and presence of lymphovascular invasion.

Multivariate analysis using Cox proportional hazard model of the NMI-MPUC patients in our study did not reveal a survival advantage with treatment with radical cystectomy (HR 0.83, 95% CI 0.58-1.35) or BCG (HR 0.62, 95% CI 0.40-0.96) compared to transurethral resection alone. This survival trend in patients treated with radical cystectomy is likely explained by incomplete risk stratification of patients due to multiple pathologic risk factors not available in the National Cancer Database. When typical UC patients with non-muscle invasive disease were analyzed, a similar trend was observed in patients treated with radical cystectomy (HR 0.87, 95% CI 1.21-1.29) compared to BCG (HR 0.75, 95% CI 0.73-0.76). This could be due to only high-risk patients with recurrent

Table 3A. Characteristics of NMI-MPBC Patients by Treatment Facility Academic Designation.

Characteristic		CCC (n=263)	ACC (n=242)	Total (n=505)	p-Value
Age (years)	Median (IQR)	73 (66-81)	69 (62-79)	71 (65-79)	0.0005
Sex, n (%)	Male	208 (79.09)	195 (80.58)	403 (79.80)	0.677
	Female	55 (20.91)	47 (19.42)	102 (20.20)	NS
CCI, n (%)	0	170 (64.64)	174 (71.9)	344 (68.12)	0.123
	1	59 (22.43)	51 (21.07)	110 (21.78)	NS
	2	23 (8.75)	10 (4.13)	33 (6.53)	NS
	3	11 (4.18)	7 (2.89)	18 (3.56)	NS
Race, n (%)	White	229 (87.07)	205 (84.71)	434 (85.94)	0.654
	Non-white	30 (11.41)	34 (14.05)	64 (12.67)	NS
	Unknown	4 (1.52)	3 (1.24)	7 (1.39)	NS
Clinical T-Stage, n (%)	Ta	25 (9.51)	13 (5.37)	38 (7.52)	0.117
	Tis	5 (1.90)	2 (0.83)	7 (1.39)	NS
	T1	233 (88.59)	227 (93.80)	460 (91.09)	NS
Grade, n (%)	Low	22 (8.37)	12 (4.96)	34 (6.73)	0.127
	High	241 (91.63)	230 (95.04)	471 (93.27)	NS
Radical Cystectomy Performed, n (%)	No RC	222 (84.41)	132 (54.55)	354 (70.10)	<0.001
	RC or exent	41 (15.59)	110 (45.45)	151 (29.9)	NS
BCG Administered, n (%)	Not administered	188 (72.87)	188 (79.32)	376 (75.96)	0.093
	BCG given	70 (27.13)	49 (20.68)	119 (24.04)	NS
Either RC or BCG Given, n (%)	No RC or BCG administered	153 (58.17)	85 (35.12)	238 (47.13)	<0.001
	RC or BCG administered	110 (41.83)	157 (64.88)	267 (52.87)	NS
Follow-up (months)	Median (IQR)	38.34 (20.96-75.33)	38.54 (21.16-71.62)	38.46 (20.93-73.3)	0.742
Vital Status, n (%)	Alive	117 (53.92)	127 (60.77)	244 (57.28)	0.153
	Deceased	100 (46.08)	82 (39.23)	182 (42.72)	NS

NS: No significance.

high-grade disease with or without CIS or lymphovascular invasion being offered with surgery.

Of the patients who underwent radical cystectomy, upstaging from NMI disease to T2-T4 disease was seen in 46.5% of the MPUC patients compared to 37.3% in patients with non-micropapillary disease (p=0.025). Upstaging to pathologic N1-3 disease was observed in 33.1% of MPUC patients compared to 11.9% non-micropapillary patients (p<0.001).

The high rates of disease malignancy in this patient population raises concern about intravesical-only therapy. This may be due to unspecified selection criteria confounding upstaging rates. Spaliviero et al. have suggested bladder conservation may be appropriate for specific patients with NMI-MPUC [18]. They reported no difference in 5-year disease specific mortality in the early cystectomy group (n=15) compared to the bladder conservation group (n=21) (17% versus 25%), p=0.08) in 36 patients with T1 micropapillary urothelial carcinoma18. Cox proportional hazard model of our study population also does not reveal an advantage to either treatment modality.

Our study demonstrated that management of NMI-MPUC varies

Table 3B. Characteristics of NMI-MPBC Patients by Use of BCG Therapy.

