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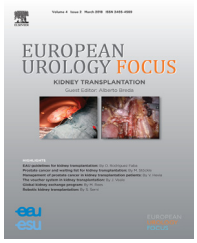

Bladder Cancer

Prognostic Implications of Treatment Delays for Patients with Non–muscle-invasive Bladder Cancer

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Abstract

Background: Delay in treatment is a prognostic factor in muscle-invasive bladder cancer.
Objective: To evaluate clinical outcomes associated with delays in diagnosis and treatment for patients with non–muscle invasive bladder cancer (NMIBC).
Design, setting, and participants: In this retrospective study we analyzed data for patients treated at our center between November 2008 and December 2016 for intermediate risk (IR) or high risk (HR) NMIBC with an additional intravesical treatment.
Outcome measurements and statistical analysis: Time delays from diagnosis to first transurethral resection (TT-TUR), from resection to restaging resection (TT-reTUR), and from the last resection to first instillation (TT-INST) of bacillus Calmette-Guérin (BCG) or mitomycin C (MMC) were documented. To identify the interval of time from which recurrence rates significantly increased, we used nonparametric series regression. Recurrence-free survival (RFS) and progression-free survival for patients in each time delay category were compared using the Kaplan-Meier method. Factors associated with tumor recurrence were analyzed in a multivariable model.
Results and limitations: A total of 434 patients were included, of whom 168 (38.7%) had IR and 266 (61.3%) had HR NMIBC. Among the patients, 34.6% had reTUR, 63.6% received BCG, and 36.4% received MMC. The median TT-TUR, TT-reTUR, and TT-INST was 4.0 wk, 6.5 wk, and 7.0 wk, respectively. At 40 mo the rate of recurrence was 28.4% and the rate of progression was 7.3%. Nonparametric analysis revealed that each week in delay increased the risk of recurrence, starting from week 6 for TT-TUR for IR and HR cases, and starting from week 7 for TT-INST for IR cases. RFS was significantly lower with TT-TUR $>$ 6 wk among patients in the IR ($p < 0.001$) and HR ($p = 0.04$) groups, and with TT-INST $>$7 wk for patients in the IR group ($p = 0.001$). TT-reTUR $>$7 wk had a significant negative impact on progression ($p < 0.017$). Multivariable analysis revealed that for IR and HR cases, multifocality ($p = 0.02$ and $p = 0.007$) and TT-TUR $>$6 wk ($p = 0.001$ and $p = 0.03$) were independent predictors of recurrence, while TT-INST $>$7 wk predicted recurrence ($p = 0.04$) for IR NMIBC.
Conclusions: Our results suggest that delays of $>$6 wk to first TUR in IR and HR NMIBC, and $>$7 wk to first instillation in IR cases are associated with increases in the risk of recurrence. TT-reTUR of $>$7 wk is also associated with higher risk of progression.
Patient summary: We evaluated the impact of treatment delays on outcomes for patients with intermediate- and high-risk bladder cancer not invading the bladder wall muscle. We found that delays from diagnosis to first bladder resection, from first

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resection to repeat resection, and from last resection to bladder instillation treatment increase the rates of cancer recurrence and progression. The medical team should avoid delays in treatment, even for low-grade bladder cancer.

1. Introduction

Worldwide, bladder cancer is the sixth most frequent cancer among men [1]. At the time of diagnosis, approximately 80% of bladder tumors are non–muscle invasive bladder cancer (NMIBC) [2]. However, up to 60% of these patients will experience relapse in the first year and in 10–20% their cancer will progress to muscle-invasive (MIBC) and/or metastatic disease [3]. Therefore, additional measures such as second-look resection [4–7] and adjuvant intravesical chemotherapy or bacillus Calmette-Guérin (BCG) for intermediate-risk (IR) and high-risk (HR) NMIBC is recommended [2]. As demonstrated for lung cancer and other fast-growing cancers, delays in confirming the diagnosis and starting treatment can impact prognosis [8]. For bladder cancer, it has been reported that a delay of >3 mo between endoscopic resection and radical cystectomy without neoadjuvant chemotherapy has a negative impact on survival [9–11]. In addition, in the case of very high-risk NMIBC and nonresponders to BCG, early radical cystectomy improves the disease-specific survival at 10 yr [12–14]. Further retrospective studies have found that delays in the provision of care, namely from symptoms to clinical endoscopic confirmation, impact negatively on survival [15–17]. In the case of NMIBC, for which local recurrence and progression are the main outcome events, the time to treatment that should be respected is not clearly defined. The aim of the present study was to identify the time intervals from diagnosis to transurethral resection (TT-TUR) of the primary tumor, from TUR to restaging resection (TT-reTUR), and from the last TUR to intravesical instillation (TT-INST) from which the rates of cancer recurrence and progression increase.

2. Patients and methods

The retrospective cohort for the study was identified using a local bladder cancer registry after approval by our institutional review board. All patients treated at our center between November 2008 and December 2016 for IR or HR NMIBC (according to the European Association of Urology [EAU] risk classification [2]) with at least 1 yr of follow-up were selected. Patients at very high risk of progression (multifocal high-grade [HG] pT1 with carcinoma in situ, HG pT1 with lymphovascular invasion, HG pT1 with prostatic invasion) who underwent immediate radical cystectomy, those with variant bladder tumor histology, patients with no adjuvant intravesical therapy, and those with active upper-urinary tract tumor were excluded. All TUR procedures were performed in our urology department and bladder samples were analyzed by the pathology department. As recommended, reTUR was performed in pT1 cases [2,18]. Patients with reTUR beyond 3 mo were excluded. Early postoperative instillation of intravesical chemotherapy is not performed at our center. Patients with HR NMIBC are treated with intravesical BCG unless contraindicated, in which case intravesical mitomycin C (MMC) is given. As recommended, IR patients had either BCG or MMC [2,18]. Intravesical BCG (Connaught strain) included an induction course (six instillations weekly) followed by maintenance (three instillations weekly at 3, 6, 12, 18, 24, 30, and 36 mo) at full dose (81 mg) [19]. During the BCG shortage (2013–2016), BCG instillation was limited to HR patients with no maintenance therapy (decision taken by the French medicine agency, ANSM). There was no dose reduction during the shortage. Intravesical MMC included a series of eight weekly 40-mg instillations. Patients were followed with cystoscopy and urine cytology at 3 and 6 mo, then every 3–6 mo for 2 yr, and thereafter according to a regimen adapted for the risk of recurrence. Recurrence was defined as the occurrence of a bladder tumor confirmed by histology. Progression was defined as tumor recurrence with muscle invasion (MIBC) or metastatic disease or NMIBC recurrence with very high-risk features requiring cystectomy.

