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Post-Bacille Calmette–Guerin surveillance for non-muscle invasive bladder cancer: do random biopsies offer an advantage?

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Abstract

Background: The optimal surveillance method for recurrence of non-muscle invasive bladder cancer (NMIBC) after intravesical BCG treatment is unknown. The aim of this study is to assess the difference between two surveillance methods: cystoscopy with bladder biopsies and office-based flexible cystoscopy in detecting NMIBC recurrence and time to recurrence.

Methods: Charts of patients who underwent transurethral resection of bladder tumor with subsequent intravesical Bacillus Calmette–Guerin (BCG) treatment were reviewed between January 2015 and December 2018. Baseline demographics and oncological parameters were compared between the two methods of surveillance. Then, the role of the surveillance method for NMIBC recurrence and time to recurrence were evaluated in backward logistic regression and hazard ratios estimated in Cox regression models, respectively.

Results: Fifty-one patients (50.5%) underwent office-based flexible cystoscopy and 50 patients (49.5%) had bladder biopsies. The patients undergoing either surveillance methods were comparable for baseline demographic and oncological parameter. The predictors of recurrence and earlier BCG relapse were increased body mass index, the presence of multifocal tumors, the presence of concurrent carcinoma in situ, and tumor size at presentation. Bladder cancer recurrence was mostly affected by multifocality of the disease [OR 3.61 95%CI (1.17–11.15)] and the presence of concomitant carcinoma in situ [4.35 (1.29–14.68)]. Yet, the surveillance method neither predicted a higher recurrence yield nor earlier diagnosis.

Conclusion: In our cohort, there is neither difference in recurrence yield nor earlier diagnosis of recurrence between office-based flexible cystoscopy and bladder biopsies. Larger prospective studies are needed to assess the generalizability of these findings.

Keywords: Bacillus Calmette–Guerin, Bladder biopsy, Bladder cancer, Non-invasive bladder cancer, Surveillance

1 Background

Bladder cancer (BC) is the ninth most commonly diagnosed cancer worldwide with an estimate 81,400 new cases and 17,980 deaths in the USA alone in 2020 [1]. It is

known to have the highest recurrence rate of any malignancy [1]. The most common bladder malignant tumor is transitional cell carcinoma (TCC), representing more than 90% of all bladder tumors in the USA [2]. Transitional cell carcinoma is further divided into non-muscle invasive and muscle invasive BC, which has a direct correlation on disease management and prognosis [2].

Non-muscle invasive bladder cancer (NMIBC) is risk-stratified to estimate the likelihood of progression

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to muscle invasive cancer. Several criteria help stratify patients with NMIBC into low-risk, intermediate-risk, and high-risk groups. Patients with high-risk disease, and in some cases intermediate-risk, should undergo intravesical Bacillus Calmette–Guerin (BCG) immunotherapy to decrease recurrence [3].

Patients selected for BCG treatment undergo a 6-week induction course that is followed by clinical surveillance. Disease surveillance is achieved by cystoscopy evaluation, cytology, biomarkers, and biopsy of erythematous lesions. Additionally, bladder biopsies are sometimes performed to evaluate disease progression [4]. New technologies like blue light and fluorescence cystoscopy allow better visualization; however, these modalities are not available in all centers [5].

Although bladder biopsies beget pathological proof of disease or absence of it, this surveillance method is more invasive and costly than the clinic-based flexible cystoscopy evaluation. Besides, there is conflicting data about the ability of bladder biopsies in increasing the yield of recurrence or allowing earlier detection [6]. Therefore, we aim to compare the efficacy of bladder biopsies versus office-based flexible cystoscopy evaluation in detecting NMIBC recurrence.

