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# BCG response and oncological outcomes in high risk nonmuscle invasive bladder cancer following previously treated upper tract urothelial carcinoma: A propensity-matched analysis

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## Abstract

**Introduction:** Metachronous bladder recurrences after prior treatment for primary upper tract urothelial carcinoma (UTUC) can occur in ∼3% to 50% of patients. Because UTUC demonstrated distinct molecular alterations, bladder recurrences in these patients may be molecularly and phenotypically different compared to primary bladder carcinoma. We aim to study the BCG efficacy in patients with primary high risk non-muscle invasive bladder cancer (P-NMIBC) and metachronous bladder recurrences after previous nephroureterectomy for UTUC (M-NMIBC).

**Methods:** We reviewed an IRB-approved prospective uro-oncology database of patients who underwent resection followed by BCG therapy for high grade NMIBC from 2017 to 2021. Clinicopathological parameters, intravesical therapies and the oncological outcomes were analyzed. Patients in the P-NMIBC group were matched to patients in the M-NMIBC cohort (control) via propensity score matching (PSM) to adjust for potential clinicopathological confounders. Nearest-neighbor PSM targeting a 4:1 ratio of study to control subjects was performed using a caliper of 0.2, aiming for an absolute standardized mean difference of <0.1 across key covariates. Secondary outcomes were progression to distant metastasis and overall survival. Logistic and cox regression analyses were performed to elucidate independent variables associated with intravesical recurrences and disease progression.

**Results:** Of the 183 patients diagnosed with NMIBC, 35 patients were identified to have a history of UTUC with radical nephroureterectomy. EAU risk stratification revealed 50 (27.3%) intermediate risk, 107 (58.5%) high risk and 26 (14.2%) very high risk groups. P-NMIBC patients were more likely to have symptomatic presentation (79.7% vs. 23.9%), and a larger mean tumor size (25.7 mm vs. 15.4 mm) than M-NMIBC. The mean follow-up duration for the study was 34.0 months. In the unmatched analysis, M-NMIBC was associated with increased risk of HG intravesical recurrence post BCG compared to P-NMIBC (54.3% vs. 28.4%, $P = 0.006$, HR 2.14, 95% CI: 1.25−3.65) and increased risk of progression to MIBC (28.6% vs. 4.7%, $P = 0.007$, HR 4.19, 95% CI: 1.47−11.95). For the propensity-matched analysis, the control group consisted of 35 M-NMIBC matched to 123 P-NMIBC patients for similar demographics, EAU risk score and BCG doses. M-NMIBC again demonstrated a higher HG intravesical recurrence rate (54.3% vs. 22.8%, $P = 0.001$, HR 2.67, 95% CI: 1.50−4.77), progression to MIBC (28.6% vs. 5.7%, $P = 0.022$, HR 3.42, 95% CI: 1.20−9.75) and progression to distant metastasis (20.0% vs. 6.5%, $P = 0.033$, HR 3.02, 95% CI: 1.09−8.35). Overall survival in both groups were not significantly different in both unmatched and matched analysis.

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**Conclusions:** Our study indicates that BCG treatment may be less effective for NMIBC patients with a history of UTUC, with a higher risk of intravesical recurrences and disease progression. This is an important consideration when counselling patients for BCG treatment and overall prognostication. 

*Keywords:* Upper tract urothelial cancer; Bacillus Calmette-Guerin; Bladder cancer; Non−muscle-invasive bladder cancer

## 1. Introduction

Upper urinary tract urothelial carcinoma (UTUC) is considered an uncommon malignancy and represents a small population of urothelial carcinomas [1]. However, despite optimal treatment for UTUC, metachronous bladder recurrences can occur in ∼3% to 50% of patients [2]. Without any specific guidelines on this, metachronous bladder recurrences after nephroureterectomy (M-NMIBC) are treated categorically similar to primary high grade nonmuscle invasive bladder cancer (P-NMIBC) with intravesical Bacillus Calmette-Guerin (BCG) to reduce recurrence and progression [3].

Most risk models predicting recurrence and progression in NMIBC focus on pathological staging, grade, presence of CIS, size and multifocality [4−5]. The implication of prior UTUC on the clinical outcomes for NMIBC is uncertain. In the same manner, the efficacy of BCG in these 2 distinct populations remains poorly described, partly owing to the rarity of M-NMIBC. More recent evidence are highlighting that M-NMIBC may portend a poorer response to BCG with greater likelihood of recurrences [6−7].

