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Impact of regular cystoscopy on prognosis in non–muscle-invasive bladder cancer: A nationwide study

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Purpose: Transurethral resection of bladder tumors (TUR-BT) requires follow-up evaluation by cystoscopy. We sought to evaluate the prognosis of non–muscle-invasive bladder cancer (NMIBC) patients within 6 months of surgery to identify the optimal timing for the first cystoscopy after TUR-BT.

Materials and Methods: In this retrospective analysis, patients newly diagnosed with NMIBC were divided into two groups according to whether they underwent cystoscopy within 6 months after TUR-BT. We considered four outcomes: recurrence, progression, cancer-specific mortality, and all-cause mortality. Inverse probability treatment weighting (IPTW)-adjusted Kaplan–Meier analysis was performed to identify the difference in survival for each outcome stratified by cystoscopy status within 6 months after the first TUR-BT. We employed Cox regression models with IPTW to estimate the hazard ratios (HRs) of each outcome according to cystoscopy status.

Results: Among 40,678 patients, 11,940 (29.4%) did not undergo cystoscopy within 6 months. The risk of recurrence was higher for patients who underwent cystoscopy than those who did not (HR 1.32, 95% confidence interval [CI] 1.26–1.38, p<0.001). By contrast, the cystoscopy group had a lower risk of progression compared to the non-cystoscopy group (HR 0.70, 95% CI 0.65–0.76, p<0.001), with lower cancer-specific mortality (HR 0.62, 95% CI 0.56–0.68, p<0.001) and all-cause mortality (HR 0.58, 95% CI 0.56–0.60, p<0.001).

Conclusions: Cystoscopy within 6 months was associated with a higher risk of recurrence but a lower risk of progression and death. Therefore, regular cystoscopy after the first TUR-BT for NMIBC is essential to ensure favorable survival outcomes.

Keywords: Cystoscopy; Non-muscle-invasive bladder cancer; Prognosis

INTRODUCTION

Bladder cancer is the second most common genitourinary tract malignancy in men and the tenth most common in both sexes worldwide [1]. Approximately 75% of bladder cancers are non–muscle-invasive bladder cancers (NMIBCs) and confined to the mucosa or submucosa [2]. NMIBCs exhibit more favorable cancer-specific mortality than their muscle-

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invasive counterparts, albeit with a higher rate of recurrence and prevalence [3]. Cystoscopy is an essential examination for diagnosis and follow-up after transurethral resection of bladder tumors (TUR-BT), as it can detect bladder cancer with high sensitivity and specificity, and other currently available methodologies, such as the use of urinary markers and cytology, can generally not replace it [4].

Clinical guidelines recommend different follow-up protocols according to risk classification [5]. The European Association of Urology guidelines recommend the first follow-up cystoscopy at 3 months both for low-risk Ta and high- or very-high-risk tumors; however, the rating strength remains weak [5]. The American Urological Association guidelines suggest the first surveillance cystoscopy be within 3–4 months to provide expert opinion, but very limited surveillance protocols for NMIBC exist [6]. A single randomized controlled trial on the follow-up protocol for NMIBC (Ta) (every 3 months vs. every 6 months) identified no significant differences in recurrence or progression [7]; however, the study may have been underpowered due to the small number of participants [7]. Various observational studies, such as those with prospective designs, have been unable to unify follow-up protocols. In reality, there are considerable variations among individuals in the timing of check cystoscopy, and only 84% perform their first cystoscopy at 3–4 months [8]. However, in these cases, the findings of the first cystoscopy are significant predictors of recurrence and progression [9]. Therefore, a unified standard for a cystoscopy follow-up protocol is needed, and the timing of the first follow-up cystoscopy is the first step in this direction. Here, we attempted to provide evidence regarding the optimal timing of the first cystoscopy after TUR-BT by assessing oncological outcomes according to the timing of the first cystoscopy in NMIBC.