2.1. Statistical analysis

Continuous variables are summarized using the number of patients, median, and interquartile range (IQR). Discrete variables are summarized using the frequency and proportion. Patients were categorized according to tumor stage, grade, EAU prognostic factor risk classification, and whether or not they had reTUR. TT-TUR was the time from diagnosis (cystoscopy or ultrasound or computed tomography) to primary TUR; TT-reTUR was the time from first TUR to reTUR; and TT-INST was the time from last TUR to first bladder instillation.

The Kruskal-Wallis test followed by Dunn's test was used to assess differences across quartiles for time intervals in the IR and HR groups.

In addition, to identify the time from which recurrence rates significantly increased, we used nonparametric series regression for nonparametric estimation of the recurrence rate as a function of the time interval [20].

The TT-TUR, TT-reTUR, and TT-INST quartiles beyond which recurrence significantly increased were used to dichotomize patients as having a significant delay or not. Variables significantly associated with recurrence-free survival (RFS) according to the log-rank test were included in a multivariable Cox proportional-hazards model. The proportion of patients with RFS and progression-free survival (PFS) was compared using the Kaplan-Meier method for each time delay category. Statistical analyses were carried out for the whole population and in subgroups (IR vs HR) using Stata v15 (StataCorp LLC, College Station, TX, USA).

3. Results

A total 810 patients were treated for bladder cancer at our institution from 2008 to 2016, of whom 434 with IR or HR NMIBC who received adjuvant intravesical therapy were included in the present analysis (Fig. 1). According to the EAU risk classification, 168 patients (38.7%) had IR NMIBC and 266 (61.3%) had HR NMIBC. ReTUR was performed in 150 patients (34.6%), 4/168 IR patients (2.4%) and 146/266 (54.9%) HR patients. The post-TUR treatment was bladder instillation of BCG for 276 patients (63.6%), of whom 151 (54.7%) completed at least 1 yr of maintenance treatment.

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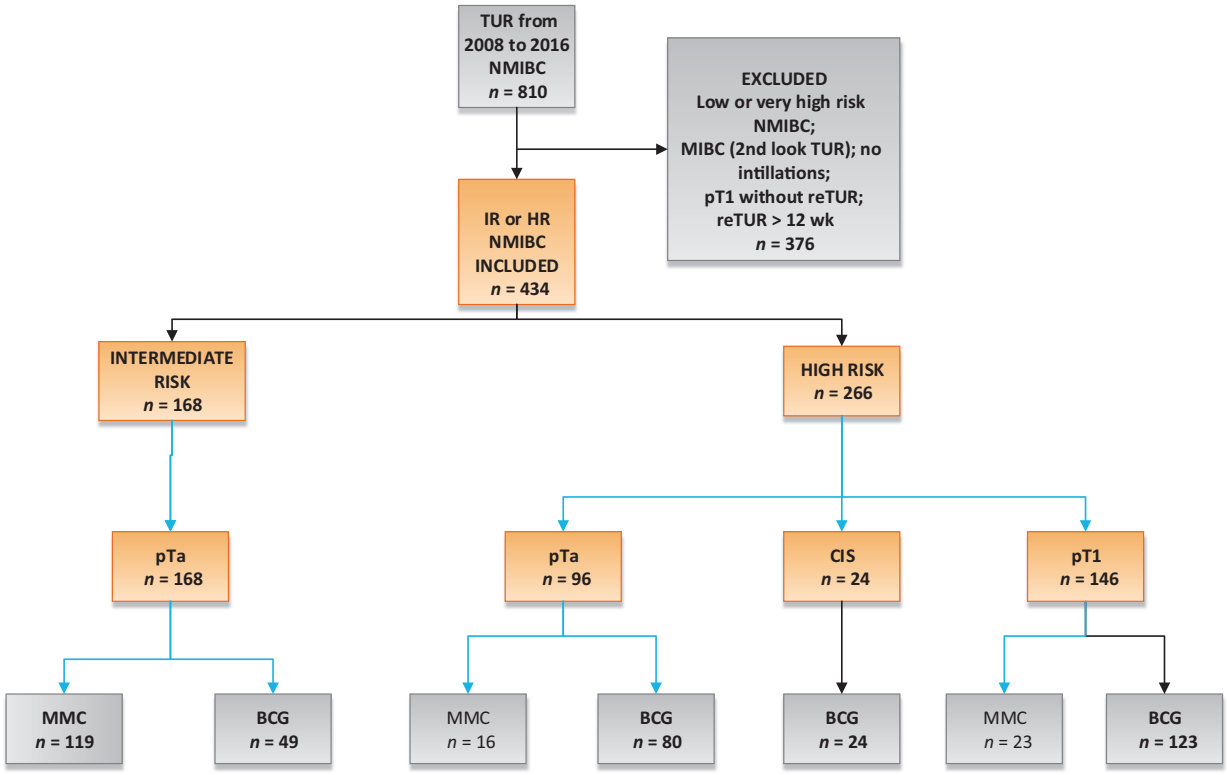

Fig. 1 – Consort diagram. BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; HR = high risk; IR = intermediate risk; MIBC = muscle-invasive bladder cancer; MMC = mitomycin C; NMIBC = non–muscle-invasive bladder cancer; reTUR = repeat TUR; TUR = transurethral resection.

The remaining patients were treated with MMC (n = 158, 36.4%; Table 1).

The median TT-TUR was 4.0 wk (IQR 3), the median TT-reTUR was 6.5 wk (IQR 3.3), and the median TT-INST was 7.0 wk (IQR 6.1). At median follow-up of 40.6 mo (IQR 39.7), the incidence of bladder tumor recurrence was estimated to be 28.4% (95% confidence interval [CI] 24.8–32.1%) and the incidence of bladder tumor progression was 7.3% (95% CI 6.3–10.4%; Table 1). The median follow-up was 41.8 mo (IQR 39.9) for IR patients and 39.9 mo (IQR 40.5) for HR patients.