Despite the histological and morphological similarities, it is increasingly clear that there are stark molecular differences between upper and lower tract urothelial tumors [8]. M-NMIBC may represent a pan-urothelial transformation and seeding that clonally resemble the parental UTUC and therefore, are likely to respond differently to adjuvant intravesical therapies, compared to P-NMIBC [9]. In light of the paucity of information studying the clinical trajectory of M-NMIBC, this study aims to evaluate if this population of M-NMIBC would be at higher risk of BCG failure and further disease progression compared to P-NMIBC.

## 2. Methods and materials

We performed a retrospective review of patients recorded under a prospective uro-oncology database who underwent transurethral resection of high grade (HG) NMIBC from 2017 to 2021. Demographic data, pathological information, BCG installations, time to recurrence, disease progression, cystectomy, and survival outcomes such as progression to distant metastasis and overall survival were collected on all patients. The clinicopathological status was then stratified according to the latest European Association of Urology (EAU) 2021 risk groups [10]. As an academic medical center, patients were treated according to established clinical guidelines, including re-transurethral resection bladder tumor (TURBT) when indicated, 1 dose intravesical chemotherapy with Mitomycin C within 24 hours, commenced and completed at least an induction course of intravesical BCG and follow up closely with upper tract imaging, cystoscopy and urine cytology to detect recurrences [11].

The primary outcomes were to evaluate HG intravesical recurrences and progression to muscle invasive bladder cancer (MIBC). The date of recurrence was determined on the date of TURBT which confirmed the return of HG NMIBC. If the histological sample confirmed the presence of muscle invasion, this was subsequently defined as tumor progression. Secondary outcomes included progression to distant metastasis, and overall survival (OS). Although these survival outcomes would potentially be confounded by the underlying UTUC disease, they were recorded to provide a wider oncological survival of the 2 groups of patients.

### 2.1. Statistical analysis

Descriptive statistics were used to summarize the data. Continuous variables were compared using t-tests or Wilcoxon's rank sum tests, as appropriate, while categorical variables were analyzed using Pearson's chi-squared test or Fisher's exact test. Univariable and multivariable logistic regression analyses were performed to identify independent predictors of bladder tumor recurrence. Additionally, multivariable Cox proportional hazards regression analysis was conducted to assess the impact of various clinicopathological parameters, particularly prior UTUC, on time to bladder tumor recurrence. All statistical analyses were carried out in R-4.3.0 using RStudio with packages "MatchIt", "meta", and "survival" and $P < 0.05$ regarded as statistically significant.

Due to differences in baseline characteristics, particularly disease status and BCG doses between M-NMIBC and P-NMIBC cohorts, a propensity score-matched (PSM) analysis was conducted to adjust for these differences. PSM was performed based on the following covariates: patient demographics (gender, age and smoking history), tumor characteristics (T staging, grade, presence of carcinoma in situ (CIS), number of tumors and tumor size), and BCG status (including total doses received). Patients in the P-NMIBC cohort were matched to patients in the M-NMIBC cohort with nearest-neighbor. PSM targeting a 4:1 ratio of

Table 1
Disease characteristic of 35 patients with subsequent NMIBC after RNU for UTUC.

| Variable | Total (%) |
|---|---|
| Number of patients, n | 35 |
| Location of tumor | |
| Both renal pelvis and ureter | 7 (20.0) |
| Renal pelvis only | 9 (25.7) |
| Ureter only | 19 (54.3) |
| Documented adjuvant systemic chemotherapy | |
| Yes | 16 (45.7) |
| No | 19 (54.3) |
| T stage of UTUC | |
| Ta | 10 (28.6) |
| T1 | 6 (17.1) |
| T2 | 9 (25.7) |
| T3 | 10 (28.6) |
| T4 | Nil |
| Histology of UTUC | |
| High grade | 32 (91.4) |
| Low grade | 3 (8.6) |
| Median time to high grade bladder recurrence after RNU (mo) | 24.0 (95% CI: 6.0–30.0) |

study to control subjects was performed using a caliper of 0.2, aiming for an absolute standardized mean difference of <0.1 [12,13]. The rationale for using 4:1 propensity score matching (PSM) in our study was to achieve a balance between maximizing the available data and maintaining statistical rigor, given the relatively small cohort of patients with M-NMIBC.