MATERIALS AND METHODS

1. Data source

We used the national health claims database released by the National Health Insurance Service (NHIS), which offers comprehensive medical care coverage to 99% of the Korean population (50 million individuals). This study was approved by the Institutional Review Board of Chung-Ang University Hospital (approval number: 1908-014-16279), and the need for informed consent was waived. The study adhered to the guidelines of the Declaration of Helsinki (2013).

2. Patient population

The study period for the original cohort was from 2002 to 2018, with a follow-up period of 15 years (2004–2018). Patients who were newly diagnosed with NMIBC and underwent TUR-BT were identified as having Korean Standard Classification of Diseases 8th edition (KCD-8) code C67 and surgical code R3512.

A total of 67,796 patients were newly diagnosed with NMIBC and underwent TUR-BT between 2004 and 2016. Patients who underwent TUR-BT prior to being diagnosed with NMIBC (n=9,464), were diagnosed with other cancer types before NMIBC (n=2,989), underwent radical cystectomy (RC) within 2 months after the first TUR-BT (n=2,351), experienced recurrence or progression, or died in the 6-month period after the first TUR-BT (n=12,314) were excluded. In total, 40,678 patients were included in this study (Fig. 1).

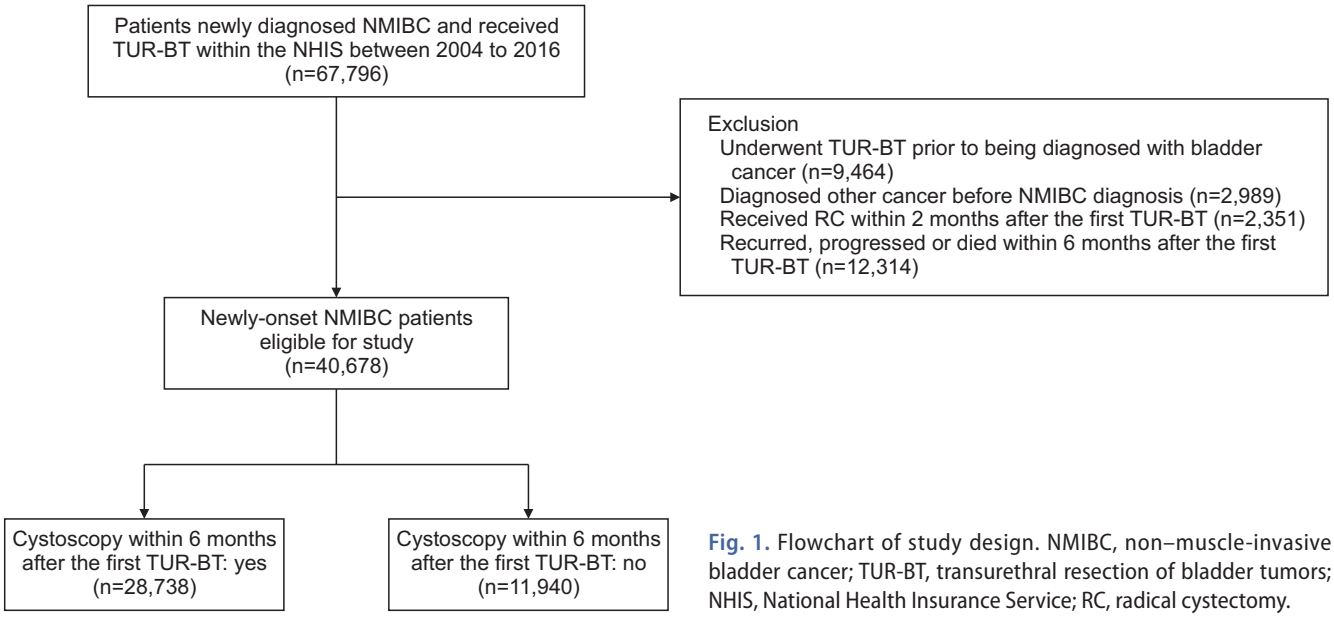

Fig. 1. Flowchart of study design. NMIBC, non–muscle-invasive bladder cancer; TUR-BT, transurethral resection of bladder tumors; NHIS, National Health Insurance Service; RC, radical cystectomy.