Nonparametric regression analysis (cubic spline) revealed that for TT-TUR, each week of delay increased the risk of recurrence, starting from week 5 for IR patients and from week 6 for HR patients (Fig. 2A). For TT-INST, there was an increase in the rate of recurrence with each additional week starting from week 7 for IR patients. There was no impact of a delay to instillation for HR patients (Fig. 2B).

In multivariable analyses, EAU risk group (p = 0.015), tumor size >3 cm (p = 0.03), multifocality ($p < 0.01$), TT-TUR >6 wk ($p < 0.001$), and TT-INST >7 wk (p = 0.02) independent predictors of recurrence. In subgroup analyses, the independent predictors of recurrence were multifocality (IR: p = 0.02; HR: p = 0.007) and TT-TUR >6 wk (IR: p = 0.001; HR: p = 0.03) for the IR and HR groups, and TT-INST >7 wk (p = 0.04) for the IR group (Table 2).

RFS was significantly lower for TT-TUR > 6 wk for the IR ($p < 0.001$) and HR groups (p = 0.04; Fig. 3A), and for TT-INST >7 wk for the IR group (p = 0.001; Fig. 3C). Regarding progression, TT-reTUR >7 wk had a significant negative impact ($p < 0.017$; Fig. 3B).

Interquartile analysis for TT-TUR revealed that recurrence was significantly more frequent in the last quartile (>6 wk) than in the first three quartiles (≤6 wk) for the IR ($p < 0.001$) and HR groups ($p < 0.01$; Fig. 4A). Regarding TT-reTUR, progression was significantly more frequent in the last two quartiles (≥7 wk; p = 0.01; Fig. 4B). The rate of recurrence increased significantly with TT-INST after 8 wk for IR patients ($p < 0.001$; Fig. 4C).

4. Discussion

The data show that delays in the provision of care for IR and HR NMIBC patients have a negative impact on bladder cancer outcomes, defined here as the time to bladder tumor recurrence and progression. The results indicate that a delay of >6 wk from diagnosis to TUR was associated with a higher recurrence rate for IR and HR patients. A delay of >7 wk from TUR to bladder instillation was associated with higher risk of recurrence for IR patients. A delay to first instillation had no impact on recurrence for HR NMIBC patients. For these patients, the impact of reTUR [4,7], the type of bladder instillation (BCG), and BCG maintenance treatment of >1 yr [21,22] on oncological outcomes outweighs the effect of the delay in initiation of first instillation.

While the rate of progression was higher among HR patients, the rate of recurrence for this group was slightly

Table 1 – Patient characteristics at the time of diagnosis

Variable	EAU bladder risk classification		Total
	Intermediate risk	High risk	
Patients, *n* (%)	168 (38.7)	266 (61.3)	434 (100)
Median age, yr (IQR)	69 (14)	70 (12)	69.4 (14)
Sex, *n* (%)			
Male	139 (82.7)	240 (90.2)	379 (87.4)
Female	29 (17.3)	26 (9.8)	55 (12.6)
Tumor stage, *n* (%)			
pTa	168 (100)	96 (36)	264 (60.8)
pT1		146 (54.9)	146 (33.7)
Carcinoma in situ		24 (9.1)	24 (5.5)
Grade			
Grade 1–2	168 (100)		168 (38.7)
Grade 3		266 (100)	266 (61.3)
Tumor size, *n* (%)			
<3 cm	101 (60.1)	190 (71.9)	291 (67)
>3 cm	67 (39.9)	76 (28.1)	143 (33)
Number of tumors, *n* (%)			
Single	80 (47.6)	210 (79.1)	290 (66.8)
Multiple	88 (52.4)	56 (20.9)	144 (33.2)
Primary tumor, *n* (%)			
Yes	116 (69)	230 (86.4)	346 (79.7)
No (recurrence)	52 (31)	36 (13.6)	88 (20.3)
Repeat TUR, *n* (%)	4 (2.4)	146 (54.9)	150 (34.6)
Bladder instillations, *n* (%)			
Bacillus Calmette-Guérin therapy	49 (29.2)	227 (85.3)	276 (63.6)
Mitomycin C	119 (70.8)	39 (14.7)	158 (36.4)
Median time to TUR, wk (IQR)	4.35 (3)	3.8 (2.8)	4.0 (3)
Median time to repeat TUR, wk (IQR)	3.7 (2.1)	6.7 (3.1)	6.5 (3.3)
Median time to instillation, wk (IQR)	8.1 (5.9)	6.8 (5.8)	7 (6.1)
Bladder cancer recurrence, *n* (%)	52 (30.9)	71 (26.7)	123 (28.4)
Bladder cancer progression, *n* (%)	6 (3.6)	26 (9.8)	32 (7.3)
Cystectomy, *n* (%)	6 (3.6)	23 (8.6)	29 (6.7)

EAU = European Association of Urology; IQR = interquartile range; TUR = transurethral resection.

lower than for the IR group. This may be related to (1) the exclusion of a population with more aggressive tumors (patients with very high-risk NMIBC who underwent radical cystectomy) and (2) the definition of progression as NMIBC recurrence with very high-risk features requiring cystectomy. Finally, 85% of HR patients had BCG therapy, compared with 30% of IR patients. The superiority of intravesical BCG therapy over chemotherapy may explain this effect [21]. The higher recurrence rate in the IR group is even more significant when there is a delay in management. Hollenbeck et al [15] observed a stronger effect of delayed management for patients with low-stage LG disease.

For patients who had reTUR, mainly HR NMIBC, a delay of >7 wk between the primary TUR and second-look TUR was associated with lower PFS, as already demonstrated in other studies [5,23]. Finally, no impact was seen of time to first resection and time to instillation on progression, which may be related in part to the small number of patients who had progressed.

