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Detrusor Muscle Sampling, Operator Experience and Repeat Transurethral Resection Findings in High-Grade Non-Muscle-Invasive Bladder Cancer Treated with BCG: A Retrospective Cohort Study

Ahmed Hussin Kddum Alzerkani *

Department of Surgery, College of Medicine, University of Wasit, Wasit, Iraq.

أخذ عيّنة العضلة النافصة وخبرة الجرّاح ونتائج إعادة الاستئصال عبر الإحليل في سرطان المثانة غير الغازي للعضلة عالي الدرجة المعالَج بلقاح *BCG*: دراسة أترابية استعادية

أحمد حسين كاظم الزركاني *
كلية الطب - فرع جراحة المسالك البولية، كلية الطب، جامعة واسط، الكوت، العراق

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Abstract:
The quality of the initial transurethral resection of bladder tumour (TURBT) governs the accuracy of staging and may influence outcomes in high-grade non-muscle-invasive bladder cancer (NMIBC), yet data from teaching hospitals in the Middle East are scarce. This retrospective cohort study evaluated detrusor muscle sampling according to operator grade, the findings of repeat TURBT (re-TURBT), and the association of initial resection quality with recurrence and progression in 241 patients with high-grade Ta/T1 urothelial carcinoma who received intravesical bacillus Calmette–Guérin (BCG) at a teaching hospital in Kut, Iraq, between 2017 and 2022. Recurrence-free and progression-free survival were estimated with the Kaplan–Meier method, and prognostic factors were assessed with Cox regression. Detrusor muscle was present in 156 of 241 initial specimens (64.7%): 77.1% of consultant-performed and 47.5% of resident-performed resections ($p<0.001$). Re-TURBT, performed in 108 patients (44.8%) after a median of 5 weeks, revealed residual tumour in 40 (37.0%) and muscle-invasive disease in 12 (11.1%). Among 229 patients with confirmed NMIBC followed for a median of 42 months, 90 (39.3%) developed recurrence and 31 (13.5%) progressed. Three-year recurrence-free survival was 69.5% with and 51.2% without detrusor muscle in the initial specimen. Absence of detrusor muscle was independently associated with recurrence (HR 1.85; 95% CI 1.18–2.90) and progression (HR 2.28; 95% CI 1.08–4.81). One-third of initial resections lacked detrusor muscle, mainly those performed by residents, and a second resection often uncovered residual or understaged disease. Closer supervision of trainee resections and consistent application of re-TURBT indications should be priorities for quality improvement.

Keywords: Non-muscle-invasive bladder cancer, Transurethral resection, Detrusor muscle, Repeat resection, BCG, Recurrence.

الملخص
تحدّد جودة الاستئصال الأولي لورم المثانة عبر الإحليل (*TURBT*) دقّةَ التصنيف المرحلي، وقد تؤثر في نتائج علاج سرطان المثانة غير الغازي للعضلة عالي الدرجة (*NMIBC*)، غير أن البيانات المتاحة من المستشفيات التعليمية في الشرق الأوسط محدودة. قيّمت هذه الدراسة الأترابية الاستعادية مدى احتواء

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عيّنات الاستئصال الأولي على العضلة النافصة بحسب درجة الجرّاح، ونتائج إعادة الاستئصال (*re-TURBT*)، وعلاقة جودة الاستئصال الأولي بالنكس والتطوّر لدى 241 مريضاً مصاباً بسرطانة ظهارية بولية عالية الدرجة بمرحلة *Ta/T1* تلقّوا العلاج داخل المثانة بلقاح عصيّات كالميت–غيران (*BCG*) في مستشفى تعليمي في مدينة الكوت، العراق، بين عامَي 2017 و2022. قُدِّرت البُقيا الخالية من النكس والبُقيا الخالية من التطوّر بطريقة كابلان–ماير، وقُيِّمت العوامل الإنذارية بانحدار كوكس. وُجدت العضلة النافصة في 156 من أصل 241 عيّنة أولية (64.7%)، بواقع 77.1% في العمليات التي أجراها الاستشاريون و47.5% في تلك التي أجراها الأطباء المقيمون (*p<0.001*). أُجريت إعادة الاستئصال لدى 108 مرضى (44.8%) بعد مدة وسيطة قدرها 5 أسابيع، وكشفت عن ورم متبقٍّ لدى 40 مريضاً (37.0%) وعن مرض غازٍ للعضلة لدى 12 مريضاً (11.1%). ومن بين 229 مريضاً تأكّدت إصابتهم بالمرض غير الغازي للعضلة وتمّت متابعتهم مدة وسيطة بلغت 42 شهراً، حدث النكس لدى 90 مريضاً (39.3%) والتطوّر لدى 31 مريضاً (13.5%). بلغت البُقيا الخالية من النكس لثلاث سنوات 69.5% عند وجود العضلة النافصة في العيّنة الأولية و51.2% عند غيابها، وارتبط غيابها ارتباطاً مستقلاً بالنكس (*HR 1.85*؛ 95% *CI 1.18–2.90*) وبالتطوّر (*HR 2.28*؛ 95% *CI 1.08–4.81*). يخلو ثلث عمليات الاستئصال الأولي من العضلة النافصة، ولا سيّما تلك التي يجريها المقيمون، وكثيراً ما تكشف إعادة الاستئصال عن مرض متبقٍّ أو مقدَّر المرحلة بأقل من حقيقته؛ لذا ينبغي إعطاء الأولوية لتشديد الإشراف على عمليات المتدرّبين والالتزام المنتظم بدواعي إعادة الاستئصال.

