

ORIGINAL PAPER

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Impact of delay in cystoscopic surveillance on recurrence and progression rates in patients with non-muscle-invasive bladder cancer during the COVID-19 pandemic

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Abstract

Purpose: To evaluate the impact of delay in cystoscopic surveillance on recurrence and progression rates in non-muscle-invasive bladder cancer (NMIBC).

Materials and methods: A total of 407 patients from four high-volume centres with NMIBC that applied for follow-up cystoscopy were included in our study prospectively. Patients' demographics and previous tumour characteristics, the presence of tumour in follow-up cystoscopy, the pathology results of the latest transurethral resection of bladder tumour (if tumour was detected) and the delay in cystoscopy time were recorded. Our primary outcomes were tumour recurrences detected by follow-up cystoscopy and progression. Multivariate logistic regression analysis was performed using the possible factors identified with univariate analyses (P values $\leq .02$).

Results: A total of 105 patients (25.8%) had tumour recurrence in follow-up cystoscopy, and 20 (5.1%) of these patients had disease progression according to grade or stage. In multivariate analysis, the number of recurrences (OR: 1.307, $P < .001$) and the cystoscopy delay time (62-147 days, OR: 2.424, $P = .002$; >147 days, OR: 4.883, $P < .001$) were significant risk factors for tumour recurrence on follow-up cystoscopy; the number of recurrences (OR: 1.255, $P = .024$) and cystoscopy delay time (>90 days, OR: 6.704, $P = .002$) were significant risk factors for tumour progression.

Conclusions: This study showed that a 2-5 months of delay in follow-up cystoscopy increases the risk of recurrence by 2.4-fold, and delay in cystoscopy for more than 3 months increases the probability of progression by 6.7-fold. We suggest that cystoscopic surveillance should be done during the COVID-19 pandemic according to the schedule set by relevant guidelines.

1 | INTRODUCTION

Bladder cancer (BC) is one of the most commonly diagnosed cancers, especially in men, with an estimated 81 400 new patients and 17 980 deaths in 2020 in the United States.¹ In newly diagnosed patients with BC, approximately 75% of patients have non-muscle-invasive

bladder cancer (NMIBC) (Ta, T1 or carcinoma in situ [CIS]).² Despite lower morbidity and mortality rates compared with muscle-invasive bladder cancer (MIBC), NMIBC has a high probability of recurrence and progression. It is known that NMIBC has up to 78% recurrence rate and 45% progression rate at the 5-year follow-up.³ After transurethral resection of the bladder tumour (TUR-BT) and histological

diagnosis, risk-group stratification must be done, and surveillance or treatment modalities must be decided for each risk group.⁴

After complete resection of the bladder tumour, risk-group stratification, and, if necessary, appropriate intravesical therapy, patients must undergo an established surveillance schedule with cystoscopy. According to the European Association of Urology (EAU) guidelines, primary, solitary, Ta, low-grade and <3-cm tumours without CIS are defined as low-risk tumours. T1, high-grade, CIS or multiple, recurrent and large Ta low-grade tumours are defined as high-risk tumours. Other tumours that are not classified as low or high risk must be defined as intermediate-risk tumours. In the surveillance protocol, patients with high-grade tumours must undergo a follow-up cystoscopy every 3 months in the first 2 years, every 6 months in the next 3 years, and every year after 5 years. Patients with low-risk tumours must undergo follow-up cystoscopy at 3 months after resection; if negative, they must undergo subsequent cystoscopy 9 months later and then yearly. Lastly, patients with intermediate-risk tumours must undergo an individualized surveillance schedule with frequencies that are between those established for patients with low- and high-risk tumours.⁵

Despite widespread usage, these suggestions are based mostly on expert opinion and not on a great amount of evidence. A previous study reported that the adjusted frequency of follow-up cystoscopies ranged from 4.6 to 6.0 over 2 years per high-risk NMIBC patient in the United States.⁶ This study showed that many of the patients with high-risk NMIBC underwent fewer cystoscopies than suggested. Actually, it is not known how much a delay in cystoscopy surveillance will adversely affect oncological results.