Previous studies have shown that a short time between the first symptom and initial examination increases disease-specific survival in bladder cancer. For instance, in a registry based study on 1537 patients treated for bladder cancer in the West Midlands in 1991, Wallace et al [16] found a mean delay of 68 d from general practitioner (GP) referral to TUR. The authors found that only the delay from symptoms to GP referral was associated with worse survival; however, all stages of bladder cancer were included (pTa, pT1, ≥pT2) [16]. In a more recent large review of the literature, Fahmy et al [11] concluded that the majority of studies showed that delays in care for bladder cancer were associated with worse outcomes. In a large cohort of 29 740 patients from the Surveillance, Epidemiology and End Results database, Holenbech et al [15] found that after a delay of 9 mo from hematuria to treatment, patients were more likely to die from bladder cancer when compared to patients treated within 3 mo (hazard ratio 1.34, 95% CI). The risk was not attenuated after adjusting for disease stage and tumor grade [15]. Overall, these studies suggest that to achieve a fair evaluation of delays of care and bladder cancer outcomes, analysis should distinguish between NMIBC and MIBC. Nonparametric analysis confirmed that the increase in the rate of recurrence started at TT-TUR of 6 wk in IR and HR NMIBC and TT-INST of 7 wk in IR NMIBC. We believe that these observations will help in developing further recommendations for the timing of TUR and when to start bladder instillations.

The impact of treatment delays has been studied for various pathologies, especially in cancer [24–26]. Several studies found an association between treatment delay and prognosis and identified different reasons [26,27]. We can distinguish social delay, which lengthens the time to diagnosis of a disease and depends on factors that include lack of medical insurance, low educational and socioeconomic

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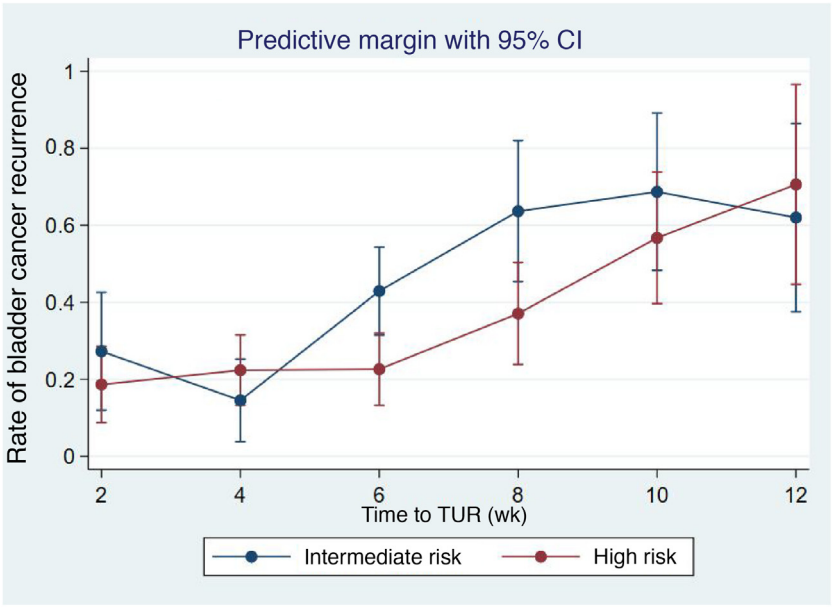

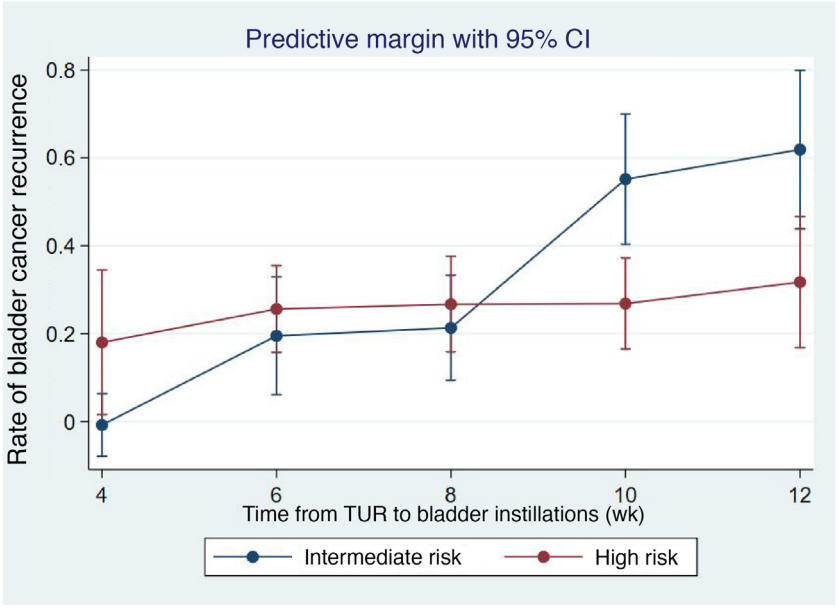

Fig. 2 – Cubic spline nonparametric regression diagram showing the rate of recurrence according to (A) time to TUR and (B) time from last TUR to instillations; predictive margins for time to repeat TUR are not presented as they were not significant ($p = 0.34$). CI = confidence interval; TUR = transurethral resection. The analysis shows that for time to TUR, each week of delay increased the risk of recurrence, starting from week 5 for intermediate risk patients, and from week 6 for high risk patients. Starting from week 7, each additional week in time to bladder instillations increased the risk of recurrence for intermediate risk patients. There is no impact of delayed instillation for high risk patients.

status, and sometimes a lack of information on cancer-related symptoms or patient denial despite alarming symptoms such as total hematuria [28,29]. The impact of a social delay can be reduced via information and screening campaigns. Unlike a social delay, a medical delay is more flexible and can be partly under the practitioner's control and therefore be optimized.

Today we are facing a health crisis caused by the COVID-19 pandemic and a similar situation could recur in the years to come. The health system may be overwhelmed and measures of triage and selection for surgery may be taken [30]. While data on the impact of delayed treatment in MIBC are robust [9–11], there is limited evidence on the impact of delayed management of NMIBC [4,5,16]. The results presented here support the hypothesis that delays in treatments for IR and HR NMIBC should be avoided, since they are associated with worse oncological outcomes, except for a delay to bladder instillation in HR NMIBC.

