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TOPIC PAPER

Prognostic impact of non-adherence to follow-up cystoscopy in non-muscle-invasive bladder cancer (NMIBC)

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Abstract

Purpose To evaluate the underexplored context of cystoscopy adherent versus non-adherent patients in the follow-up of urothelial high-risk non-muscle-invasive bladder cancer (NMIBC).

Methods We performed a retrospective study (2005–2016) that evaluated patients´ demographical characteristics, histopathological data, recurrence, progression and cancer-specific mortality between adherent and non-adherents patients in the first 3 years of a proposed cystoscopy protocol.

Results Among the 198 included patients, comparing cystoscopy non-adherent ($n=36$, 18%) and adherent patients ($n=162$, 82%), there was no demographic or histopathological differences; the rates of disease recurrence, progression and cancer-specific mortality were 15 (41.7%) versus 68 (42.2%), $p=0.58$; 12 (33.3%) versus 28 (17.9%), $p=0.014$ and 4 (11.1%) versus 19 (11.7%), $p=0.98$, respectively. Cystoscopy non-adherence was associated with an inferior number of urinary cytology ($p<0.001$) and 2.33 HR for cancer progression, $p=0.014$, (95% CI 1.18–4.59).

Conclusions Non-adherence to follow-up cystoscopy in NMIBC is associated with more than twice progression risk. Future studies are needed to confirm our results and correlate cystoscopy non-adherence to other covariates.

Keywords Bladder cancer · Cystoscopy · Follow-up · Recurrence · Progression · Survival

Introduction

Bladder cancer (BCa) is the second most common malignancy of the genitourinary tract and represents a significant cause of cancer morbidity and mortality. At the moment of presentation, 80–85% of the BCa are restricted to the bladder, and 85% of these are non-muscle invasive (NMIBC) [1].

Its protracted course, the necessity of constant monitoring and morbidity arising from the required treatment surgeries are some of the factors responsible for the enormous costs involved with the care of these patients [2].

After initial management with complete transurethral resection of bladder tumor (TURB), a bladder-sparing treatment is indicated for the majority of the NMIBC, and in this scenario, the most important tool for follow-up is the performance of periodic cystoscopy given its high rates of recurrence and progression [3].

While all guidelines suggest cystoscopy with urine cytology at regular intervals, there is no high-level evidence to support definitive recommendations of specific follow-up schedules [4].

The goals of the present study were to identify the index of non-adherence to the initially proposed cystoscopies, potential related factors and impact in terms of recurrence, progression and cancer-specific mortality on our prospectively maintained database including intermediate- and high-risk patients.

Methods

After ethics committee approval (1.273.975), all consecutive patients on our prospectively maintained database with the pathological diagnosis of NMIBC according to TNM staging [5] and WHO/ISUP 2004 grading [6] system between January 2005 and January 2016 who underwent a complete [7] TURB (including muscular layer in Ta and restaging TURB in T1 tumors) were analyzed and

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classified as adherent and non-adherent to the proposed surveillance cystoscopy protocol.

Inclusion criteria were the presence of any risk factor such as a recurrent tumor, or multiple tumors, or a tumor bigger than 3 cm, or high-grade, or the presence of CIS or T1 (characterizing- intermediate or high-risk patients), [8] and free access to the government-supported health system. Subjects were excluded if they had a muscle-invasive disease, incomplete resection or variant histology.

All patients underwent staging abdominal and pelvic CT scan. Urine cytology and standard white-light cystoscopy were performed every 3 months during the first 2 years following TURB and then every 6 months. After 5 years, cystoscopy was performed annually. No chemotherapy instillation was offered immediately after TURB. Urinary tract ultrasound investigation was ordered in the follow-up according to the treating physician's judgment.

Factors related to non-adherence to the cystoscopy protocol in the first 3 years of follow-up (< 10 cystoscopies) and its impact on outcomes was evaluated.