2 Methods

2.1 Study design

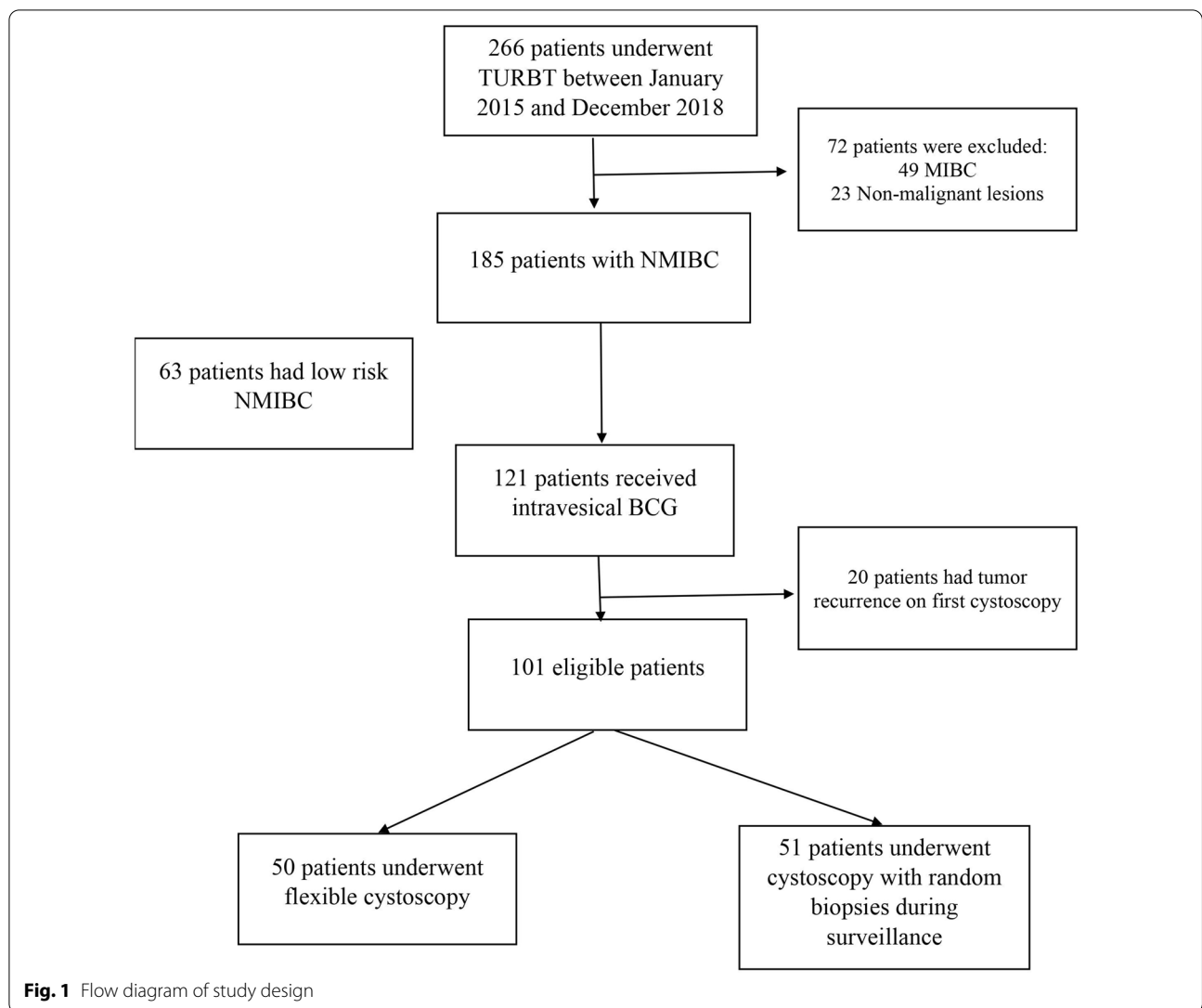
In order to consider a significant difference in the recurrence rate between the two surveillance modalities, a 20% difference in proportion of recurrence was chosen. Hence, based on the sample size calculations for a difference in two proportions, a 0.8 power, and an α of 0.05; a sample size of at least 97 patients is needed to detect a significant difference in recurrence rates. Therefore, after receiving institutional review board approval, retrospective chart review was done for patients who underwent transurethral resection of bladder tumor (TURBT) at our institution between January 2015 and December 2018. For the designated period, 266 consecutive patients underwent TURBT. Patients with muscle invasive bladder cancer (MIBC) ($n=49$) and patients with non-malignant lesions ($n=23$) were excluded. Among patients with NMIBC ($n=185$), 121 patients fulfilled the criteria for receiving intravesical BCG induction. Then, 20 patients were also excluded for pathologically proven recurrence on the post-induction cystoscopy evaluation at 3 months. Included in the analysis are 50 patients who underwent surveillance by flexible office-based cystoscopy and 51 patients who underwent rigid cystoscopy with bladder cold-cup biopsies (Fig. 1). Surveillance method was performed based on the treating physician's idiosyncratic preference; whereby half of the faculty members ($n=2$) perform routine bladder biopsies and the other