## 3. Results

Of the 183 patients diagnosed with HG NMIBC, there were 35 (19.1%) patients who had previous UTUC treated with radical nephroureterectomy (RNU) with negative bladder cuff margins (Table 1). In this subpopulation of M-NMIBC, the median time to HG NMIBC recurrence was 24 (95% CI: 6–30) months after RNU. The M-NMIBC group consisted of 25 men and 10 women with a mean age of 75.0 years, compared to the P-NMIBC group, which included 113 men and 35 women with a similar mean age of 77.02 years.

Regarding the initial diagnosis of HG NMIBC, only 23.9% of the M-NMIBC group presented with symptoms, predominantly haematuria or irritative symptoms, compared to 79.7% in the P-NMIBC group ($P = < 0.001$). The mean size of the largest tumor in the M-NIMBC group was 15.4 mm, which was comparably smaller than the P-NIMBC group of 25.7 mm ($P = 0.001$). Pathological T staging in the M-NMIBC group showed 48.6% Ta, 37.1% T1, and 14.3% primary CIS, compared to 44.6% Ta and 55.4% T1 in the P-NMIBC group. There was 0 cases of isolated primary CIS in the P-NMIBC group. Risk categorization according to the EAU 2021 NMIBC prognostic factor risk group revealed that 17 (48.6%) patients in the M-NMIBC group were considered intermediate risk, 13 (37.1%) high risk, and 5 (14.3%) very high risk. In contrast, the P-NMIBC group had a relatively lower proportion of intermediate risk ($n = 33$, 22.3%) and higher proportion of high risk ($n = 94$, 63.5%) and very high risk ($n = 21$, 14.2%). The P-NMIBC had a greater presentation of variant subtype ($n = 21$, 14.2%) compared to M-NMIBC ($n = 1$, 2.9%), albeit not statistically significant. The mean total BCG doses completed were 5.84 in M-NMIBC and 5.81 in P-NMIBC, with a similar mean follow-up duration of 37.9 and 33.8 months respectively (Tables 2 and 3).

In the unmatched analysis, M-NMIBC was associated with an increased risk of intravesical HG recurrence, with 19 (54.3%) developing recurrence compared to 42 patients (28.4%) in the P-NMIBC group with multivariate analysis (Fig. 1) ($P = 0.012$, HR 3.12 95% CI: 1.28–7.62). The mean time to bladder recurrence was relatively similar for both groups (11.2 months for M-NMIBC vs. 13.2 months

Table 2
Clinicopathological characteristics of patients included in this study.

| | Before matching | | | After propensity matching | | |
|---|---|---|---|---|---|---|
| Variable | M-NIMBC | P-NMBIC | *P*-value | P-NMBIC | *P*-value | SMD |
| Number of patients, n | 35 | 148 | | 123 | | |
| Gender, n (%) | | | 0.697 | | 0.555 | 0.153 |
| Men | 25 (71.4) | 113 (76.4) | | 96 (78.0) | | |
| Female | 10 (28.6) | 35 (23.6) | | 27 (22.0) | | |
| Age at NMIBC diagnosis (mean [SD]) | 75.00 (±10.37) | 77.02 (±9.82) | 0.280 | 77.01 (±9.13) | 0.267 | 0.206 |
| Smoker (%) | | | 0.542 | | 0.701 | 0.161 |
| Active smoker | 6 (17.1) | 35 (23.6) | | 27 (22.0) | | |
| Ex-smoker | 11 (31.4) | 35 (23.6) | | 31 (25.2) | | |
| Nonsmoker | 18 (51.4) | 78 (52.7) | | 65 (52.8) | | |
| ECOG (%) | | | 0.056 | | 0.115 | 0.612 |
| 0–1 | 31 (88.6) | 97 (65.5) | | 83 (67.5) | | |
| 2 or more | 4 (11.4) | 51 (34.5) | | 40 (32.5) | | |

(*continued*)