Among them:

- Demographic aspects: age, gender, race, smoking load (packs/year), Charlson comorbidity index [9], urinary cytology and bacillus Calmette–Guerin (BCG) use.
- Histopathological aspects: tumor size, multiplicity, stage, grade, and CIS coexistence.
- Outcomes: recurrence, progression, and cancer-specific death.

Intravesical adjuvant BCG was offered if two or more of the above-mentioned risk factors were present (characterizing high-risk patients), [8] and was started 2–3 weeks after TURB, the protocol was 6 weekly, 12 monthly, 4 trimonthly and 2 half-yearly doses, with a total of 24 doses.

Recurrence was defined as any tumor relapse without grade or stage upgrade, while progression was defined as any rise in the stage or grade, confirmed by TURB and histologic assessment.

The Mann–Whitney test compared continuous data (age, smoking burden, Charlson criteria). The Chi square test was used to verify whether distributions of two or more unrelated samples differed significantly in relation to a given variable. The Fisher's test evaluated differences between two independent groups, in relation to any variable that supports two alternatives as a response: yes or no. The Kaplan–Meier curves and log-rank test were used to evaluate the recurrence-free, progression-free and disease-specific survivals and Cox regression to determine the hazard ratio (HR). The level of significance was 5%.

Results

Among 476 patients, 198 met the inclusion criteria; of these 162 (82%) were adherent to the proposed cystoscopy follow-up protocol, while 36 (18%) were non-adherent. Among the non-adherent patients, 33 failed consecutive cystoscopies and 3 failed non-consecutive cystoscopies and recurrence/progression was associated with symptoms in 8 cases. The median interval between missed cystoscopy exams in the non-adherent patients was 11.1 months.

Mean follow-up was 112.4 (22–168), median 79.2 months. Among 198 patients, 83 (41.9%) presented recurrence, 40 (20.2%) progression and 23 (11.6%) cancer-specific death.

All included patients presented high-grade tumors (Ta and T1), and all but ten patients (95%) were classified as high-risk [8] and underwent adjuvant BCG treatment. Between BCG-treated patients, 23.5% (8/34) of non-adherent and 13% (20/154) of adherent patients to the cystoscopy follow-up completed less than 1-year maintenance BCG (< 18 doses), $p = 0.10$.

Comparing cystoscopy non-adherent and adherent patients, there was no demographic (Table 1) or histopathological

Table 1 Demographic aspects, divided into two groups

Variables	Non-adherents ($n = 36$)	Adherents ($n = 162$)	p value
Age (± SD)	67.2 (± 9.9)	64.7 (± 12.4)	0.63
Smoking load (± SD) Packs/year	201 (± 800.4)	162 (± 426)	0.43
Gender: Female/male (%)	5/31 (13.9%)	38/124 (23.5%)	0.27
Race (Caucasian): no/yes (%)	5/31 (13.9%)	23/139 (14.2%)	1.00
Charlson score (± SD)	5.8 (± 2)	5.2 (± 1)	0.29
Ultrasound* no/yes (%)	15/21 (41.7%)	42/120 (25.9%)	0.07
Urinary cytology** no/yes (%)	19/17 (52.8%)	32/130 (19.7%)	< 0.001
BCG*** no/yes (%)	2/34 (6.1%)	8/154 (4.9%)	1.00

*Ultrasound done after the first TURBT

**Urinary cytology collected after the first TURBT

***Treated with the BCG protocol

Table 2 Histopathological aspects between cystoscopy non-adherents and adherents

Histopathology	Non-adherents ($n=36$)	Adherents ($n=162$)	p value
Stage (Ta/T1)	12/24 (33.3%)	77/85 (47.5%)	0.14
CIS (yes/no)	2/34 (5.5%)	7/155 (4.6%)	0.67
Tumor size, cm (±SD)	4.1 (±2.5)	3.1 (±1.8)	0.08
Multiplicity* (no/yes)	17/19 (47.2%)	69/93 (42.6%)	0.71

*Presence of ≥2 lesions

Table 3 Outcomes between cystoscopy non-adherents and adherents

Outcomes	Non-adherents ($n=36$)	Adherents ($n=162$)	p value*
Recurrence	15 (41.7%)	68 (42.0%)	1.000
Progression	12 (33.3%)	28 (17.3%)	0.039
Cancer-specific mortality	4 (11.1%)	19 (11.7%)	1.000