3. Outcomes and variables

We considered the following outcomes: (1) recurrence, defined as patients who underwent TUR-BT or RC; (2) progression, defined as patients who underwent chemotherapy or RC; (3) cancer-specific mortality, defined as patients who died due to cancer after progression; and (4) all-cause mortality, defined as patients who died. The index date was defined as 6 months after TUR-BT. Participants were followed up from the index date until death, loss to follow-up, or the end of follow-up in 2018, whichever came first.

The exposure variable was cystoscopy status within 6 months after the first TUR-BT, which was a binary variable defined as whether the patients received their first cystoscopy within 6 months after the first TUR-BT. We adjusted for the following predictors: age at NMIBC diagnosis, sex, year of NMIBC diagnosis, Charlson comorbidity index (CCI) score based on comorbidities before NMIBC diagnosis, and upper tract urothelial cancer (UTUC) occurrence before NMIBC diagnosis. Age at NMIBC diagnosis was categorized into four groups: <55, 55–64, 65–74, and ≥75 years. CCI score, a measure of comorbidities, was categorized into three groups: 0–1, 2–3, and ≥4. Year of NMIBC diagnosis was divided into three periods: 2004–2008, 2009–2012, and 2013–2016.

4. Statistical analyses

The baseline demographic and clinical characteristics are presented as means±standard deviations, medians (interquartile ranges), or numbers with percentages. To balance the baseline characteristics between the cystoscopy and non-cystoscopy groups, an inverse probability treatment weighting (IPTW) analysis was performed. A logistic regression model was used for the propensity score, incorporating factors such as age, sex, diagnosis year, NMIBC diagnosis year, CCI score, repeat TUR-BT, bacillus Calmette–Guérin (BCG) usage, and UTUC occurrence before NMIBC diagnosis. The balance of the covariates between the two groups was assessed using standardized mean differences (SMDs). The IPTW-adjusted Kaplan–Meier curves were generated to compare survival probabilities based on cystoscopy status, and the IPTW-adjusted log-rank test was performed. We used Cox proportional hazards models with IPTW to estimate the hazard ratios (HRs) according to cystoscopy status. We conducted subgroup analyses according to age (<55, 55–64, 65–74, and ≥75 years), sex, CCI score (0–1, 2–3, and ≥4), repeat TUR-BT, BCG usage, and UTUC occurrence. Data were statistically analyzed using SAS version 7.0 (SAS Institute Inc.) and R software version 4.0.1 (R Foundation for Statistical Computing). Statistical significance was set at $p<0.05$.

RESULTS

1. Baseline patient characteristics

A total of 40,678 patients newly diagnosed with NMIBC who underwent TUR-BT were included in this study; 28,738 (70.6%) underwent cystoscopy within 6 months after the first TUR-BT, while 11,940 (29.4%) did not. The baseline characteristics of the patients are summarized in Table 1. Among the eligible patients, 32,920 (80.9%) were male and 7,758 (19.1%) were female, indicating that males were more likely to undergo cystoscopy within 6 months than females ($p<0.001$). Patients who underwent cystoscopy within 6 months were diagnosed with NMIBC at a younger age than those who did not ($p<0.001$). Furthermore, a higher number of patients underwent TUR-BT in 2013–2016 than in 2004–2008 or 2009–2012 ($p<0.001$). Among all patients, 2,927 (7.2%) underwent repeat TUR-BT, and a lower proportion of the cystoscopy group underwent repeat TUR-BT compared to the non-cystoscopy group ($p<0.001$). A greater proportion of the cystoscopy group received BCG (44.5%) compared to the non-cystoscopy group (18.0%; $p<0.001$). There was no significant difference in the occurrence of UTUC before the diagnosis of NMIBC between the cystoscopy and non-cystoscopy groups. The SMDs were less than 10% for all evaluated covariates, indicating that covariates were well balanced between the two groups after IPTW.