Table 2 (***Continued***)

| Variable | Before matching | | | After propensity matching | | |
|---|---|---|---|---|---|---|
| | M-NIMBC | P-NMBIC | *P*-value | P-NMBIC | *P*-value | SMD |
| BMI (mean [SD]) | 24.43 (± 4.43) | 24.07 (± 4.38) | 0.666 | 23.69 (± 4.18) | 0.372 | 0.171 |
| Symptom present at diagnosis (%) | | | <0.001 | | <0.001 | 1.352 |
| Symptomatic | 8 (23.9) | 129 (79.7) | | 97 (78.9) | | |
| Asymptomatic | 27 (77.1) | 30 (20.3) | | 26 (21.1) | | |
| Number of tumors (%) | | | 0.481 | | 0.298 | 0.254 |
| 1−2 | 29 | 100 | | 89 | | |
| 3 or more | 6 | 48 | | 34 | | |
| Size of largest tumor (mm [mean {SD}]) | 15.4 (± 9.6) | 25.7 (±15.3) | 0.001 | 27.3 (±15.5) | <0.001 | 0.928 |
| T staging on diagnosis (%) | | | <0.001 | | <0.001 | 0.605 |
| Ta | 17 (48.6) | 66 (44.6) | | 59 (48.0) | | |
| T1 | 13 (37.1) | 82 (55.4) | | 64 (52.0) | | |
| Isolated Cis | 5 (14.3) | 0 (0.0) | | 0 (0.0) | | |
| CIS (%) | | | 0.505 | | 0.304 | 0.234 |
| Positive | 9 (25.7) | 28 (28.9) | | 20 (16.3) | | |
| Negative | 26 (74.3) | 120 (81.1) | | 103 (83.7) | | |
| EAU NMIBC risk stratification (%) | | | 0.284 | | 0.567 | 0.200 |
| Intermediate risk | 17 (48.6) | 33 (22.3) | | 31 (25.2) | | |
| High risk | 13 (37.1) | 94 (63.5) | | 80 (65.0) | | |
| Very high risk | 5 (14.3) | 21 (14.2) | | 12 (9.8) | | |
| Presence of variant histology during TURBT (%) | | | 0.118 | | 0.075 | 0.468 |
| Yes | 1 (2.9) | 21 (14.2) | | 20 (16.3) | | |
| No | 34 (97.1) | 127 (85.8) | | 103 (83.7) | | |

Table 3
Univariable and multivariable analysis for HG NMIBC recurrence after induction BCG.

| Variable | Number of patients (%) | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|---|
| | | Hazard Ratio (95%CI) | *P*-value | Hazard Ratio | *P*-value |
| Age (years) | | | | | |
| ≤70 | 38 (20.7) | | | | |
| >70 | 145 (79.3) | 0.57 (0.28−1.16) | 0.123 | 0.62 (0.16−2.40) | 0.49 |
| Gender | | | | | |
| Male | 138 (75.4) | | | | |
| Female | 45 (24.6) | 0.77 (0.43−1.4) | 0.396 | 0.40 (0.14− 1.17) | 0.093 |
| Smoking history | | | | | |
| Nonsmoker | 96 (52.5) | | | | |
| Smoker | 87 (47.5) | 1.89 (0.92−3.91) | 0.085 | 1.70 (0.44−6.57) | 0.443 |
| EUA risk score | | | | | |
| Intermediate | 45 (24.6) | | | | |
| High | 114 (62.3) | 1.92 (0.96−3.83) | 0.046 | 2.84 (0.94−11.1) | 0.047 |
| Very high | 24 (13.1) | 1.92 (0.96−4.61) | 0.145 | 1.20 (0.22−6.62) | 0.838 |
| Number of bladder tumors | | | | | |
| ≤2 | 129 (70.5) | | | | |
| >3 | 54 (29.5) | 1.45 (0.85−2.49) | 0.177 | 1.53 (0.61− 3.91) | 0.365 |
| Underwent re-TURBT | | | | | |
| No | 98 (53.6) | | | | |
| Yes | 85 (46.4) | 1.08 (0.65−1.78) | 0.769 | 1.33 (0.53−3.32) | 0.540 |
| Maintenance BCG (up to 6 mo) | | | | | |
| Completed | 33 (18.0) | | | | |
| Not completed | 150 (82.0) | 3.28 (1.25−8.62) | 0.016 | 5.49 (1.52−19.9) | 0.009 |
| History of UTUC | | | | | |
| P-NMIBC | 148 (80.9) | | | | |
| M-NMIBC | 35 (19.1) | 2.14 (1.25−3.65) | 0.006 | 3.12 (1.28−7.62) | 0.012 |