half ($n=2$) perform office-based cystoscopy. All patients had an ultrasound or computed tomography imaging for evaluation of the bladder lesion. On follow-up, cystoscopic evaluation was performed at 3-month intervals for the first year and later every 6 months. Intravesical BCG (MEDAC) was given to patients with moderate to high-risk features as per the AUA classification [7]. All patients were given an induction course followed by a maintenance course as per the SWOG trial [8]. Moreover, upper tract imaging was performed regularly by computed tomography to monitor for metachronous tumors. Exclusion criteria included patients who were lost to follow-up, those who had no clinical information available, patients who did not receive BCG due to contra-indications, patients with a history of bladder tumors, and patients with low grade tumors or muscle invasive disease, as well as BCG refractory patients (recurrence at 3 months post-BCG $n=120$). There was no standardized map for the bladder biopsies, and most biopsies were taken from the previous tumor resection site(s). All patients received the standard 81 mg intravesical dose of BCG (MEDAC) once a week for 6 consecutive weeks. All adverse events were classified according to the revised Clavien–Dindo classification [9].

Medical charts were reviewed for clinical, operative, and pathological data including age, gender, medical comorbidities, smoking status, type of surveillance (cold-cup biopsies or diagnostic flexible cystoscopy evaluation), tumor stage, grade, patient stratification according to AUA guidelines, tumor multifocality, size of the primary tumor, recurrence, and time to recurrence. A recurrence by flexible cystoscopy was denoted by visualization of papillary growth or suspicious lesions deemed worthy for further investigation followed by pathologic diagnosis. Data on complications due to the intravesical therapy or the TURBT were also recorded [10]. Recurrence was defined as positive results on bladder biopsies or at the time of flexible cystoscopy that were later confirmed with pathology.

2.2 Statistical analysis

The patients' demographics and oncological parameters were compared using Mann–Whitney U test for continuous variables and Chi-square or Fisher's exact tests were used for categorical variables. The predictors for NMIBC recurrence were evaluated by a binary logistic regression. Kaplan–Meier survival analysis factored by surveillance method (Log rank test) as well as Cox regression was conducted for the outcome time to recurrence. Both models were performed by the enter method and were adjusted for age, body mass index, hypertension, diabetes, smoking status, tumor size, grade, and stage as well as the surveillance method chosen. The Statistical Package for the



Social Sciences (SPSS) version 25 (IBM Corp., Armonk, N.Y., USA) was used to conduct statistical analysis.

3 Results

A total of 101 patients underwent surveillance for NMIBC post BCG induction. Fifty-one patients (50.5%) underwent office-based flexible cystoscopy and 50 patients (49.5%) had bladder biopsies. Table 1 compares the basic demographics between the two surveillance methods. Both groups were comparable for age, body mass index, hypertension, diabetes, and smoking status ($p > 0.05$). The tumor size was similar for the flexible cystoscopy group (2.43 ± 1.1) and bladder biopsy group (2.3 ± 0.9 ; $p = 0.453$). In comparison with bladder biopsy group, the proportion of patients in the flexible cystoscopy group with multifocal tumor, pathological

high grade tumor, the presence of concurrent carcinoma in situ (CIS), and stage T1 disease were also similar (47.1% vs. 54.0%; 86.3% vs. 94.0%; 25.5% vs. 28.0%; 78.4% vs. 88.0%, respectively) (Table 1). Additionally, the two groups did not differ in AUA risk distribution ($p = 0.1$).