*Fisher's test

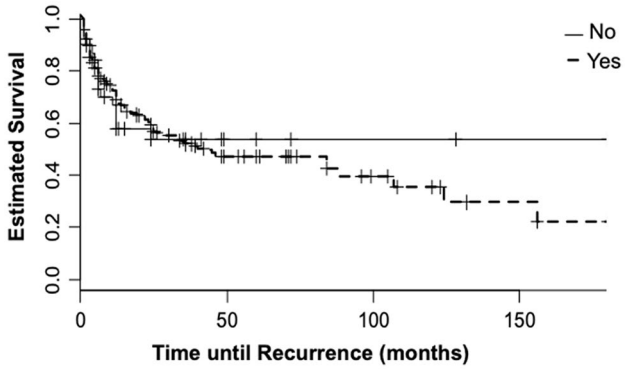

Fig. 1 Cystoscopy surveillance yes versus no time for recurrence Kaplan–Meier curves ($p=0.58$)

(Table 2) differences and the rates of disease recurrence, progression and cancer-specific mortality (Table 3) were 15 (41.7%) vs. 68 (42.2%), $p=0.58$; 12 (33.3%) vs. 28 (17.9%), $p=0.014$ and 4 (11.1%) vs. 19 (11.7%), $p=0.98$, respectively.

Figures 1, 2 and 3 illustrate Kaplan–Meier curves for time to recurrence, progression, and disease-specific mortality, respectively.

Cystoscopy non-adherence was associated with an inferior number of urinary cytology ($p<0.001$) and 2.33 HR for progression, $p=0.014$, (95% CI 1.18–4.59).

Discussion

In this study, we compared homogeneous groups of patients with the same access to the health system that have adhered or not to a cystoscopy follow-up protocol after TURB for

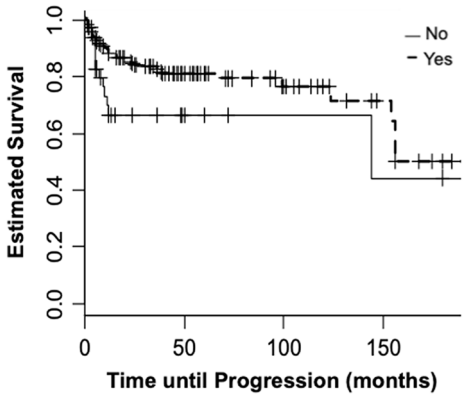

Fig. 2 Cystoscopy surveillance yes versus no time for progression Kaplan–Meier curves ($p=0.014$)

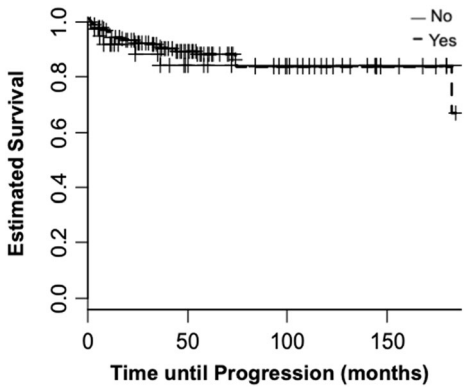

Fig. 3 Cystoscopy surveillance yes versus no time for disease-specific mortality Kaplan–Meier curves ($p=0.98$)

NMIBC with at least one high-risk feature. There was not any demographic or histopathological factors related to adherence.

Patients who did not complete the proposed cystoscopies protocol in the first 3 years presented significantly higher progression rates, though recurrence and cancer-specific mortality rates were not different. The reported cohort represents patients deserving the highest follow-up attention once 95% were high risk [8].

To our knowledge, this is the first study to demonstrate the impact of cystoscopy non-adherence, associated with

more than twice progression risk. Bladder cancer progression in a group of patients with high-risk features is devastating, since the vast majority is treated by radical cystectomy with significant impact on quality of life, some already being incurable.