Since early 2020, the coronavirus disease of 2019 (COVID-19) has been spreading all over the world, and the World Health Organization (WHO) declared a pandemic on 11 March 2020. COVID-19 has had a devastating effect on healthcare systems. Many changes had to be taken in the provision of healthcare services because of the medical and economic burden that COVID-19 brought to the healthcare system. Many medical doctors had to take part in the care of patients with COVID-19, not their specialty, and delays were experienced in the diagnosis and treatment of many diseases other than COVID-19, including cancer. All healthcare institutions and healthcare workers focused on the pandemic and patients with COVID-19. As a result of this situation, many patients with NMIBC could not undergo a follow-up cystoscopy on time, and serious delays were experienced.

In this study, we aimed to evaluate the impact of delay in cystoscopic surveillance on recurrence and progression rates after TUR-BT.

2 | MATERIALS AND METHODS

This observational prospective cohort study was conducted between June–September 2020, after institutional ethical committee approval. Informed consent was obtained from all patients when they were enrolled. Patients with NMIBC who applied for

What's known

- Cystoscopy follow-up is extremely important for the surveillance of bladder cancer.
- However, suggestions for the schedule of cystoscopy are mostly depend on expert opinions and poor-quality research.

What's new

- This study showed the negative impact of cystoscopy delay in patients with non-muscle-invasive bladder cancer and found that a delay of more than 3 months in the time of cystoscopy causes a significant increase in progression rates.

follow-up cystoscopy after the pandemic restrictions were lifted were included in our study. Patients with MIBC, no history of bladder tumour diagnosis, incomplete resection at previous TUR-BT and unknown bladder tumour pathology results before or after the follow-up cystoscopy were excluded from the study. A total of 407 patients from four high-volume centres were included in our study.

Patients with NMIBC who had applied for follow-up cystoscopy underwent the procedure with rigid or flexible cystoscope under local or general anaesthesia. The EAU surveillance schedule described above was used for timing the follow-up cystoscopies. TUR-BT was recommended for patients with tumours detected on follow-up cystoscopy. Patients' demographic characteristics such as age, sex, Charlson Comorbidity Index (CCI), smoking status, previous tumour characteristics, such as the number of recurrences, highest TUR-BT stage, grade, presence of CIS, EAU risk group, and intravesical therapy were recorded. Delays starting from the date of planned cystoscopy according to the EAU risk classification and EAU surveillance schedule were noted as "cystoscopy delay time." The presence of a tumour in follow-up cystoscopy was defined as "recurrence." If a recurrence was detected, the pathological characteristics of sequential TUR-BT were noted. Our primary outcomes were tumour recurrences and progression detected by follow-up cystoscopy. Any advancement in grade (low to high grade) or stage (Ta to T1 or any T2) in TUR-BT, which was performed after the follow-up cystoscopy, was accepted as "progression." Tumour stage and grade were assessed according to the 2017 Tumor Node Metastasis (TNM) classification and 2004/2016 WHO grading system, respectively.

SPSS v.21 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Kolmogorov Smirnov and Shapiro-Wilk tests were used to assess normality. Results were presented using median (25th–75th percentile) for continuous variables and frequency and percentage for categorical variables. Comparisons of the groups for continuous variables were performed by Mann-Whitney U-test, χ^2 -test or Fisher's exact test was used to analyse categorical variables, where

appropriate. Cystoscopy delay time cut-offs for recurrence and progression were assessed by using Receiver Operating Characteristic (ROC) analysis. Multivariate logistic regression analysis was performed by using the possible factors identified with univariate analyses (P values $\leq .2$). To avoid possible multicollinearity, only one of the highly correlated variables, the one with a high contribution to the model, was included in the multivariable logistic regression analysis. Results were presented as Odds Ratio (OR) and 95% Confidence Intervals (95% CI). Significance level was accepted as $P < .05$.