2. Risk of recurrence, progression, cancer-specific mortality, and all-cause mortality for patients with NMIBC who underwent TUR-BT

Fig. 2 shows the IPTW-weighted Kaplan–Meier survival curves of recurrence, progression, cancer-specific survival, and overall survival stratified by cystoscopy status. The cystoscopy group had a higher probability of recurrence than the non-cystoscopy group. Conversely, the cystoscopy group demonstrated higher survival probabilities for progression, cancer-specific mortality, and all-cause mortality than the non-cystoscopy group.

Table 2 presents the incidence rates (IRs) and IPTW-adjusted HRs for recurrence, progression, cancer-specific mortality, and all-cause mortality in IPTW-weighted data. For recurrence, the IR was higher for those who underwent cystoscopy (IR 6.38, 95% confidence interval [CI] 6.25–6.51) than for those who did not (IR 4.95, 95% CI 4.76–5.13), and the risk was also higher (HR 1.32, 95% CI 1.26–1.38, $p<0.001$). For progression, however, the risk was lower in the cystoscopy group than in the non-cystoscopy group (HR 0.70, 95% CI 0.65–0.76, $p<0.001$). The cystoscopy group also had a lower risk of cancer-specific mortality (HR 0.62, 95% CI 0.56–0.68,

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Table 1. Baseline characteristics of patients with NMIBC and TUR-BT

	Total (n=40,678)	Cystoscopy (n=28,738)	Non-cystoscopy (n=11,940)	p-value	SMD after IPTW
Sex				<0.001	-0.018
Male	32,920 (80.9)	23,410 (81.5)	9,510 (79.6)		
Female	7,758 (19.1)	5,328 (18.5)	2,430 (20.4)		
Age in NMIBC diagnosis year				<0.001	
<55	7,093 (17.4)	5,214 (18.1)	1,879 (15.7)		0.010
55–64	9,345 (23.0)	7,042 (24.5)	2,303 (19.3)		-0.015
65–74	13,090 (32.2)	9,592 (33.4)	3,498 (29.3)		0.003
≥75	11,150 (27.4)	6,890 (24.0)	4,260 (35.7)		0.002
NMIBC diagnosis year				<0.001	
2004–2008	12,414 (30.5)	8,323 (29.0)	4,091 (34.3)		0.013
2009–2012	12,853 (31.6)	9,197 (32.0)	3,656 (30.6)		0.003
2013–2016	15,411 (37.9)	11,218 (39.0)	4,193 (35.1)		-0.015
CCI score				0.003	
0–1	12,670 (31.1)	8,919 (31.0)	3,751 (31.4)		0.009
2–3	12,412 (30.5)	8,910 (31.0)	3,502 (29.3)		-0.000
≥4	15,596 (38.3)	10,909 (38.0)	4,687 (39.3)		-0.009
Repeat TUR-BT	2,927 (7.2)	506 (1.8)	2,421 (20.3)	<0.001	-0.019
BCG usage	14,942 (36.7)	12,788 (44.5)	2,154 (18.0)	<0.001	-0.011
UTUC occurrence before NMIBC diagnosis	2,012 (4.9)	1,457 (5.1)	555 (4.6)	0.078	0.001

Values are presented as number (%).
NMIBC, non–muscle-invasive bladder cancer; TUR-BT, transurethral resection of bladder tumors; SMD, standardized mean difference; IPTW, inverse probability treatment weighting; CCI, Charlson comorbidity index; BCG, bacillus Calmette–Guérin; UTUC, upper tract urothelial cancer.

p<0.001) and all-cause mortality (HR 0.58, 95% CI 0.56–0.60, p<0.001) compared to the non-cystoscopy group.

Fig. 3 presents the results of the subgroup analysis by age, sex, CCI score, repeat TUR-BT, and BCG usage. Patients who underwent repeat TUR-BT showed no difference in recurrence (HR 1.20, 95% CI 0.99–1.46, p=0.065), nor did patients who received BCG (HR 1.03, 95% CI 0.94–1.13, p=0.496) or those with UTUC occurrence (HR 0.98, 95% CI 0.83–1.17, p=0.851). The cystoscopy group showed lower risks of progression in all subgroups except for the ≥75 age group (HR 0.87, 95% CI 0.73–1.05, p=0.138), the repeat TUR-BT group (HR 0.77, 95% CI 0.58–1.02, p=0.071), and the UTUC occurrence group (HR 0.77, 95% CI 0.59–1.02, p=0.073). Additionally, the risks of progression, cancer-specific mortality, and all-cause mortality were lower in all subgroups of the cystoscopy group than in those of the non-cystoscopy group.