الكلمات المفتاحية: سرطان المثانة غير الغازي للعضلة، الاستئصال عبر الإحليل، العضلة النافصة، إعادة الاستئصال، لقاح *BCG*، النكس.

Introduction

Bladder cancer accounted for approximately 614,000 new cases and 220,000 deaths worldwide in 2022 [1]. Most patients present with non-muscle-invasive bladder cancer (NMIBC), which comprises papillary Ta tumours, T1 tumours invading the lamina propria, and carcinoma in situ (CIS). High-grade NMIBC carries a substantial risk of recurrence and of progression to muscle-invasive disease, so accurate initial staging and risk-adapted adjuvant treatment are central to its management [2–5].

Transurethral resection of bladder tumour (TURBT) is both the first therapeutic step and the basis of pathological staging. The presence of detrusor muscle in the specimen is widely used as a marker of resection quality, because its absence prevents exclusion of muscle invasion and is associated with residual disease and early recurrence [2, 6, 7]. Recurrence rates at the first follow-up cystoscopy vary considerably between institutions, suggesting that surgical technique and experience contribute to outcome [6], and detrusor muscle sampling has been shown to depend on operator experience [7].

Repeat TURBT (re-TURBT) detects residual tumour in a large proportion of patients with high-grade disease and identifies muscle invasion that was missed at the first resection [8, 9]. The European Association of Urology (EAU) therefore recommends re-TURBT within 2–6 weeks after an incomplete initial resection, in T1 tumours, and when detrusor muscle is absent from the specimen, with specified exceptions [2].

Most of this evidence originates from high-volume centres. In teaching hospitals with limited resources, the level of trainee supervision, the completeness of pathology reporting and the availability of maintenance BCG may differ substantially, and these differences could translate into poorer staging accuracy and outcomes. The present study therefore aimed to assess detrusor muscle sampling according to operator grade, to describe the findings of re-TURBT, and to examine the association between initial resection quality and recurrence and progression in patients with high-grade NMIBC treated with bacillus Calmette–Guérin (BCG) at a teaching hospital in Iraq.

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Material and methods

Study design and patients

This single-centre retrospective cohort study included patients with histologically confirmed high-grade Ta or T1 urothelial carcinoma, with or without concomitant CIS, who underwent TURBT and started intravesical BCG at Al-Zahraa Teaching Hospital, Kut, Iraq, between January 2017 and December 2022. A minimum of 12 months of documented follow-up was required unless recurrence or progression occurred earlier. Patients with muscle-invasive disease at initial TURBT, non-urothelial histology, upper urinary tract urothelial carcinoma, previous pelvic radiotherapy, or incomplete operative or pathology records were excluded. The study was approved by the Ethics Committee of the College of Medicine, University of Wasit (WAS-8427; 15 January 2023), which waived the requirement for informed consent because of the retrospective design; all data were anonymised before analysis. Reporting follows the STROBE statement [11].

Surgical technique and pathology

TURBT was performed with a bipolar resectoscope under spinal or general anaesthesia. Tumours were resected en bloc when feasible or otherwise in fractions, with separate sampling of the tumour base to include muscularis propria. The grade of the operating surgeon (consultant or resident) was recorded. Pathology reports were reviewed for stage, grade, presence of CIS and explicit mention of detrusor muscle. Re-TURBT was performed at the discretion of the treating surgeon and included resection of the previous tumour site and any visible residual lesion.