3 | RESULTS

A total of 407 patients with NMIBC, 348 (85.5%) men and 59 (14.5%) women, were included in our study. The median age of the patients was 65 years, and CCI was 5. A total of 100 (24.6%) patients were non-smokers, 241 (59.2%) were past smokers and 66 (16.2%) were active smokers. According to EAU risk group stratification, 71 (17.4%) patients were classified as low risk, 103 (25.3%) as intermediate risk and 233 (57.2%) as high risk. Patients' previous tumour characteristics are shown in Table 1. A total of 105 (25.8%) patients have had

TABLE 1 Characteristics of all patients, patients with/without recurrence and patients with/without progression*

Parameters	Overall	Recurrence		P value	Progression		P value
		Without (n = 302)	With (n = 105)		Without (n = 371)	With (n = 20)	
Age (year)	65 (59-72)	65 (58.8-71.3)	66 (59.5-74.5)	.047 ^a	65 (58-72)	68 (62-72.8)	.192 ^a
Sex (male)	348 (85.5)	261 (86.4)	87 (82.9)	.371 ^b	316 (85.2)	18 (90)	.551 ^b
CCI	5 (4-6)	4.5 (3-5)	5 (4-6)	.016 ^a	5 (3-5)	5 (5-6)	.054 ^a
Smoking status				.312 ^b			.152 ^c
None	100 (24.6)	72 (23.8)	28 (26.7)		89 (24)	7 (35)	
Past smoker	241 (59.2)	185 (61.3)	56 (53.3)		223 (60.1)	8 (40)	
Active smoker	66 (16.2)	45 (14.9)	21 (20)		59 (15.9)	5 (25)	
Number of recurrences	1 (0-2)	0 (0-2)	2 (1-3)	<.001 ^a	1 (0-2)	2 (1-3)	<.001 ^a
Cystoscopy delay time (day)	30 (0-90)	30 (0-90)	90 (30-150)	<.001 ^a	30 (0-90)	91 (41-150)	<.001 ^a
Highest T stage				.041 ^c			.052 ^c
PLUMP	6 (1.5)	6 (2)	0 (0)		6 (1.6)	0 (0)	
Ta	246 (60.6)	190 (63.1)	56 (53.3)		229 (61.9)	8 (40)	
T1	154 (37.9)	105 (34.8)	49 (46.6)		135 (36.4)	12 (60)	
Highest grade				.119 ^b			.020 ^b
Low	185 (45.6)	144 (47.8)	41 (39)		172 (46.5)	4 (20)	
High	221 (54.4)	157 (52.2)	64 (61)		198 (53.5)	16 (80)	
EAU risk stratification				.003 ^b			.024 ^b
Low	71 (17.4)	64 (21.2)	7 (6.7)		69 (18.6)	0 (0)	
Intermediate	103 (25.3)	74 (24.5)	29 (27.6)		96 (25.9)	3 (15)	
High	233 (57.2)	164 (54.3)	69 (65.7)		206 (55.5)	17 (85)	
Intravesical therapy				.471 ^b			.181 ^c
None	142 (35)	102 (33.9)	40 (38.1)		131 (35.4)	6 (30)	
Postop single-dose MMC	24 (5.9)	20 (6.6)	4 (3.8)		24 (6.5)	0	
MMC	20 (4.9)	13 (4.3)	7 (6.7)		17 (4.6)	3 (15)	
BCG	220 (54.2)	166 (55.1)	54 (51.4)		198 (53.5)	11 (55)	

Abbreviations: BCG: Bacillus Calmette-Guerin, CCI: Charlson Comorbidity Index, CIS: carcinoma in situ, EAU: European Association of Urology, LVI: lymphovascular invasion, MMC: mitomycin, PUNLMP: papillary urothelial neoplasm of low malignant potential, TUR: transurethral resection.

^aMann-Whitney U -test;

^b χ^2 -test;

^cFisher's exact test.

*Continuous variables were given as median (25th-75th percentile), categorical variables were given as n (%).

Parameters	Adjusted* OR	95% CI	P value
EAU risk group (Ref: Low)			
Intermediate	2.217	0.841-5.843	.108
High	2.056	0.840-5.029	.114
Number of recurrences	1.307	1.133-1.508	<.001
Cystoscopy delay time (Ref: <62 days)			
62-147 days	2.424	1.376-4.270	.002
>147 days	4.883	2.476-9.629	<.001

Abbreviations: EAU: European Association of Urology; Ref: reference; TUR: transurethral resection.