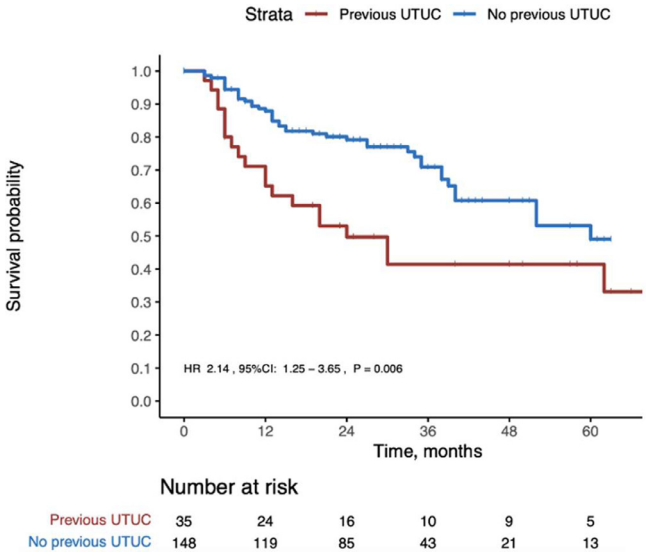


Figure 1. Kaplan−Meier analysis of intravesical recurrence free survival in unadjusted NMIBC with and without pre-existing diagnosis of UTUC without propensity score matching.

for P-NMIBC, $P = 0.548$). Apart from history of previous UTUC, other clinicopathological factors associated with a higher risk of intravesical HG recurrence on multivariate analyses were a high EAU risk score ($P = 0.047$, HR 2.84 95% CI: 0.94− 11.1) and failure to continue maintenance BCG up to 6 months ($P = 0.009$, HR 5.49 95% CI: 1.52 −19.9). In addition, 10 patients (28.6%) in the M-NMIBC group eventually progressed to MIBC, which was significantly greater than the P-NMIBC group of only 7 patients (4.7%) who experience disease progression (Fig. 2)

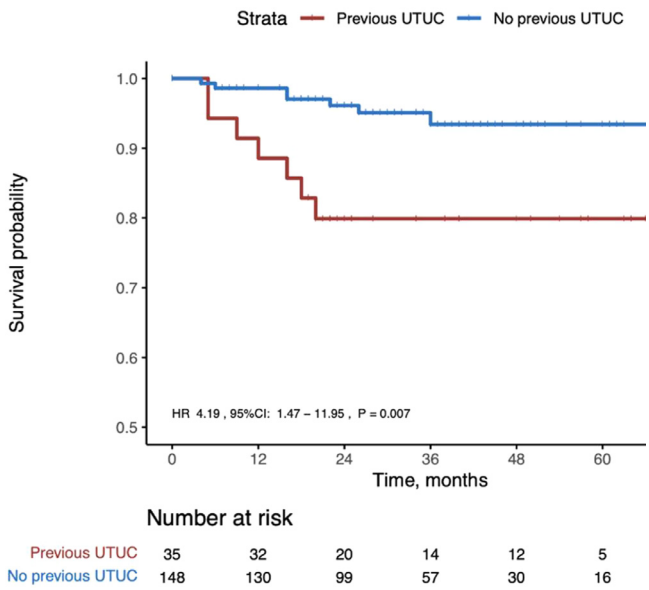


Figure 2. Kaplan−Meier analysis of progression to MIBC in unadjusted NMIBC with and without pre-existing diagnosis of UTUC without propensity score matching.

($P = 0.007$, HR 4.19 95% CI: 1.47−11.95) (Table 4). The M-NMIBC group also demonstrated higher progression to distant metastasis (Fig. 3) (20% vs. 6.5%, $P = 0.017$, HR 3.33 95% CI: 1.24−8.96). Overall survival was not significantly different in the non−propensity-matched analysis (8.6% vs. 18.4%, $P = 0.248$, HR 0.44 95% CI: 0.13−1.47).

In the propensity-matched analysis, the control group consisted of 35 M-NMIBC patients matched to 123 P-NMIBC patients. M-NMIBC patients again demonstrated a higher intravesical HG recurrence rate (Fig. 4) (54.3% vs. 22.8%, $P = 0.001$, HR 2.67 95% CI: 1.50−4.77), progression to MIBC (28.6% vs. 5.7%, $P = 0.022$, HR 3.42 95%CI: 1.20−9.75), and progression to metastasis (Figs 5 and 6) (20.0% vs. 6.5%, $P = 0.033$, HR 3.02 95% CI: 1.09−8.35). The 2 groups were well adjusted with no differences in patient demographics, EAU risk scores, and BCG doses in our multivariate analysis. Overall survival was not significantly different in the propensity-matched analysis (8.6% vs. 18.8%, $P = 0.134$, HR 0.40 95% CI: 0.12−1.33).