All cystoscopy follow-up protocols after an initial complete TURB for patients with NMIBC are not only variable but also not evidence based [10–12]. Our own protocol is covered by the American Urological Association´s (AUA) recommendations in which cystoscopy for high risk is recommended with 3–4 months interval for 2 years, 6 months interval for 3–4 years, and annually afterward [8].

The importance of the adherence to a cystoscopy protocol to make a premature diagnosis of recurrence can be vital; in our cohort eight non-adherent patients were diagnosed by symptoms. Furthermore, it is undeniable that a worse BCa stage/grade is directly connected to worse outcomes like mortality. The subsequent treatment like cystectomy, while compromising quality of life might have positively impacted outcomes and also our follow-up might have been not long enough to correlate cystoscopy non-adherence to mortality.

Our hypothesis is that under-diagnosed recurrence might turn to an increase in the rate of progression and it is interesting to see that the non-adherent group tend to present more recurrences, as illustrated in the Kaplan–Meier curve (Fig. 1), potentially due to missing the recurrences in the non-adherent group.

The non-adherence to the proposed follow-up is frequent worldwide [3, 13], as we also showed in our study (18% overall rate). Some authors revealed an astonishing non-adherence rate higher than 50%, due to limited access, high costs, discomfort, and morbidities such as infection or urethral/bladder trauma [14].

Other publications already reported a significant relation of non-adherence to different factors as socioeconomic and cultural level, indiscipline, lack of explanation from the physician in clarify the severity of BCa and the importance of frequent attendance, age and tobacco load [15], although these last two factors did not have a relation to adherence in our study.

It is interesting to observe that though not significant, 23.5% (8/34) of non-adherent compared to 13% (20/154) of adherent patients have not completed the 1-year maintenance BCG protocol (< 18 doses), which might undermine the prognosis.

Also, while no demographical or histopathological factor associated to the non-adherence was identified, future studies are needed to correlate non-adherence to other covariates and to determine specific follow-up protocol. Moreover, a recent paper observed that in some cases, paradoxically, the urologists were responsible for not respecting the recommended frequency of cystoscopies, particularly in low-risk NMIBC [16].

Regarding the quality of the performed white-light cystoscopy (WLC) used in this study, several technological innovations have appeared to improve urologist's ability to fulfill a more complete exam, including photodynamic diagnosis (PDD) cystoscopy and narrow-band imaging. PDD, also known as fluorescence cystoscopy, facilitates visualization of bladder tumors compared with standard WLC and can be especially helpful in the detection of CIS [17, 18].

A meta-analysis of raw data assessing the effect of PDD on detection and recurrence in NMIBC was performed on 1345 patients from 9 prospective studies and additional detection of T1 tumors compared with white-light cystoscopy was 10.8% [odds ratio (OR) 2.25; $p = 0.050$] [19].

On the other hand, while we have not routinely offered postoperative chemotherapy instillation, the European Association of Urology (EAU) does not recommend it in high-risk patients [20], which is the case in 95% of our patients.

In fact, literature about this theme is very scarce and limited to a few retrospective papers, most based in the United States' cancer centers database. Even though our study is also retrospective and with a limited number of patients, it is a pioneering study as it has significantly observed the negative impact of a deficient cystoscopy follow up on high-risk NMIBC progression.

The current study is not without limitations. There are potential biases related to retrospective design and ignored prognostic factors such as lymphovascular invasion and tumor characterization as primary or recurrent. Also, though relatively small, the non-adherence group should ideally not exist, mainly considering the fact that our study showed a clinically significant impact of cystoscopy non-adherence.

Conclusion

Non-adherence to follow-up cystoscopy in high-risk NMIBC is associated with more than twice progression risk. The clinical interpretation of the study outcome would further emphasize our existing protocol to encourage patients to attend follow-up visits. Future studies are needed to confirm our results and correlate cystoscopy non-adherence to other covariates.

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Compliance with ethical standards

Conflict of interest None declared.

Research involving human participants Local ethics committee approval (1.273.975).

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