Characteristic		No BCG Administered (n=378)	BCG Administered (n=120)	Total (n=498)	p-Value
Age (years)	Median (IQR)	71 (64-79)	74 (66-81)	71 (65-79)	0.060
Sex, n (%)	Male	294 (77.78)	103 (85.83)	397 (79.72)	0.056
	Female	84 (22.22)	17 (14.17)	101 (20.28)	NS
CCI, n (%)	0	258 (68.25)	81 (67.50)	339 (68.07)	0.958
	1	81 (21.43)	28 (23.33)	109 (21.89)	NS
	2	26 (6.88)	7 (5.83)	33 (6.63)	NS
	3	13 (3.44)	4 (3.33)	17 (3.41)	NS
Race, n (%)	White	317 (83.86)	110 (91.67)	427 (85.74)	0.068
	Non-white	54 (14.29)	10 (8.33)	64 (12.85)	NS
	Unknown	7 (1.85)	0 (0.00)	7 (1.41)	NS
Hospital type	CCC	188 (50.00)	70 (58.82)	258 (52.12)	0.093
	ACC	188 (50.00)	49 (41.18)	237 (47.88)	NS
Clinical T-Stage, n (%)	Ta	31 (8.20)	6 (5.00)	37 (7.43)	0.493
	Tis	5 (1.32)	2 (1.67)	7 (1.41)	NS
	T1	342 (90.48)	112 (93.33)	454 (91.96)	NS
Grade, n (%)	Low	30 (7.94)	3 (2.5)	33 (6.63)	0.037
	High	348 (92.06)	117 (97.50)	465 (93.37)	NS
Radical Cystectomy Performed, n (%)	No RC	230 (60.85)	117 (97.50)	347 (69.68)	<0.001
	RC or exent	148 (39.15)	3 (2.50)	151 (30.32)	NS
Follow-up (months)	Median (IQR)	36.5 (20.04-70.18)	45.9 (23-85.98)	38.46 (20.93-73.3)	0.052
Vital Status, n (%)	Alive	184 (56.27)	59 (63.44)	243 (57.86)	0.217
	Deceased	143 (43.73)	34 (36.56)	177 (42.14)	NS

NS: No significance.

greatly. Initial BCG therapy continues to be utilized frequently (24.1% of NMI-MPUC) and at similar rates between academic and community cancer centers (20.7% versus 27.1%, p=0.09). 29.9% of patients underwent initial radical cystectomy for NMI-MPUC, with a higher proportion undergoing surgery observed at the academic cancer centers (45.5%, p<0.001). Based on our logistic regression analysis, initial radical cystectomy was more likely to be performed at academic cancer centers when compared to community cancer centers (OR = 4.29, 95% CI 2.73-6.76) after adjusting for clinico-pathologic covariates. Reasons for differences in treatment patterns at academic centers compared to cancer care centers is not transparent. Patients referred to academic care centers for rare variant histology may have already failed previous bladder preservation protocols. Given the lack of guideline statements on non-muscle invasive bladder cancer, physicians at academic care centers may have more knowledge of studies reporting high rates of disease upstaging in MPUC patients, which may increase a preference for more aggressive surgical extirpation.

The study has few limitations including the design of a retrospective study and limitations in data collection. Survival data in the National Cancer Database is limited to overall survival, so differences in mortality are primarily attributed to malignant progression. Clinical and pathologic risk factors important in the management of non-muscle invasive bladder cancer, including the presence of lymphovascular invasion, concomitant carcinoma in situ, or multiple disease recurrences, are unavailable in the National Cancer Database [19]. Therefore, treatment decisions regarding NMI-MPUC may be confounded. Another important limitation relates to the inability to follow patient during BCG therapy owing to the lack of individual oncological profiles.

Table 4. Characteristics of Patients with Non-Muscle Invasive Disease Who Underwent Radical Cystectomy.

Characteristic		UCB (n=10.236)	MPBC (n=152)	Total (n=10,388)	p-Value
Age (years)	Median (IQR)	68 (61-75)	67 (60-72.5)	68 (61-75)	0.271
Sex, n (%)	Male	8,112 (79.25)	120 (78.95)	8,232 (79.25)	0.927
	Female	2,124 (20.75)	32 (21.05)	2,256 (20.75)	NS
CCI, n (%)	0	7,114 (69.50)	104 (68.42)	7,218 (69.48)	0.715
	1	2,211 (21.60)	31 (20.39)	2,242 (21.58)	NS
	2	644 (6.29)	11 (7.24)	655 (6.31)	NS
	3	267 (2.61)	6 (3.95)	273 (2.63)	NS
Race, n (%)	White	8,605 (84.07)	134 (88.16)	8739 (84.13)	0.318
	Non-white	1,522 (14.87)	16 (10.53)	1,538 (14.81)	NS
	Unknown	109 (1.06)	2 (1.32)	11`1 (1.07)	NS
Hospital type	CCC	4,332 (42.72)	41 (27.15)	4,373 (42.49)	<0.001
	ACC	5,808 (57.28)	110 (72.85)	5,918 (57.51)	NS
Grade, n (%)	Low	804 (7.85)	2 (1.32)	806 (7.76)	0.003
	High	9,423 (92.15)	150 (98.68)	9,582 (92.24)	NS
Clinical T-Stage, n (%)	Ta	1,324 (12.93)	3 (1.97)	1,327 (12.77)	<0.001
	Tis	717 (7.00)	1 (0.66))	718 (6.91)	NS
	T1	8,195 (80.06)	14 (97.37)	8,343 (80.31)	NS
	T0	320 (3.26)	7 (4.64)	327 (3.28)	0.017
Pathologic T stage, n (%)	Ta or Tis or T1	5,193 (52.91)	69 (45.70)	5,262 (52.80)	NS
	T2	1,525 (15.54)	31 (20.53)	1,556 (15.61)	NS
	T3	1,203 (12.26)	22 (14.57)	1,225 (12.29)	NS
	T4	549 (5.59)	13 (8.61)	562 (5.64)	NS
Pathologic N stage, n (%)	N0	7.305 (88.12)	93 (66.91)	7,398 (87.77)	<0.001
	N1-3	985 (11.88)	46 (33.09)	1,031 (12.23)	NS
Follow-up (months)	Median (IQR)	46.38 (23.75-78.38)	35.91 (23.36 - 56.64)	46.13 (23.75-78.16)	<0.001
Vital Status, n (%)	Alive	5,509 (59.18)	85 (65.38)	5,594 (59.26)	0.153
	Deceased	3,800 (40.82)	45 (34.62)	3,845 (40.74)	NS
Neo-adjuvant chemo	No	8,107 (88.82)	126 (91.30)	8,233 (88.86)	0.358
	Yes	1,020 (11.18)	12 (8.70)	1,032 (11.14)	NS