## 4. Discussion

In this present study, we have demonstrated that M-NMIBC after previous treatment for UTUC, despite undergoing complete TURBT and receiving BCG, is associated with a poorer response to BCG, with a more than twofold increased risk of intravesical high-grade recurrence (HR 2.67 95% CI: 1.50−4.77) and a higher risk of progression to MIBC (HR 3.42 95% CI: 1.20−9.75) compared to the P-NMIBC population. This translates to almost half of the patients being refractory to BCG and with a significant proportion progressing to MIBC, which is a concerning figure. These findings are congruent with the few previous studies in this field evaluating outcomes of intravesical BCG in patients with M-NMIBC. Miyake et al. [14] conducted one of the first multicenter studies comparing 75 patients with M-NMIBC to 352 patients with P-NMIBC and reported that the M-NMIBC were poor responders to BCG, with higher recurrence rates but no difference in progression-free survival. Kelly Bree et al. reported a retrospective cohort of 482 patients with P-NMIBC and 34 patients who received intravesical BCG instillation for subsequent NMIBC after RNU. In an unmatched analysis, the latter group exhibited a higher intravesical RFS rate, increased risk of disease progression and progression to metastatic disease bladder progression-related survival [15]. Synchronously, these findings support that despite similarities in histological findings, HG NMIBC recurrence in patients with a previous history of UTUC significantly differs from P-NMIBC in terms of clinical behavior, progression, and biological characteristics. These M-NMIBCs may possibly represent UTUC clonal recurrences rather than de novo transformation of P-NMIBC [16]. In that aspect, BCG response for M-NMIBC may appear closer to BCG therapy in UTUC, which is generally poorer with higher recurrences and progression [17−18].

Table 4
Oncological outcomes of studied patients.

| | Before matching | | | | After propensity matching | | | |
|---|---|---|---|---|---|---|---|---|
| | M-NIMBC | P-NMBIC | Hazard Ratio (95% CI) | *P*-value | P- NMIBC | Hazard Ratio (95%CI) | *P*-value | SMD |
| Mean number of BCG given (mean [SD]) | 5.84 (± 0.80) | 5.81 (±0.79) | - | 0.886 | 5.87 (±0.61) | - | 0.825 | 0.047 |
| Duration of follow up months (mean [SD]) | 37.91 (±18.49) | 33.80 (±17.18) | - | 0.212 | 32.66 (±17.70) | - | 0.128 | 0.290 |
| Intravesical HG recurrence (%) | 19 (54.3) | 42 (28.4) | 2.14 (1.25− 3.65) | 0.006 | 28 (22.8) | 2.67 (1.50−4.77) | 0.001 | 0.750 |
| Progression to MIBC (%) | 10 (28.6) | 7 (4.7) | 4.19 (1.47−11.95) | 0.007 | 7 (5.7) | 3.42 (1.20−9.75) | 0.022 | 0.438 |
| Progression to distant metastasis (%) | 7 (20.0) | 8 (6.5) | 3.33 (1.24−8.96) | 0.017 | 8 (6.5) | 3.02 (1.09−8.35) | 0.033 | 0.406 |
| Overall survival (%) | 3 (8.6) | 26 (18.4) | 0.44 (0.13−1.47) | 0.248 | 22 (18.8) | 0.40 (0.12−1.33) | 0.134 | 0.301 |