*Adjusted for age, sex and Charlson Comorbidity Index.

TABLE 2 Risk factors of recurrence on follow-up cystoscopy

	Adjusted* OR	95% CI	P value
Low			
Number of recurrences	1.657	0.047-58.765	.782
Cystoscopy delay time (day)	1.019	1.003-1.037	.023
Intermediate			
Number of recurrences	1.725	1.204-2.471	.003
Cystoscopy delay time (day)	1.006	1.001-1.012	.045
High			
Number of recurrences	1.214	1.042-1.415	.013
Cystoscopy delay time (day)	1.008	1.004-1.013	<.001

*Adjusted for age, sex and Charlson Comorbidity Index.

TABLE 3 Risk factors for recurrences in follow-up cystoscopy according to EAU risk stratification

tumour recurrence on follow-up cystoscopy, and 20 (5.1%) patients have had tumour progression on subsequent TUR-BT.

Sex of the participants was comparable between the two groups with or without recurrence. In univariate analysis, there was a significant difference in age ($P = .047$), CCI ($P = .016$), number of recurrences ($P < .001$), follow-up cystoscopy delay time ($P < .001$), highest TUR T stage ($P = .041$) and EAU risk group ($P = .003$) between the groups with and without recurrence on follow-up cystoscopy (Table 1). Cystoscopy delay time cut-offs for recurrence were determined as 62 days and 147 days by using ROC analysis. In multivariate analysis, number of recurrences (adjusted OR: 1.307; 95% CI: 1.133-1.508; $P < .001$) and cystoscopy delay time (reference <62 days) (for 62-147 days; adjusted OR: 2.424; 95% CI: 1.376-4.270; $P = .002$) (>147 days; adjusted OR: 4.883; 95% CI: 2.476-9.629; $P < .001$) were independent risk factors of tumour recurrence on follow-up cystoscopy (Table 2). In subgroup analysis according to EAU risk group stratification, cystoscopy delay time was an independent predictor of tumour recurrence on follow-up cystoscopy in all three risk group patients. For intermediate- and high-risk tumours, the number of recurrences was also an independent risk factor for tumour recurrences (Table 3).

Age, sex and CCI were comparable between the two groups with or without progression. In univariate analysis, there was a significant difference in number of recurrences ($P < .001$), follow-up cystoscopy delay time ($P < .001$) and highest TUR grade ($P = .020$) and EAU risk group ($P = .024$) between the groups with and without tumour

progression (Table 1). Cystoscopy delay time cut-offs for progression were determined as 40 days and 90 days by using ROC analysis. In multivariate analysis, number of recurrences (adjusted OR: 1.255; 95% CI: 1.031-1.529; $P = .024$) and cystoscopy delay time (reference <40 days) (>90 days; adjusted OR: 6.704; 95% CI: 1.973-22.780; $P = .002$) were independent risk factors of tumour progression (Table 4).

4 | DISCUSSION

During the COVID-19 pandemic, many diagnostic, therapeutic or surveillance procedures, such as cystoscopy, had to be postponed. In addition to this, some patients did not apply to the hospital because of stay-at-home advisories despite the necessity of cancer surveillance. In these times, many urological societies published roadmaps for urologists about deferrable or non-deferrable diseases, especially in the area of uro-oncology. General recommendations about surveillance cystoscopy were that, if patients have low-risk tumours, follow-up cystoscopy can be safely postponed, but, in high-risk patients, more caution must be taken about delaying.^{7,8} However, these suggestions mostly depend on expert opinions, and it is not known how much delay can negatively affect our oncologic outcomes.

In this study, we evaluated the impact of delay of follow-up cystoscopy in patients with NMIBC. Our investigations and analyses

TABLE 4 Risk factors of progression

Parameters	Adjusted* OR	95% CI	P-value
The highest grade (Ref: Low)			
High	2.087	0.642-6.787	.222
Number of recurrences			
	1.255	1.031-1.529	.024
Cystoscopy delay time (Ref: <40 days)			
40-90 days	2.689	0.724-9.986	.140
>90 days	6.704	1.973-22.780	.002

Abbreviations: Ref: reference; TUR: transurethral resection.