Intravesical therapy and follow-up

Induction BCG (Razi strain, 50 mg) was given weekly for six weeks, starting 2–4 weeks after the final resection. Maintenance therapy according to a modified Southwest Oncology Group (SWOG) schedule [10] was offered when the drug was available. Surveillance consisted of cystoscopy and urine cytology every 3 months for the first 2 years and every 6 months thereafter.

Variables and outcomes

Collected variables were age, sex, smoking history, T category, concomitant CIS, tumour multiplicity, largest tumour diameter (≥3 cm), primary or recurrent presentation, operator grade, detrusor muscle in the initial specimen, documented completeness of resection, receipt of re-TURBT and receipt of maintenance BCG. Recurrence was defined as histologically confirmed urothelial carcinoma detected during surveillance; tumour found at re-TURBT was classified as residual disease and not as recurrence. Progression was defined as pathological muscle invasion (≥pT2) or regional or distant metastasis. Time to event was measured from the initial TURBT to the event or to the last cystoscopic follow-up.

The 12 patients found to have muscle-invasive disease at re-TURBT no longer met the definition of NMIBC and were excluded from the survival analyses, which therefore included 229 patients.

Statistical analysis

Categorical variables are presented as numbers and percentages and were compared with the χ^2 test; continuous variables are presented as medians with interquartile ranges (IQR) and were compared with the Mann–Whitney U test. Recurrence-free survival (RFS) and progression-free survival (PFS) were estimated with the Kaplan–Meier method and compared with the log-rank test. Univariable and multivariable Cox proportional-hazards regression was used to identify factors associated with recurrence and progression, and the proportional-hazards assumption was checked with Schoenfeld residuals [12]. Because only 31 progression events occurred, the multivariable progression model was limited to the two strongest predictors to avoid overfitting [13]. The recurrence model was additionally adjusted for receipt of re-TURBT; because re-TURBT took place after the start of follow-up and was selected according

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to risk, its own hazard ratio is not interpreted as a treatment effect. A two-sided p value <0.05 was considered significant. Analyses were performed with IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA).

Results

Patients and quality of the initial resection

Of 312 patients screened, 71 were excluded (muscle-invasive disease at initial TURBT, n=18; non-urothelial histology, n=12; upper tract disease, n=9; previous pelvic radiotherapy, n=7; incomplete records, n=25), leaving 241 patients. Of these, 194 (80.5%) were men, and the median age was 63 years (IQR 55–70).

Detrusor muscle was identified in 156 of 241 initial specimens (64.7%). The rate was 77.1% (108/140) for consultant-performed and 47.5% (48/101) for resident-performed resections (p<0.001).

Baseline characteristics of the 229 patients included in the survival analysis are shown in Table 1, according to whether they underwent re-TURBT. Patients selected for re-TURBT more often had T1 tumours (68.8% vs 43.6%; p<0.001) and less often had detrusor muscle in the initial specimen (41.7% vs 78.2%; p<0.001), consistent with selection according to guideline indications. The other characteristics did not differ significantly.

Table 1. Baseline characteristics of patients included in the survival analysis (n=229), according to receipt of re-TURBT

Characteristic	All (n=229)	Re-TURBT (n=96)	No re-TURBT (n=133)	p value
Age, years, median (IQR)	63 (55–70)[a]	64 (56–71)	62 (54–69)	0.18
Male sex	184 (80.3)	78 (81.3)	106 (79.7)	0.77
Smoking history	132 (57.6)	55 (57.3)	77 (57.9)	0.93
T1 (vs Ta)	124 (54.1)	66 (68.8)	58 (43.6)	<0.001
Concomitant CIS	37 (16.2)	19 (19.8)	18 (13.5)	0.20
Multiple tumours	84 (36.7)	37 (38.5)	47 (35.3)	0.62
Largest tumour ≥3 cm	75 (32.8)	33 (34.4)	42 (31.6)	0.66
Recurrent (vs primary) tumour	90 (39.3)	39 (40.6)	51 (38.3)	0.73
Detrusor muscle in initial specimen	144 (62.9)	40 (41.7)	104 (78.2)	<0.001
Initial TURBT by consultant	138 (60.3)	55 (57.3)	83 (62.4)	0.44
Complete resection documented	191 (83.4)	84 (87.5)	107 (80.5)	0.16
Maintenance BCG received	116 (50.7)	52 (54.2)	64 (48.1)	0.37
Follow-up, months, median (IQR)	42 (28–56)	44 (30–58)	40 (26–54)	0.22

Values are n (%) unless stated otherwise. [a]Median age of the full cohort (n=241). CIS, carcinoma in situ; IQR, interquartile range; BCG, bacillus Calmette–Guérin.