Since the median was not reached in either group, the 75th percentile survival was 18 ± 1 months for the flexible cystoscopy group and 14 ± 3 months for the bladder biopsy group (Fig. 2). The surveillance method did not impact the yield of recurrence (Mantel-Cox $p = 0.5$). At the multivariate level, every one-unit increase in BMI resulted in 23% increase odds and 13% increase hazard of NMIBC recurrence (logistic regression) and earlier recurrence (Cox Regression), respectively. In the logistic regression, recurrence was also predicted by the presence of concurrent CIS [OR 4.35 95% CI (1.29–14.68)],

Table 1 Baseline demographics and oncological parameters in patients who underwent either flexible cystoscopy or cystoscopy with repeat biopsies for non-muscle invasive bladder cancer

Variables	Flexible cystoscopy (N = 51)	Repeat Biopsy (N = 50)	p value
	N (%); $\bar{x} \pm SD$	N (%); $\bar{x} \pm SD$	
Demographics			
Age (years)	66.2 \pm 12.2	65.5 \pm 10.0	0.5
Male	43 (84.3%)	42 (84.0%)	0.9
BMI (kg/m ²)	27.4 \pm 3.4	26.9 \pm 4.4	0.5
Hypertension	36 (70.6%)	36 (72.0%)	0.9
Diabetes	11 (21.6%)	14 (28.0%)	0.5
Smoking	30 (58.8%)	25 (50.0%)	0.4
Oncological variables			
Tumor size (cm)	2.43 \pm 1.1	2.3 \pm 0.9	0.5
Multifocal	24 (47.1%)	27 (54.0%)	0.5
High grade	44 (86.3%)	47 (94.0%)	0.3
Concurrent CIS	13 (25.5%)	14 (28.0%)	0.8
Stage T1	40 (78.4%)	44 (88.0%)	0.2
AUA risk stratification			
Moderate risk	13 (25.5%)	7 (14.0%)	0.147
High risk	38 (74.5%)	43 (86.0%)	

multifocal tumors at presentation [3.61; (1.17–11.15)], and tumor size [2.23 (1.23–4.03)] (Table 2). Furthermore, in the Cox regression, earlier recurrence was more likely in patients with concurrent CIS [2.46 (1.08–5.58)]. Besides, every one-centimeter increase in size of tumor results in 52% increased hazard of earlier recurrence. Nevertheless, the surveillance method neither predicted recurrence (logistic regression) nor the earlier diagnosis of recurrence (Cox regression).

3.1 Complications

No serious complications were encountered (no Clavien III or IV complications were recorded). Of the patients undergoing TURBT, 5 patients had prolonged bleeding (3%), 2 (1%) patients had post-operative urinary infection, 6 (4%) patients had urinary retention. Only 5 (5%) patients developed a low-grade fever secondary to BCG treatment. Yet, no patient discontinued the course due to side effects. Patients who underwent flexible cystoscopy or cystoscopy with bladder biopsies had no procedure specific grade II or higher complications. No mortalities were encountered in the follow-up of included patients.

4 Discussion

Guidelines for the management of NMIBC address the disease's biological inclination for recurrence or progression [4, 11]. Therefore, we sought to determine the

optimal NMIBC surveillance method post BCG induction: whether to perform bladder biopsies in the operating room or to resort to office-based flexible cystoscopy. While bladder biopsy surveillance has an added cost on the healthcare system, results in discomfort to the patient, and augments procedural risks; surveillance flexible cystoscopy begets no objective patho-oncological feedback.

There are multiple risk factors, whether tumor-specific or patient-specific, that can predict NMIBC recurrence. In our cohort, patients who experienced a recurrence had a higher BMI. A higher BMI is associated with hormonal changes and systemic inflammatory response increasing the risk of recurrence and progression of NMIBC [12]. Although the current smoking status was shown to be associated with recurrence, this was not the case in our study [13].

Initial tumor size, tumor multifocality, tumor grade, history of recurrence, a shorter timing of intravesical therapy, and presence of CIS are all disease specific variables associated with recurrence [14–16]. Similarly, in our cohort, tumor size, tumor multifocality, and the presence of concomitant CIS were associated with higher odds of recurrence and time to recurrence for NMIBC recurrence. Tumor size and tumor multifocality make it harder for complete surgical resection [14]. Furthermore, multifocality implies a biological predisposition where the entire transitional epithelium is subject to genetic instability [14].