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Table 2 – Univariable and multivariable time analysis of factors associated with tumor recurrence in IR NMIBC, HR NMIBC, and all NMIBC cases [a]

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
All NMIBC patients (*n* = 434; tumor recurrence *n* = 123)				
Age (<75 vs ≥75 yr)	1.30 (0.97–2.05)	NS	1.02 (0.98–1.84)	NS
EAU bladder risk classification (IR vs HR)	1.80 (1.05–3.3)	0.01	1.32 (1.1–2.48)	0.015
Tumor grade (low vs high)	1.69 (0.64–2.29)	NS	1.59 (0.79–1.78)	NS
Tumor stage (pT1 or CIS vs pTa)	1.37 (0.67–3.22)	NS	1.29 (0.54–2.15)	NS
Recurrence (yes vs no)	1.48 (1.03–2.11)	0.03	1.36 (0.93–1.97)	NS
Tumor size (<3 vs >3 cm)	1.4 (1.08–2.32)	0.03	1.60 (1.04–2.46)	0.03
Tumor multifocality (single vs multiple)	1.88 (1.31–2.7)	0.001	1.68 (1.15–2.44)	<0.01
Time from diagnosis to TUR (wk)	1.46 (1.02–1.06)	<0.001	1.02 (0.98–1.05)	NS
Time from diagnosis to TUR (<6 vs ≥6 wk)	2.15 (1.2–3.06)	<0.001	1.84 (1.20–2.84)	< 0.001
Time from TUR to BI (wk)	1.00 (0.96–1.04)	NS	1.00 (0.99–1.10)	NS
Time from TUR to BI (<7 vs ≥7 wk)	1.46 (1.01–2.10)	0.04	1.38 (1.1–2.23)	0.02
Intermediate-risk NMIBC (*n* = 168; tumor recurrence *n* = 52)				
Age (<75 vs ≥75 yr)	1.22 (0.67–2.21)	NS	1.02 (0.89–1.05)	NS
Recurrence (yes vs no)	1.22 (0.70–2.14)	NS	1.04 (0.64–1.97)	NS
Tumor size (<3 vs >3 cm)	1.89 (0.97–3.69)	NS	1.72 (0.82–3.60)	NS
Tumor multifocality (single vs multiple)	1.63 (1.21–2.89)	0.01	1.29 (1.69–2.32)	0.02
Time from diagnosis to TUR (wk)	1.46 (1.07–1.7)	<0.001	1.02 (0.98–1.05)	NS
Time from diagnosis to TUR (<6 vs ≥6 wk)	3.66 (2.12–6.32)	<0.001	1.92 (1.34–2.76)	0.001
Time from TUR to BI (wk)	1.88 (1.21–2.12)	0.01	1.9 (1.29–2.35)	0.04
Time from TUR to BI (<7 vs ≥7 wk)	2.64 (1.43–4.88)	0.04	1.70 (0.86–3.37)	NS
High-risk NMIBC (*n* = 266; tumor recurrence *n* = 71)				
Age (<75 vs ≥75 yr)	1.12 (0.89–1.05)	NS	1.02 (0.98–1.04)	NS
Tumor stage (pT1 or CIS vs pTa)	0.87 (0.6–1.28)	NS	0.8 (0.53–1.24)	NS
Recurrence (yes vs mo)	1.68 (1.05–2.6)	0.02	1.44 (0.88–2.35)	NS
Tumor size (<3 vs >3 cm)	1.12 (0.66–1.89)	NS	1.47 (0.84–2.57)	NS
Tumor multifocality (single vs multiple)	2.1 (1.31–3.34)	0.002	1.96 (1.19–3.21)	0.007
Time from diagnosis to TUR (wk)	1.2 (1.05–1.31)	0.03	1.02 (0.93–1.50)	NS
Time from diagnosis to TUR (<6 vs ≥6 wk)	1.95 (1.13–3.63)	0.01	1.82 (1.7–2.31)	0.03
Time from TUR to BI (wk)	1.08 (0.93–1.12)	NS	1.02 (0.95–1.12)	NS
Time from TUR to BI (<7 vs ≥7 wk)	0.95 (0.6–1.91)	NS	1.00 (0.73–1.45)	NS

BI = bladder instillation; CI = confidence interval; CIS = carcinoma in situ; EAU = European Association of Urology; HR = high risk; IR = intermediate risk; NMIBC = non–muscle-invasive bladder cancer; NS = not significant; TUR = transurethral resection.

[a] In multivariable analysis, the independent predictors of recurrence were the EAU bladder risk classification, tumor size >3 cm, multifocality, time to TUR >6 wk, and time to instillation >7 wk. In subgroup analysis, the independent predictors of recurrence were multifocality and time to TUR >6 wk for IR and HR NMIBC, and time to bladder instillation for IR NMIBC. No analysis was performed for progression because of the low number of events.

Our study has several limitations that should be mentioned. Owing to insufficient follow-up and a low number of patients who experienced disease progression, the impact of a delay in care for NMIBC on specific survival cannot be fairly evaluated.

We do not perform postoperative instillation of intravesical chemotherapy owing to organizational and infrastructural difficulties in our department, but we are in the process of implementing this practice. We recognize that this is a limitation in our practice and our study, especially for the intermediate risk population. However, continuous saline irrigation is systematically performed for at least 16 h postoperatively to reduce the risk of early recurrence [31].

Some 55% of our HR population had a second-look resection; this is related to the absence of resection in the case of HG pTa according to the EAU [2]. Only 53% of patients who received bladder instillation of BCG had at least 1 yr of treatment. This is explained by the shortage of BCG during 2013–2016 [32] (when most HR patients only had induction treatment), intolerance to BCG [33], and poor patient compliance. The BCG shortage affected our cohort by increasing the recurrence and progression rates [32].

The absence of detrusor muscle in TUR specimens was not reported, which is a well-recognized predictor of recurrence for HR NMIBC, while it plays a negligible role in recurrence for patients with LG Ta NMIBC [34]. However, these patients had a second-look resection.

No analysis of the delay from time of symptom onset to diagnosis could be carried out because of the retrospective nature of the study, as the type of symptoms and the precise timing of their appearance are missing. This is an important limitation of our study, as the true time to care may be misjudged, since this delay is a known prognostic factor [16].

The ranges for the treatment delays are wide; however, this allowed us to observe the effect of delayed management on oncological outcomes. The reasons for important delays are mainly related to social factors (poor compliance). In addition, delays to first bladder instillation are related to persistent side effects after TUR or associated comorbidities.

A clear identification of the causes of delays could help to identify and implement corrective measures and facilitate or accelerate access to care from the first consultation to TUR and to bladder instillations.