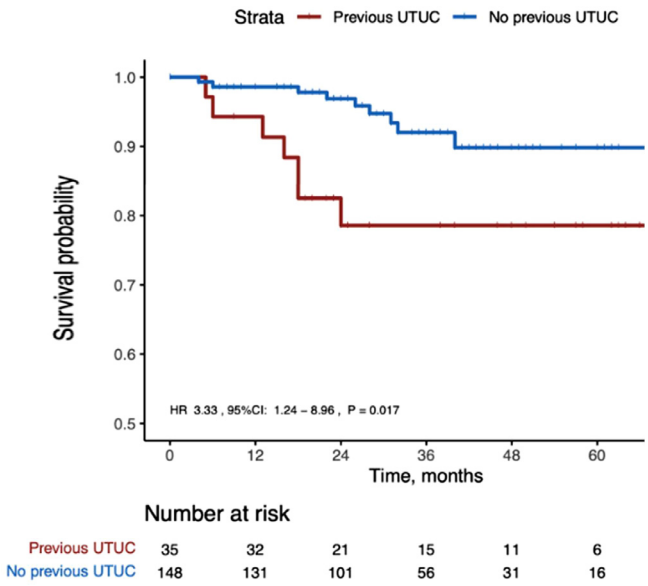


Figure 3. Kaplan−Meier analysis of progression to metastatic disease in unadjusted NMIBC with and without pre-existing diagnosis of UTUC without propensity score matching.

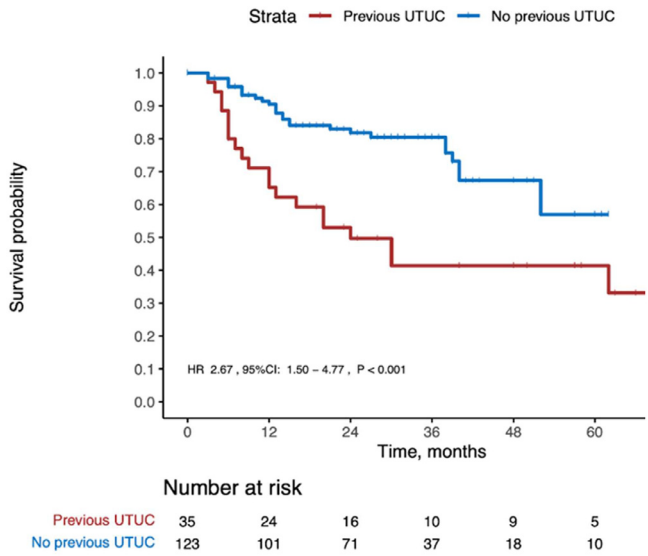


Figure 4. Kaplan−Meier analysis of intravesical recurrence free survival in adjusted NMIBC with and without pre-existing diagnosis of UTUC with propensity score matching.

An interesting observation unique to our study was that the M-NMIBC group had smaller tumors and was less likely to be symptomatic, likely due to regular cystoscopic surveillance following UTUC treatment. Furthermore, the M-NMIBC group had a lower proportion of high and very high risk profiles. Despite these seemingly favorable clinicopathological characteristics, M-NMIBC demonstrated greater resistance to BCG therapy, suggesting a more aggressive and resistant tumor biology. This was reflected in the significantly higher progression to distant metastasis observed in the M-NMIBC cohort compared to the P-NMIBC group (20.0% vs. 6.5%, HR 3.02 95% CI: 1.09 −8.35). However, this did not translate into a statistically significant difference in overall survival between the 2 groups (8.6% vs. 18.8%, HR 0.40 95% CI: 0.12−1.33). We postulate that this discrepancy may be attributed to the short follow up period that limits a potential survival difference observation.

We postulate that M-NIMBC may contain genetic expression pathways more similar to UTUC compared to P-NIMBC. Van Doeveren highlighted that more than 90% of paired primary UTUC and subsequent urothelial bladder carcinoma appear to be clonally lending weighed to the hypothesis of pan-urothelial transformation and tumor seeding as possible explanation for M-NMIBC being UTUC clonal-related recurrence [19]. One potential genetic difference observed was the upregulation of receptor tyrosine kinases such as fibroblast growth factor receptor 3 (FGFR3) in M-NMIBC compared to P-NMIBC. Robinson BD et al. has shown that higher rates of FGFR3 results in a T-cell-