Although bladder biopsies have been found to increase the yield and tumor upstaging at the time of initial TURBT, the literature is divided regarding its role in the surveillance stage [17, 18]. While May et al. found that bladder biopsies had a positive impact on therapeutic decisions of all NMIBC patients, Highshaw et al. found that bladder biopsies are unnecessary in case of negative findings on cystoscopy [17, 19]. Similarly, biopsies were found to be unwarranted when cytology and flexible cystoscopy are combined for surveillance [20, 21]. To the authors' knowledge, this study is the first to assess the time to recurrence when comparing bladder biopsies to flexible cystoscopy. In our cohort, bladder biopsies were as effective as office-based cystoscopy as a surveillance method in terms of recurrence detection or even earlier NMIBC uncovering. Despite the fact that both bladder biopsies and flexible cystoscopy were equally safe and not associated with any grade II or higher Clavien complications, surveillance with bladder biopsies subjects patients to unnecessary anesthesia and added cost [22].

New technologies such as narrow band imaging and blue light cystoscopy increase the yield of detection [23, 24]. However, most developing countries lack these new technologies due to cost issues as well as due to the

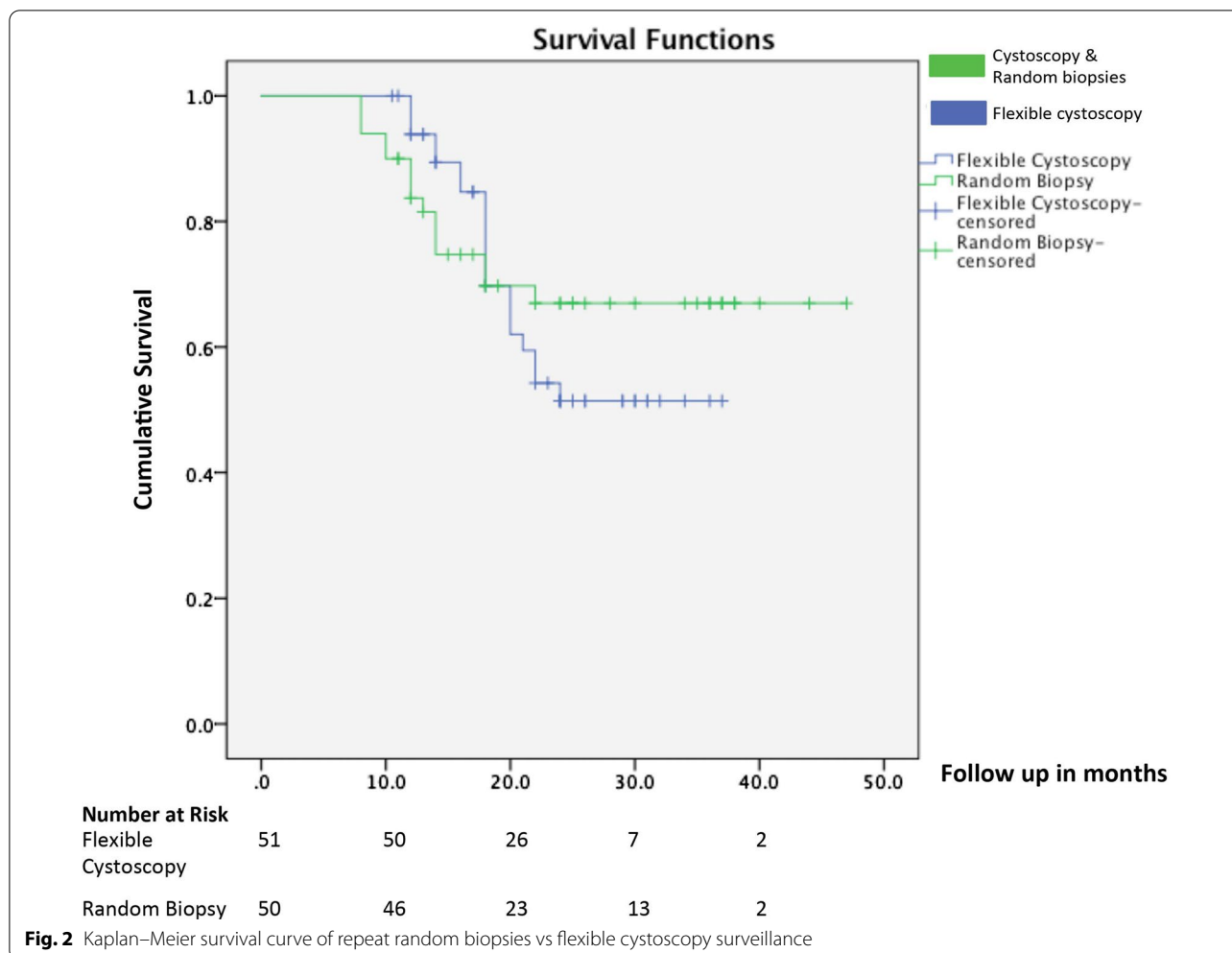


Table 2 Predictors of recurrence and time to recurrence in patients with non-invasive muscle bladder cancer

Variable	Recurrence ^a Odds ratio (95% CI)	Time to recurrence ^b Hazard ratio (95% CI)
Age	0.99 (0.94–1.04)	1.00 (0.96–1.04)
Body mass index (kg/m ²)	1.23 (1.06–1.43)	1.13 (1.03–1.23)
Hypertension	1.04 (0.30–3.56)	1.29 (0.53–3.12)
Diabetes	0.96 (0.29–3.23)	0.83 (0.32–2.16)
Smoking	1.15 (0.40–3.37)	0.94 (0.44–2.02)
Surveillance method ^c	0.63 (0.22–1.80)	0.97 (0.48–2.00)
Size (cm)	2.23 (1.23–4.0)	1.52 (1.08–2.14)
Concurrent CIS	4.35 (1.29–14.68)	2.46 (1.08–5.58)
Multifocality	3.61 (1.17–11.15)	1.93 (0.83–4.47)
High grade tumor ^d	2.17 (0.39–12.20)	1.06 (0.34–3.36)
Stage T1 ^e	0.40 (0.08–1.96)	0.57 (0.20–1.59)

^a Binary logistic regression (Enter Method)

^b Estimated coefficients in the Cox proportional hazards regression model (Enter Method)

^c Flexible cystoscopy as reference to cystoscopy with repeat biopsy

^d Low grade tumor as a reference to high grade tumor

^e Ta as a reference to T1 s

marginal improvement these tools bring about in overall outcome from a public health standpoint. Moreover, urinary biomarkers have been on the rise recently in the surveillance of NMIBC, but these are currently under investigation and are not for use in clinical practice [24].