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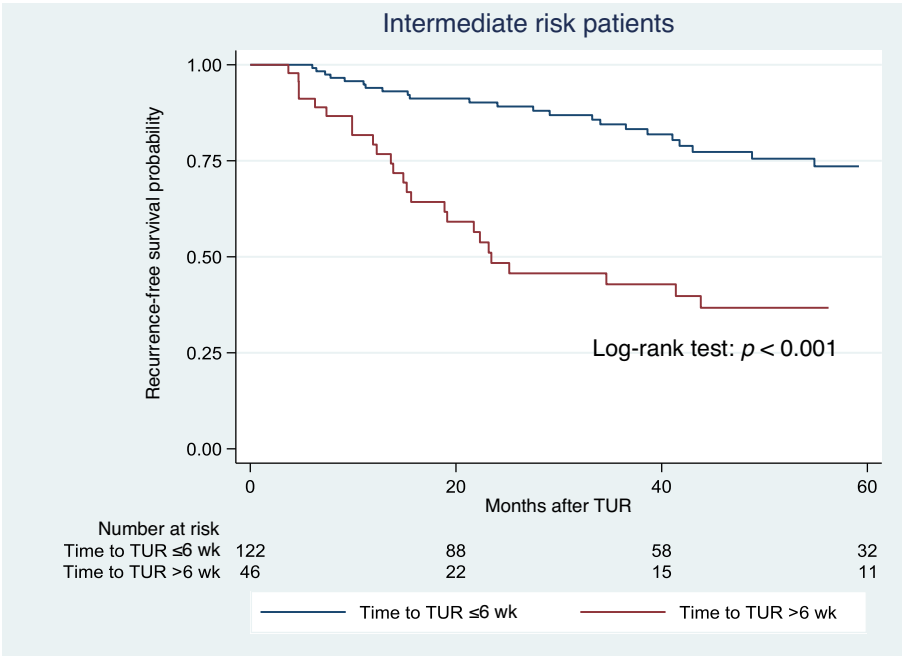


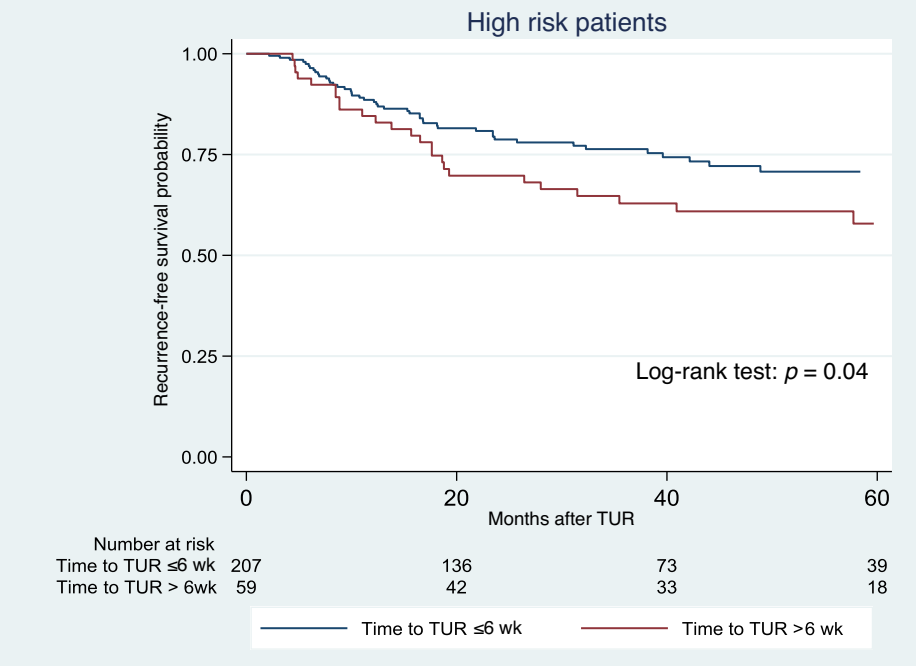
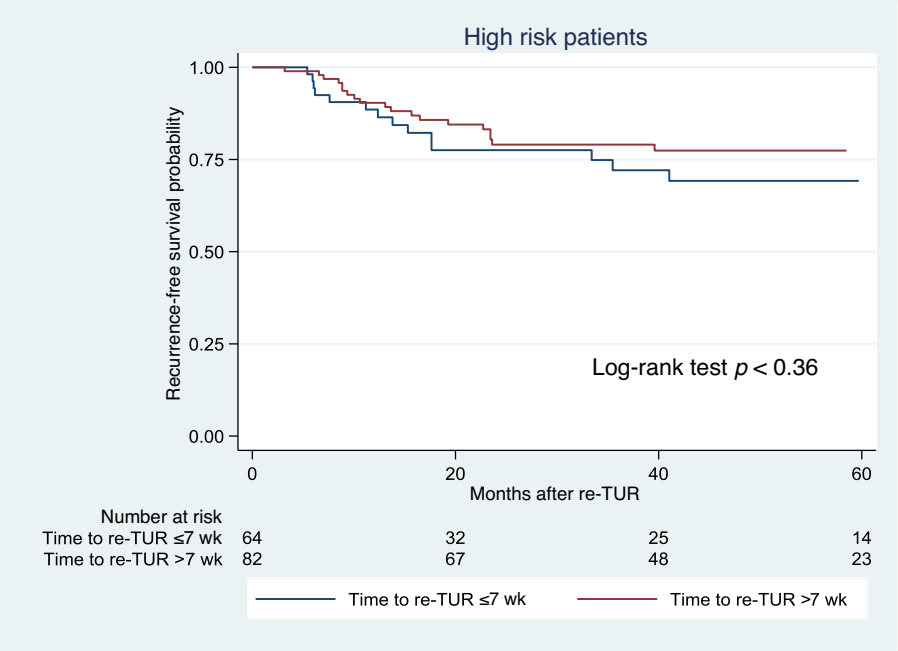


Fig. 3 – (A) Recurrence-free survival probability according to time from diagnosis to TUR in patients with intermediate risk and high risk NMIBC. (B) Recurrence-free and progression-free survival probability according to time from TUR to re-TUR in high-risk NMIBC. (C) Recurrence free survival probability according to time from last TUR to bladder instillations in intermediate and high-risk patients. NMIBC = non–muscle-invasive bladder cancer; re-TUR = repeat TUR; TUR = transurethral resection. There was significantly lower recurrence-free survival with a delay of >6 wk between diagnosis and TUR for patients with intermediate risk ($p < 0.001$) and high risk ($p = 0.04$), and with a delay of >7 wk between the last TUR and bladder instillations for patients with intermediate risk ($p = 0.001$). Regarding progression, a delay of >7 wk between TUR and re-TUR had a significant negative impact on progression-free survival for patients with high risk ($p < 0.017$).