NS: No significance.

Table 5A. Logistic Regression Predicting Use of Cystectomy in NMI-MPBC Patients.

Characteristic		Multivariate Analysis		
		OR	95% CI	p-Value
	Age (Continuous)	0.93	0.91-0.95	0.000
Sex	Female	1.19	0.69-2.05	0.528
	1	1.06	0.62-1.82	0.821
CCI	2	1.92	0.80-04.59	0.143
	3	1.4	0.42-4.68	0.588
Race	Non-White	0.62	0.31-1.24	0.175
Grade	High grade	4.77	1.02-22.24	0.047
	Ta	1	Referrant	NS
Clinical T-Stage	Tis	0.76	0.055-10.48	0.836
	T1	2.51	0.68-9.34	0.167
Academic Hospital Status	ACC	4.29	2.73-6.76	0.000

NS: No significance.

Table 5B. Cox Proportional Hazards Model Evaluating Overall Survival in NMI-MPBC Patients.

Characteristic		Multivariate Analysis		
		HR	95% CI	p-Value
	Age (Continuous)	1.05	1.03-1.07	0.000
Sex	Female	1.77	1.28-2.46	0.931
	1	1.32	0.94-1.87	0.113
CCI	2	1.12	0.62-2.02	0.709
	3	2.09	0.91-4.80	0.082
Race	Non-White	1.02	0.66-1.57	0.931
	Ta	1	Referrant	NS
Clinical T-Stage	Tis	0.95	0.21-4.23	0.947
	T1	1.79	0.99-3.23	0.053
Academic Hospital Status	ACC	0.88	0.65-1.19	0.401
	BCG	0.62	0.40-0.96	0.031
Treatment	RC	0.83	0.58-1.35	0.577
	Chemo	0.89	0.56-1.24	0.336
Grade	High grade	1.13	0.65-1.96	0.662
	90-day mortality	1.28	1.20-1.22	0.000

NS: No significance.

Despite being the largest study evaluating MPUC, the sample size of 509 patients remains small for this rare condition, which limits statistical analysis.

Conclusion

Over half of the patients with non-muscle invasive MPUC do not receive further treatment with BCG or radical cystectomy following diagnosis. Patients treated at academic cancer centers are more likely to receive initial radical cystectomy. Presence of micropapillary variant histology increases the odds of disease upstaging and node-positive disease, but no survival advantage was discernible when comparing treatment with BCG or radical cystectomy in this patient population.

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Ethical policy

Approval was taken from institutional ethical committee. The study was performed in accordance with the Declaration of Helsinki. Patients gave their informed consent for their participation.

Author contributions

KG, protocol/project development, data collection, data analysis, manuscript writing/editing; DO, protocol/project development, manuscript writing/editing; LC, manuscript writing; WM, manuscript editing; IL, manuscript editing; KS, protocol/project development, manuscript editing.

Competing interests

The authors have no significant conflicts of interest with any companies or organization whose products or services may be discussed in this article.

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Informed consent

Informed consent was not required for this study given the utilization of retrospective de-identified variables. The University Hospitals Cleveland Medical Center (UH CMC) Institutional Review Board granted an exemption for this study on November 11, 2020.

Research involving Human Participants and/or Animals

Neither human or animal participants were recruited for this study. The National Cancer Database (NCDB) is a nationally-validated clinical oncology database sourced from hospital registry data collected in more than 1,500 Commission on Cancer (CoC)-accredited facilities, used to analyze and track patients with malignant neoplastic diseases. Data are retrospective de-identified variables regarding treatment and outcomes. Therefore, the University Hospitals Cleveland Medical Center (UH CMC) Institutional Review Board granted an exemption for this study. The IRB exemption protocol was approved on November 11, 2020. Approved by the institutional ethical and research committee.

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