Findings at repeat resection

Re-TURBT was performed in 108 of 241 patients (44.8%) at a median of 5 weeks (IQR 4–7) after the initial resection. Residual tumour was found in 40 patients (37.0%), most often at the

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site of the original resection (34 patients, 31.5%), and 12 patients (11.1%) were upstaged to muscle-invasive disease (Table 2).

Table 2. Findings at re-TURBT (n=108)

Finding	Value
Interval from initial TURBT, weeks, median (IQR)	5 (4–7)
No residual tumour	68 (63.0)
Any residual tumour	40 (37.0)
At the initial resection site	34 (31.5)
Muscle-invasive disease (≥T2)	12 (11.1)

Values are n (%) unless stated otherwise. IQR, interquartile range.

Recurrence

During a median follow-up of 42 months (IQR 28–56), 90 of 229 patients (39.3%) developed recurrence, 38 (16.6%) of them at the first surveillance cystoscopy. Three-year RFS was 69.5% in patients with detrusor muscle in the initial specimen and 51.2% in those without (log-rank p=0.003). In multivariable analysis, absence of detrusor muscle (HR 1.85; 95% CI 1.18–2.90), T1 stage (HR 1.98; 95% CI 1.26–3.11), concomitant CIS (HR 2.25; 95% CI 1.36–3.72), multiple tumours (HR 1.58; 95% CI 1.01–2.47) and recurrent presentation (HR 1.80; 95% CI 1.15–2.82) were independently associated with recurrence. Operator grade, tumour size, age and induction-only BCG were not significant in the adjusted model (Table 3). Patients who did not undergo re-TURBT also had a higher adjusted hazard of recurrence (HR 2.24; 95% CI 1.42–3.54), but because of immortal-time bias and confounding by indication this estimate was not interpreted as an effect of the procedure.

Table 3. Cox regression analysis of factors associated with recurrence (229 patients, 90 events)

Variable	Univariable HR (95% CI)	Multivariable HR (95% CI)	p value[a]
Detrusor muscle absent in initial specimen	1.95 (1.29–2.95)	1.85 (1.18–2.90)	0.007
Resident (vs consultant) surgeon	1.45 (0.95–2.21)	1.38 (0.89–2.14)	0.15
T1 (vs Ta)	2.18 (1.42–3.35)	1.98 (1.26–3.11)	0.003
Concomitant CIS	2.40 (1.48–3.89)	2.25 (1.36–3.72)	0.002
Multiple tumours	1.70 (1.11–2.60)	1.58 (1.01–2.47)	0.045
Largest tumour ≥3 cm	1.55 (0.99–2.42)	1.45 (0.91–2.31)	0.12
Recurrent (vs primary) tumour	1.92 (1.25–2.95)	1.80 (1.15–2.82)	0.010
Induction only (vs maintenance) BCG	1.60 (1.03–2.48)	1.48 (0.94–2.33)	0.09
Age (per 10 years)	1.06 (0.90–1.25)	1.03 (0.86–1.23)	0.76
No re-TURBT (vs re-TURBT)[b]	—	2.24 (1.42–3.54)	<0.001

HR, hazard ratio; CI, confidence interval. [a]p value for the multivariable model, which was additionally adjusted for receipt of re-TURBT. [b]Re-TURBT took place after the start of follow-up and was selected according to risk; it was entered only as an adjustment variable in the multivariable model, and its hazard ratio is shown for completeness and should not be interpreted as a treatment effect.

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Progression

Progression occurred in 31 of 229 patients (13.5%). Three-year PFS was 92.8% with and 82.5% without detrusor muscle in the initial specimen (log-rank p=0.009). In multivariable analysis, absence of detrusor muscle (HR 2.28; 95% CI 1.08–4.81; p=0.031) and T1 stage (HR 2.95; 95% CI 1.34–6.48; p=0.007) were independently associated with progression (Table 4).

Table 4. Cox regression analysis of factors associated with progression (229 patients, 31 events)

Variable	Univariable HR (95% CI)	Multivariable HR (95% CI)	p value
Detrusor muscle absent in initial specimen	2.45 (1.18–5.08)	2.28 (1.08–4.81)	0.031
T1 (vs Ta)	3.25 (1.50–7.05)	2.95 (1.34–6.48)	0.007

HR, hazard ratio; CI, confidence interval.