DISCUSSION

In this study, 40,678 patients with newly diagnosed NMIBC who underwent TUR-BT were analyzed, with 70.6% having undergone cystoscopy within 6 months after the procedure. The recurrence risk was higher in the cystoscopy group, whereas the progression, cancer-specific mortality, and all-cause mortality risks were lower. Subgroup analysis generally supported the benefits of cystoscopy in terms of progression risk, except in patients who underwent repeat TUR-BT or received BCG. Cystoscopy is the gold standard for the follow-up of patients with NMIBC. Many guidelines encourage the first follow-up cystoscopy at around 3 months [10,11], but as many as 30% of patients with NMIBC receive their first cystoscopy at 6 months in reality in South Korea. Approximately 30% of patients did not undergo cystoscopy within 6 months after TUR-BT, a proportion that was notably higher than anticipated. The findings of this study underscore the critical importance of adhering to guideline-recommended cystoscopic protocols for optimizing patient outcomes. Therefore, it is essential to promote awareness of appropriate guidelines among physicians managing NMIBC.

We divided the timing of cystoscopy into 6-month periods, because when we set it at 3 months, patients who underwent cystoscopy slightly later than 3 months were excluded. Additionally, we included patients who underwent BCG instillation and repeat TUR-BT. BCG induction conventionally starts during the 14- to 28-day period after the recovery of the urothelium to prevent BCG side effects [12]. Repeat TUR-BT is recommended within 2–6 weeks from the first TUR-BT [13]. Guidelines recommend that the first cystoscopy