*Adjusted for age, sex and Charlson Comorbidity Index.

showed that a 2-5 months of delay in follow-up cystoscopy increases the risk of recurrence by 2.4-fold, and a delay in cystoscopy for more than 3 months increases the probability of progression by 6.7-fold. Subgroup analysis revealed that the increased risk for recurrence caused by the delay in cystoscopy was valid in all three risk groups. In intermediate- and high-risk patients, the number of recurrences was also the significant predictor of recurrence.

Patients with low-risk NMIBC have an approximately 30% recurrence rate in the 5-year follow-up, but, despite high recurrence rates, they have progression rates under 2%.³ Because of the very low progression rates, active surveillance protocols have been studied in this patient cohort.⁹ Hernandez et al designed a prospective study and included patients with NMIBC in an active surveillance program. They followed up 186 patients with a median of 72 months and stated that only 4 (2%) patients had progression to MIBC, but all of them previously had T1 disease.¹⁰ Similarly, Hurle et al reported that there was no progression to MIBC in their active surveillance study, which included 122 Ta-T1a patients.¹¹ Because of these findings, many experts state that cystoscopy follow-ups may be delayed in low-risk NMIBC. In our study, we found that delayed follow-up cystoscopy in low-risk disease significantly increases recurrence rates. However, in our cohort, there were no patients with low-risk disease that showed progression.

In contrast with the low-risk diseases, high-risk NMIBC has high progression rates up to 45%.³ Because of the high recurrence and especially on account of the progression rates, many urological associations and societies suggest not to defer follow-up cystoscopy.¹² In routine practice, we perform follow-up cystoscopy every 3 months in the first 2 years to detect recurrences at a more curable stage. In a recent study, Rezaee et al investigated the impact of low (1-5 cystoscopies in the first 2 years) versus high (6 or more cystoscopies in the first 2 years) intensity follow-up cystoscopy in patients with NMIBC. They reported that patients with low-intensity surveillance underwent fewer TURs (37 vs 99 per 100 person-years; $P < .001$). They did not, however, experience an increased risk of progression.¹³ In contrast to this study, we found a significant risk increase in progression rates with a 3-month delay in NMIBC. Consequently, we support the recommendations not to delay follow-up cystoscopy in patients with NMIBC.

To our knowledge, this is the first study investigating the impact of delay in follow-up cystoscopy on oncological outcomes.

Previously, Wallace et al studied the impact of delays in the diagnosis and treatment of patients with primary urothelial cancer and concluded that the negative impact of delay seems to be most pronounced for patients with pT1 tumours.¹⁴ In another study, Ngo B et al reported a median of 38 days from general practitioner (GP) referral to urology consultation and 28 days from urology consultation to cystoscopy. In this analysis, patients with visible haematuria (vs non-visible haematuria) and suspicious findings on imaging (vs none/not done) had a shorter time interval from GP referral to urology consultation.¹⁵

Our study has several limitations that should be noted. First, we only had a small number of patients with progression, and, because of this limitation, we could not evaluate the impact of delay in follow-up cystoscopy for progression by EAU risk group. Second, we have a limited follow-up time, which did not allow us to do a survival analysis. We could not analyse the impact of delay in cystoscopy for cancer-specific or overall survival. However, we think that this study provides evidence-based data on not delaying cystoscopy, these days when the pandemic is still ongoing; therefore, we did not prolong our follow-up for cancer specific or overall survival analyses.

5 | CONCLUSIONS

In our analysis, it is demonstrated that a 2-5 months of delay in follow-up cystoscopy increases the risk of recurrence by 2.4-fold, and delay in cystoscopy for more than 3 months increases the probability of progression by 6.7-fold. As a consequence of these findings, we suggest that cystoscopic surveillance for NMIBC should be done in as timely a manner as possible according to the relevant guidelines during the COVID-19 pandemic.

DISCLOSURES

All authors declare that they have no conflict of interest.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

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