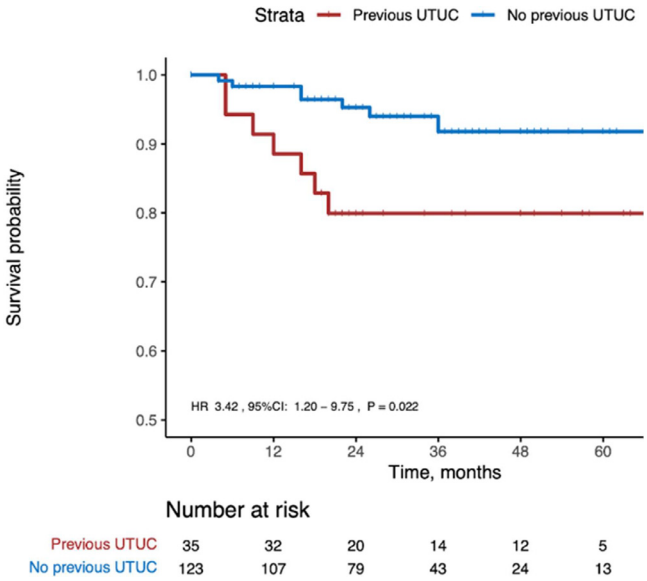


Figure 5. Kaplan–Meier analysis of progression to MIBC in unadjusted NMIBC with and without pre-existing diagnosis of UTUC with propensity score matching.

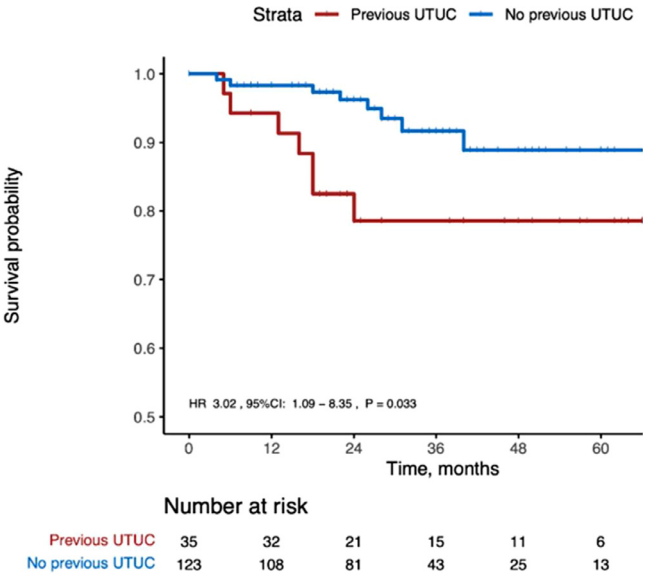


Figure 6. Kaplan–Meier analysis of progression to metastatic disease in adjusted NMIBC with and without pre-existing diagnosis of UTUC with propensity score matching.

depleted immune microenvironment for M-NMIBC**,** and has been associated with a luminal-like papillary urothelial formation [20]. This subgroup tends to drive an immune suppressive response and therefore, may lead to a poorer immune activation following intravesical BCG therapy which impairs its antitumoral activity [21–22].

Other observed genetic alterations include both microsatellite instability and DNA hypermethylation, which are more frequently observed in M-NMIBC than in P-NMIBC [23], which in turn are often associated with a more aggressive tumor biology and advanced disease [24]. On the tumor front, these distinct DNA hypermethylation can promote cancer proliferation by affecting DNA repair, cell cycle regulation and silencing the tumor suppressor genes [25–26]. In addition, DNA hypermethylation can also affect BCG uptake in urothelial and immune cells by downregulating endocytosis and chemokine signaling, thereby impacting the subsequent effective response [27–28]. These observations reinforced the molecular differences between M-NMIBC and P-NMIBC and the implications on BCG response and recurrences. At the time of writing this manuscript, we are performing an in-depth molecular immune-profiling to provide a greater understanding of the epigenetic differences.

The present study does have its limitations. Firstly, the sample size is small as it reflects the rarity of M-NMIBC after UTUC. The small retrospective sample size of M-NMIBC patients may have introduced selection bias, and residual confounders not accounted for in the analysis. These could have influenced the studied outcomes despite the use of propensity score matching (PSM). Secondly, there were 5 patients with isolated CIS in the M-NMIBC but absence of primary CIS in the P-NMIBC. To circumvent the differences, the composite EAU-risk score, which provides a more comprehensive tumoral assessment, was used for matching. While most patients completed the induction BCG course, few received maintenance BCG. This highlighted the practical challenges such as BCG side effects and shortages. Nonetheless, the cohort was matched appropriately for BCG doses to reduce potential biases.

In conclusion, M-NMIBC after previous UTUC treatment confers a worse prognosis with a higher intravesical HG recurrence rate and progression to MIBC after intravesical BCG, indicating a poorer response rate towards BCG. It is questionable if BCG therapy is truly an effective treatment for this group of patients, or should other alternatives be considered. Risk stratification and models ought to factor the presence of UTUC as an important prognosticator, and patients should be counselled appropriately.

## Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRediT authorship contribution statement

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