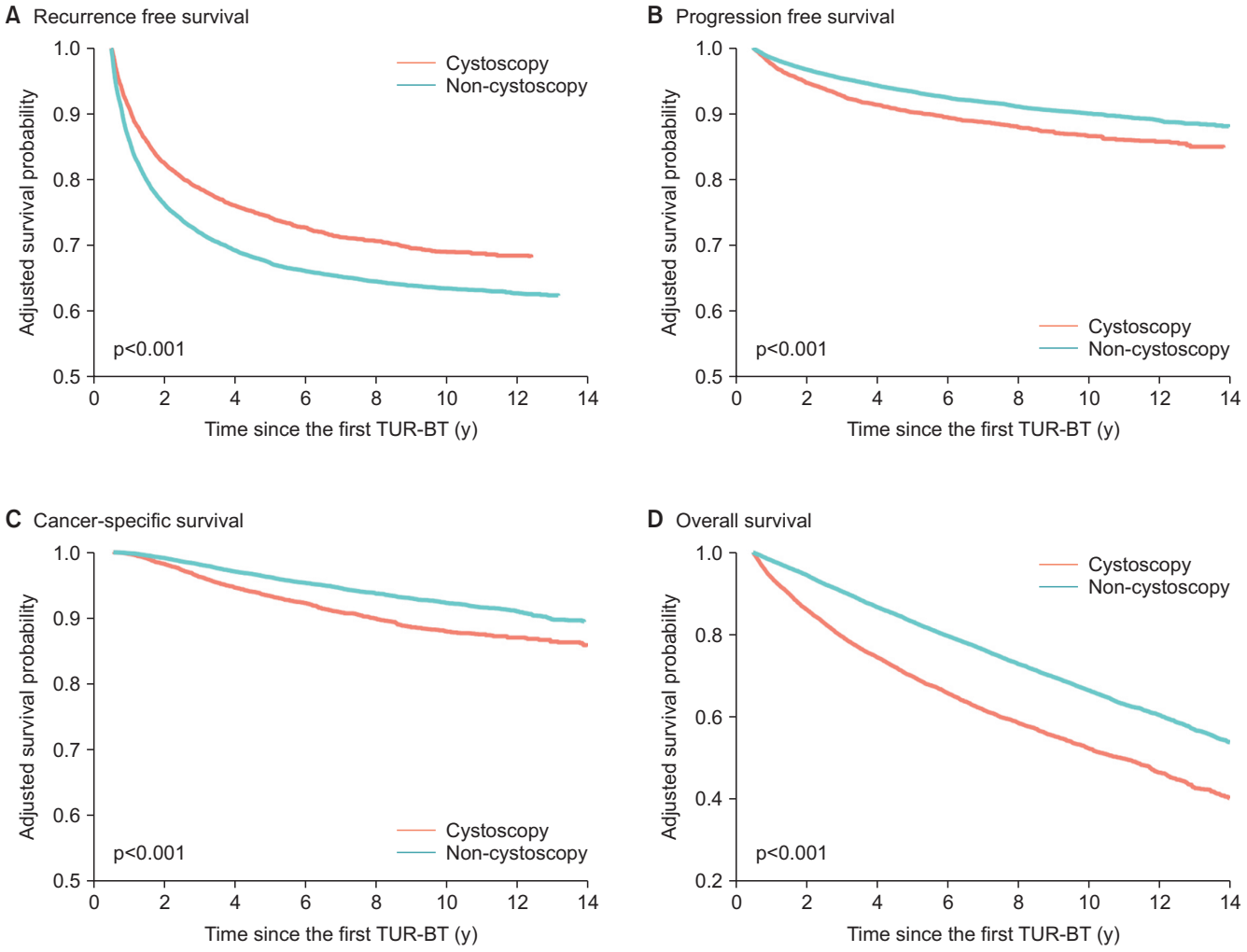

Fig. 2. Inverse probability treatment weighting-adjusted Kaplan–Meier curves and inverse-probability of treatment weighting-adjusted log-rank tests for recurrence, progression, cancer-specific mortality, and overall mortality according to cystoscopy status within 6 months after first transurethral resection of bladder tumors (TUR-BT).

be performed 3–4 months after the primary TUR-BT [10,11] because early recurrence is associated with the completeness of the primary TUR-BT and administration of intravesical treatment [14], regardless of whether repeat TUR-BT has been performed. In another study, we confirmed through a time-to-treatment initiation approach that the most appropriate timing for performing cystoscopy is at 3–4 months [15]. However, in reality, the first cystoscopy can be postponed because of BCG side effects, repeat TUR-BT, or schedule delays due to external causes. Therefore, we chose the broader criterion of up to 6 months for the timing of cystoscopy.

Regular cystoscopy within 6 months was able to detect more bladder tumor recurrences. The finding that the cystoscopy group had a higher recurrence rate may be due to detection bias (i.e., the more frequent follow-up resulted in the earlier detection of recurrences). The five main recurrence mechanisms include undetected cancer during primary treatment, local residual disease after transurethral resection, tumor re-implantation, a drop in metastasis from UTUC, and a field change cancerization effect [16]. Cancer-related alterations can sometimes be subtle, causing them to be missed during TUR-BT [17]. Carcinoma in situ is specifically defined as a flat lesion within the urothelium marked by the presence of cytologically malignant cells that are associated with a poor prognosis [18]. Tumors that are not detected during TUR-BT will continue to grow and be noticeable during the subsequent cystoscopy. The natural progression of NMIBC is difficult to predict because of its heterogeneous course, with some patients experiencing rapid advancement to muscle invasion and metastasis and others following a more indolent growth pattern. However, even among those with low-risk NMIBC, more than 50% have recurrences within 1 year and more than 30% have recurrences within 6 months [19,20].

