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. In newly diagnosed patients with BC, approximately 75% of patients have non-muscle-invasive bladder cancer (NMIBC) (Ta, T1 or carcinoma in situ [CIS]). 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. 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.\(^5\)

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.\(^5\)

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 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, \(\chi^2\)-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 ≤ .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 | Progression |
|---------------------|---------|------------|-------------|
|                     | (n = 407) | Without (n = 302) | With (n = 105) | P value |
|                     | (n = 371) | Without (n = 371) | With (n = 20) | P value |
| Age (year)          | 65 (59-72) | 65 (58.8-71.3) | 66 (59.5-74.5) | .047^ |
|                     | 65 (58.72) | 68 (62-72.8) | .192^ |
| Sex (male)          | 348 (85.5) | 261 (86.4) | 87 (82.9) | .371^- |
| CCI                 | 5 (4-6) | 4.5 (3-5) | 5 (4-6) | .016^- |
| Smoking status      | .312^ |
| None                | 100 (24.6) | 72 (23.8) | 28 (26.7) | .192^ |
| Past smoker         | 241 (59.2) | 185 (61.3) | 56 (53.3) | .192^ |
| Active smoker       | 66 (16.2) | 45 (14.9) | 21 (20) | .192^ |
| Number of recurrences | 1 (0-2) | 0 (0-2) | 2 (1-3) | .001^ |
| Cystoscopy delay time (day) | 30 (0-90) | 30 (0-90) | 90 (30-150) | .001^- |
| Highest T stage     | .041^- |
| PLUMP               | 6 (1.5) | 6 (2) | 0 (0) | .192^ |
| Ta                  | 246 (60.6) | 190 (63.1) | 56 (53.3) | .192^ |
| T1                  | 154 (37.9) | 105 (34.8) | 49 (46.6) | .192^ |
| Highest grade       | .119^- |
| Low                 | 185 (45.6) | 144 (47.8) | 41 (39) | .192^ |
| High                | 221 (54.4) | 157 (52.2) | 64 (61) | .192^ |
| EAU risk stratification | .003^- |
| Low                 | 71 (17.4) | 64 (21.2) | 7 (6.7) | .192^ |
| Intermediate        | 103 (25.3) | 74 (24.5) | 29 (27.6) | .192^ |
| High                | 233 (57.2) | 164 (54.3) | 69 (65.7) | .192^ |
| Intravesical therapy | .471^- |
| None                | 142 (35) | 102 (33.9) | 40 (38.1) | .192^ |
| Postop single-dose MMC | 24 (5.9) | 20 (6.6) | 4 (3.8) | .192^ |
| MMC                 | 20 (4.9) | 13 (4.3) | 7 (6.7) | .192^ |
| BCG                 | 220 (54.2) | 166 (55.1) | 54 (51.4) | .192^ |

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

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. 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 2: Risk factors of recurrence on follow-up cystoscopy

| 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| $<.001$   |

*Adjusted for age, sex and Charlson Comorbidity Index.

### Table 3: Risk factors for recurrences in follow-up cystoscopy according to EAU risk stratification

| Parameters                              | 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.

**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. 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
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%. Because of the very low progression rates, active surveillance protocols have been studied in this patient cohort. 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. Similarly, Hurle et al reported that there was no progression to MIBC in their active surveillance study, which included 122 Ta–T1a patients. 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%. 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. 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, Rezaei 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. 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. In another study, Ngo 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.

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 of overall survival 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.

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 a timely 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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REFERENCES
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7-30.
2. Burger M, Catto JWF, Dalbagni G, et al. Platinum priority—review—bladder cancer epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013;63:234-241.
3. Sylvester RJ, van der Meijden APM, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol. 2006;49:466-477.
4. Soukup V, Čapoun O, Cohen D, et al. Risk stratification tools and prognostic models in non–muscle-invasive bladder cancer: a critical assessment from the European Association of Urology Non-muscle-invasive Bladder Cancer Guidelines Panel. Eur Urol Focus. 2020;6:479-489.
5. EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam; 2020.
6. Schroeck FR, Lynch KE, Chang JW, et al. Extent of risk-aligned surveillance for cancer recurrence among patients with early-stage bladder cancer. JAMA Netw open. 2018;1:1-12.
7. Wallis CJD, Novara G, Marandino L, et al. Risks from deferring treatment for genitourinary cancers: a collaborative review to aid triage and management during the COVID-19 pandemic. Eur Urol. 2020;78:29-42.
8. Tachibana I, Ferguson EL, Mahenthiran A, et al. Delaying cancer cases in urology during COVID-19: review of the literature. J Urol. 2013;10:1-13.
9. Marcq G, Hénon F, Ouzaid I, Fantoni JC, Hermieu JF, Xylinas E. Active surveillance for non-muscle invasive bladder cancer. Transl Androl Urol. 2019;8:54-60.
10. Hernández V, Llorente C, de la Peña E, Pérez-Fernández E, Guijarro A, Sola I. Long-term oncological outcomes of an active surveillance program in recurrent low grade Ta bladder cancer. Urol Oncol. 2016;34:165.e19-165.e23. https://doi.org/10.1016/j.urolonc.2015.11.005
11. Hurle R, Pasini L, Lazzeri M, et al. Active surveillance for low-risk Non-Muscle Invasive Bladder Cancer (NMIBC): a confirmatory and resource consumption study from Bladder cancer Italian Active Surveillance (BIAS) project. J Urol. 2018;192:401-406.
12. Amparore D, Campi R, Checcucci E, et al. Forecasting the future of urology practice: a comprehensive review of the recommendations by International and European Associations on priority procedures during the COVID-19 pandemic. Euro Urol Focus. 2020;6:1032-1048. https://doi.org/10.1016/j.euf.2020.05.007
13. Rezaee ME, Lynch KE, Li Z, et al. The impact of low- versus high-intensity surveillance cystoscopy on surgical care and cancer outcomes in patients with high-risk non-muscle-invasive bladder cancer (NMIBC). PLoS One. 2020;15:1-13. https://doi.org/10.1371/journal.pone.0230417
14. Wallace DMA, Bryan RT, Dunn JA, Begum G, Bathers S. Delay and survival in bladder cancer. BJU Int. 2002;89:868-878.
15. Ngo B, Papa N, Perera M, Bolton D, Sengupta S. Predictors of delay to cystoscopy and adequacy of investigations in patients with haematuria. BJU Int. 2017;119:19-25.

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