Discussion

This study identified two clear opportunities for improving the care of high-grade NMIBC in our institution. First, about one-third of initial resections did not include detrusor muscle, and the rate was much lower in resections performed by residents. Second, re-TURBT, performed in fewer than half of the patients, found residual tumour in more than one-third of them and muscle-invasive cancer in one in nine. Absence of detrusor muscle in the initial specimen was independently associated with both recurrence and progression.

A detrusor muscle rate of 64.7% means that, in one-third of patients, muscle invasion could not be excluded after the first resection. The 30-percentage-point difference between consultants and residents is in line with the observation by Mariappan et al. [7] that muscle sampling depends on operator experience. This difference may also reflect tumour complexity or case allocation, which we could not assess. Operator grade itself was not independently associated with recurrence, suggesting that its effect may operate largely through the quality of the resection. Practical measures include direct consultant supervision of trainee resections, separate submission of the tumour base, and a structured operative note documenting the completeness and depth of resection.

Our re-TURBT findings agree with the systematic review by Cumberbatch et al. [8], in which residual tumour was common after an initial resection of high-risk NMIBC and upstaging to muscle-invasive disease occurred in a clinically relevant proportion of patients. In our cohort, re-TURBT was performed more often when the initial specimen lacked detrusor muscle or the tumour was T1 (Table 1), in accordance with the EAU recommendations [2]; nevertheless, fewer than half of all patients underwent a second resection. The 12 patients upstaged at re-TURBT would have been undertreated with BCG alone, which illustrates the diagnostic value of a second resection.

Absence of detrusor muscle was associated with an 85% higher hazard of recurrence and a more than twofold hazard of progression, after adjustment for established risk factors such as T1 stage, CIS, multiplicity and recurrent presentation [4, 5]. The association of recurrence with T1 stage and CIS, and the trend towards more recurrence with induction-only BCG, are consistent with the EORTC risk tables and with the benefit of maintenance BCG shown in the SWOG trial [4, 10]. Only half of our patients received maintenance BCG, which reflects local drug supply and may have contributed to the overall recurrence rate of 39.3%.

We did not attempt to estimate the effect of re-TURBT itself on recurrence or progression. Re-TURBT took place after the start of follow-up, so a simple comparison of patients who did and did not undergo the procedure would be subject to immortal-time bias. In addition, the

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procedure was selected for patients with T1 tumours and without detrusor muscle, introducing confounding by indication. Gontero et al. [9] reported that, in T1 high-grade tumours treated with BCG, re-TURBT appeared to improve outcomes mainly when detrusor muscle was absent from the initial specimen. Assessment of this question in our population would require a time-dependent or landmark analysis using individual procedure dates.

Strengths and limitations

The strengths of this study include a homogeneous population of high-grade NMIBC treated with BCG, systematic review of pathology reports for detrusor muscle, and a median follow-up of 42 months. The study also has limitations. It is retrospective and single-centre, and the decision to perform re-TURBT was not standardised. Excluding the 12 patients upstaged at re-TURBT from the survival analysis was clinically appropriate but means that the survival cohort is enriched for patients with less aggressive disease. The multivariable recurrence model was adjusted for receipt of re-TURBT, a post-baseline variable that partly depends on detrusor muscle status; this may have attenuated the estimated association with detrusor muscle. The same model included ten covariates for 90 events (about nine events per variable), so some estimates may be imprecise. BCG dose delivery and treatment interruptions could not be verified for every patient. Finally, the number of progression events was small, which limited the multivariable progression analysis.

Conclusion

In this cohort of patients with high-grade NMIBC treated with BCG, one-third of initial resections lacked detrusor muscle, with markedly lower rates among resident-performed procedures. Re-TURBT revealed residual tumour in 37% and muscle-invasive disease in 11% of patients, and absence of detrusor muscle was independently associated with recurrence and progression. Supervised training in resection technique, mandatory reporting of detrusor muscle and consistent application of re-TURBT indications should be adopted as quality standards. Prospective studies with time-dependent analysis are needed to define the effect of re-TURBT on long-term outcomes in this setting.

Declarations

Ethics approval and consent to participate: The study was approved by the Ethics Committee of the College of Medicine, University of Wasit (WAS-8427; 15 January 2023). The requirement for informed consent was waived because of the retrospective design, and all patient data were anonymised.

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Conflicts of interest: The authors declare no conflicts of interest.

Data availability: De-identified data are available from the corresponding author on reasonable request, subject to ethics approval and institutional policy.

Author contributions (CRediT): . All authors approved the final manuscript.

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