(B)



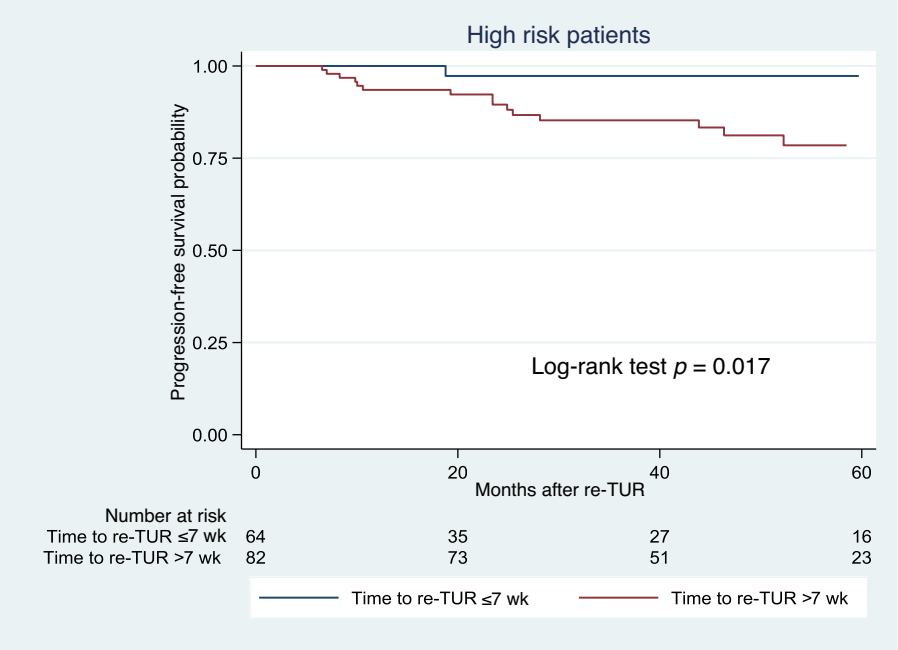


Fig. 3. (*Continued*).

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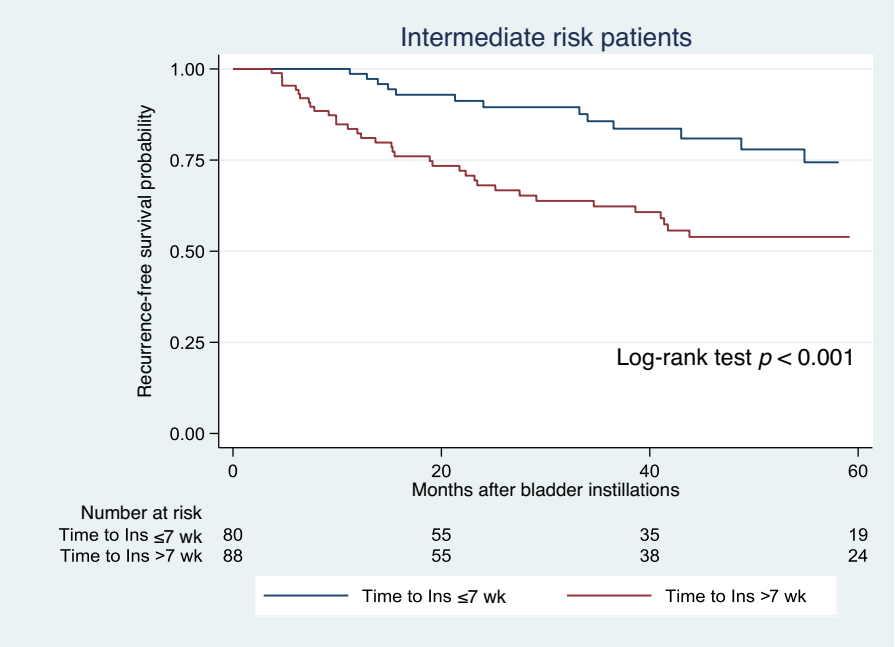
(C)



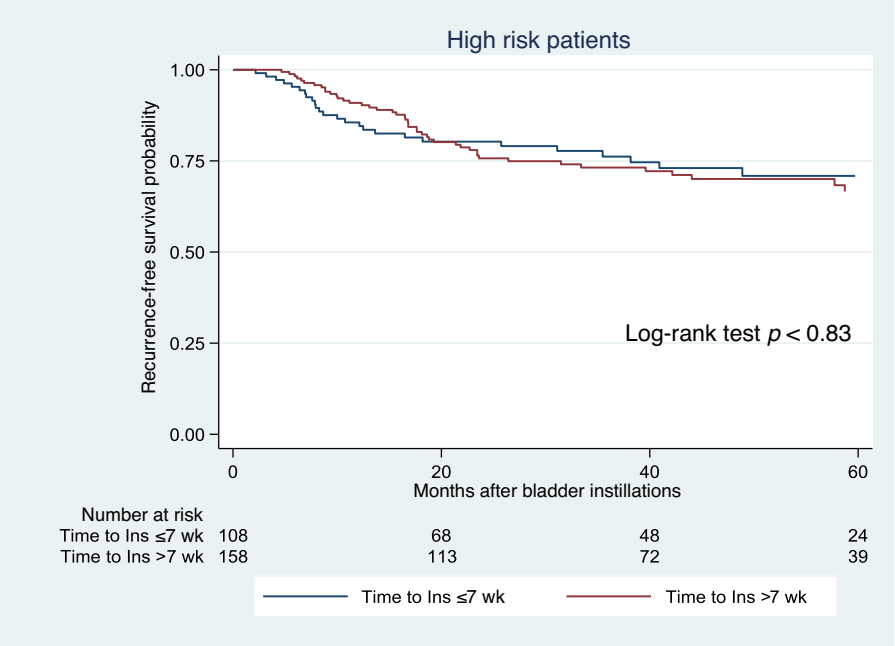


Fig. 3. (*Continued*).