4.1 Limitations

Although the data was retrospectively collected, the cohort encompassed non-selected consecutive patients presenting at our tertiary care center. Despite the relatively small sample size, our site is a referral center of neighboring countries ensuring the diversity of our population. The surveillance was performed by different urologists at our institution with each their preference of the method. Additionally, there was no standardized mapping of the bladder biopsies performed and the number of biopsies taken was not recorded in both methods. Furthermore, cystoscopy findings were extracted from operative reports and not from videotaped procedures. Also,

in cases of flexible cystoscopy surveillance ascertainment of recurrence has to be with a pathologic specimen.

5 Conclusion

NMIBC is a disease characterized by a high recurrence rate. In our cohort, bladder biopsies for surveillance of patients with history of NMIBC neither offered an increased detection of recurrence nor an earlier uncovering. Yet, larger cohorts and prospective studies are needed to assess the generalizability of our findings.

Abbreviations

BCG: Bacillus Calmette–Guerin; BC: Bladder cancer; MIBC: Muscle invasive bladder cancer; NMIBC: Non-muscle invasive bladder cancer; TCC: Transitional cell carcinoma; TURBT: Transurethral resection of bladder tumor.

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None.

Authors' contributions

NAH and RN contributed to concept; NAH contributed to design; AE and RK contributed to supervision; ML contributed to data collection and/or processing and analysis and/or interpretation; ML and AA were involved in literature search; NA, MB, and RK contributed to writing manuscript; MB, AE, RK, and RN contributed to critical review. All authors have read and approved the manuscript.

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Availability of data and materials

Available upon request.

Declarations

Ethics approval and consent to participate

This is a study that received Institutional Review Board approval at the American University of Beirut (AUB-IRB-BIO-0069). Consent does not apply since this is a retrospective chart review.

Consent for publication

This study is a retrospective chart review and does not require individual consent from the participants.

Competing interests

The authors have no conflicts of interest to declare.

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