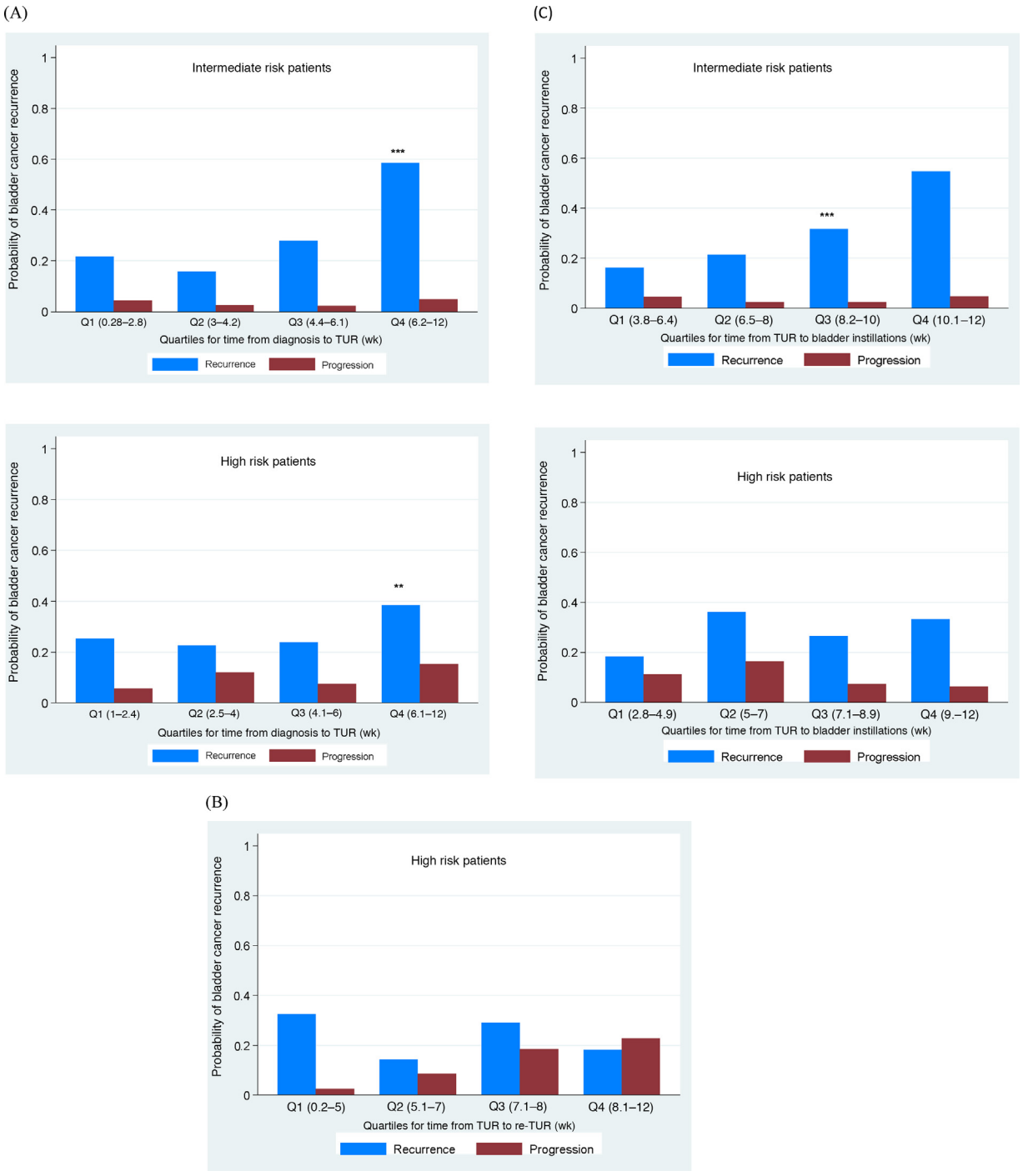


Fig. 4 – Bar charts showing rates of recurrence and progression by quartiles for (A) time from diagnosis to TUR, (B) time from TUR to re-TUR and (C) time from TUR to bladder instillations for patients with intermediate risk and high risk. The equality of populations regarding recurrence and progression was assessed using the Kruskal-Wallis rank test (*p* values) followed by Dunn's multiple pairwise comparisons test ($p < 0.01$, *** $p < 0.001$ for comparison of each quartile with the lower quartile). re-TUR = repeat TUR; TUR = transurethral resection. For time to TUR, patients in the last quartile (>6 wk) had significantly more recurrence than patients in the first three quartiles (≤6 wk; intermediate risk: $p < 0.001$; high risk: $p < 0.01$). For time to re-TUR, the rate of progression was significantly greater ($p < 0.01$) in the last two quartiles (≥7 wk) for high risk patients. For time to bladder instillations, the rate of recurrence increased significantly ($p < 0.001$) with the time to bladder instillations after 8 wk (3rd and 4th quartiles) for intermediate risk patients. In the high risk group, there was no significant impact of delayed instillation on recurrence or progression.**

5. Conclusions

In conclusion, our results suggest that delays in care of >6 wk to first resection in IR and HR NMIBC, and >7 wk to first instillation in IR cases are associated with a higher risk of recurrence. Time to restaging resection of >7 wk is associated with higher risk of progression, mainly in HR NMIBC. Additional confirmatory observational studies with prospective data collection are needed to provide more precisely the date of symptom onset and the reasons for

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management delays (eg, medical, social, and health system–related factors).

Author contributions: Said Ourfali had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Colombel, Ourfali, Badet.
Acquisition of data: Ourfali, Colombel, Matillon, Benoit-Janin, Ricci.
Analysis and interpretation of data: Colombel, Ourfali, Fassi Fehri, Matillon.
Drafting of the manuscript: Colombel, Ourfali, Badet, Fassi Fehri, Matillon.
Critical revision of the manuscript for important intellectual content: Ourfali , Colombel, Matillon, Fassi Fehri, Ricci, Benoit-Janin, Badet.
Statistical analysis: Colombel, Ourfali.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Colombel, Fassi Fehri, Badet.
Other: None.

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