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Table 2. HRs for risks of each outcome according to cystoscopy status within 6 months after first TUR-BT

Outcome	Cystoscopy (n=28,738)		Non-cystoscopy (n=11,940)		HR (95% CI)	p-value
	Event	IR (per 1,000 person-years)	Event	IR (per 1,000 person-years)		
Recurrence	9,097 (31.7)	6.38 (6.25–6.51)	2,799 (23.4)	4.95 (4.76–5.13)	1.32 (1.26–1.38)	<0.001
Progression	2,224 (7.7)	1.20 (1.15–1.25)	1,095 (9.2)	1.64 (1.55–1.74)	0.70 (0.65–0.76)	<0.001
Cancer-specific mortality	1,496 (5.2)	0.78 (0.74–0.82)	860 (7.2)	1.24 (1.16–1.33)	0.62 (0.56–0.68)	<0.001
All-cause mortality	7,109 (24.7)	3.72 (3.63–3.80)	5,489 (46.0)	7.94 (7.73–8.15)	0.58 (0.56–0.60)	<0.001

Values are presented as number (%).
HRs were estimated using Cox proportional hazards models with inverse probability treatment weighting to adjust for age, sex, year of diagnosis, Charlson comorbidity index score, occurrence of upper tract urothelial cancer, and bacillus Calmette–Guérin use.
HR, hazard ratio; TUR-BT, transurethral resection of bladder tumors; IR, incidence rate; CI, confidence interval.

Early recurrence detection is important for planning subsequent treatments. Failure of complete cure due to delayed detection may be associated with decreased survival or quality of life in patients. The identification of appropriate local or regional recurrence can lead to timely surgical or salvage treatment. In addition, early RC could show more favorable outcomes in high-risk cases of bladder cancer than in recurrent and progressed cases [21]. According to our findings, undergoing the first cystoscopy within 6 months was related to an increased risk of recurrence detection but lower risks of progression, cancer-specific mortality, and all-cause mortality.

Subgroup analysis demonstrated that patients who underwent repeat TUR-BT or received BCG had no difference in recurrence. The efficacy of intravesical BCG instillation in reducing recurrence and progression is well known [22]. Repeat TUR-BT can also improve subsequent tumor recurrence and progression [23]. However, BCG or repeat TUR-BT should not delay the first cystoscopy. In our study, the risks of progression, cancer-specific mortality, and all-cause mortality within 6 months were lower in the cystoscopy group than in the non-cystoscopy group. In addition, early recurrent cases may exhibit more aggressive features, resulting in worse prognosis [24].

Despite its key findings, our retrospective study had some limitations. First, as the type of cystoscopy was chosen by each clinician, selection bias could not be avoided. Propensity score matching can be used to adjust for confounders; however, in this paper, we applied the IPTW method for adjustment because matching resulted in substantial sample loss. As this study was based on population-level data, selection bias was minimized. We chose to collect nearly complete enumeration data for South Korea because insurance services cover the high treatment costs of patients with cancer, and almost all Koreans are enrolled in the NHIS. Therefore, we were able to show the actual conditions of the follow-up protocol for the first cystoscopy. Second, the NHIS data did not include any tumor (e.g., pathology of grade or stage), radiologic imaging, or patient (e.g., smoking or performance status) characteristics. The NHIS database can provide smoking status from the general health checkup questionnaire. However, due to structural limitations in the database, health checkup data were not incorporated when this dataset was constructed. Smoking is the most significant risk factor for bladder cancer, and a patient's physical health is also related to disease prognosis [25,26]. Lastly, we excluded patients who experienced recurrence, progression, or death within 6 months. While this exclusion might have led to the omission of some early recurrent NMIBC cases, it was necessary to reduce survival bias between the two groups, as patients in the group without cystoscopy within 6 months inherently did not experience recurrence, progression, or death during that period.

CONCLUSIONS

Nationwide data from South Korea revealed that approximately 30% of patients did not undergo cystoscopy within 6 months after TUR-BT. The performance of cystoscopy within 6 months after the initial TUR-BT was associated with NMIBC prognosis. Cystoscopy within 6 months was associated with a higher risk of recurrence but a lower risk of progression as well as cancer-specific and all-cause mortality. Therefore, regular cystoscopy after the first TUR-BT for NMIBC is essential to ensure favorable survival outcomes.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

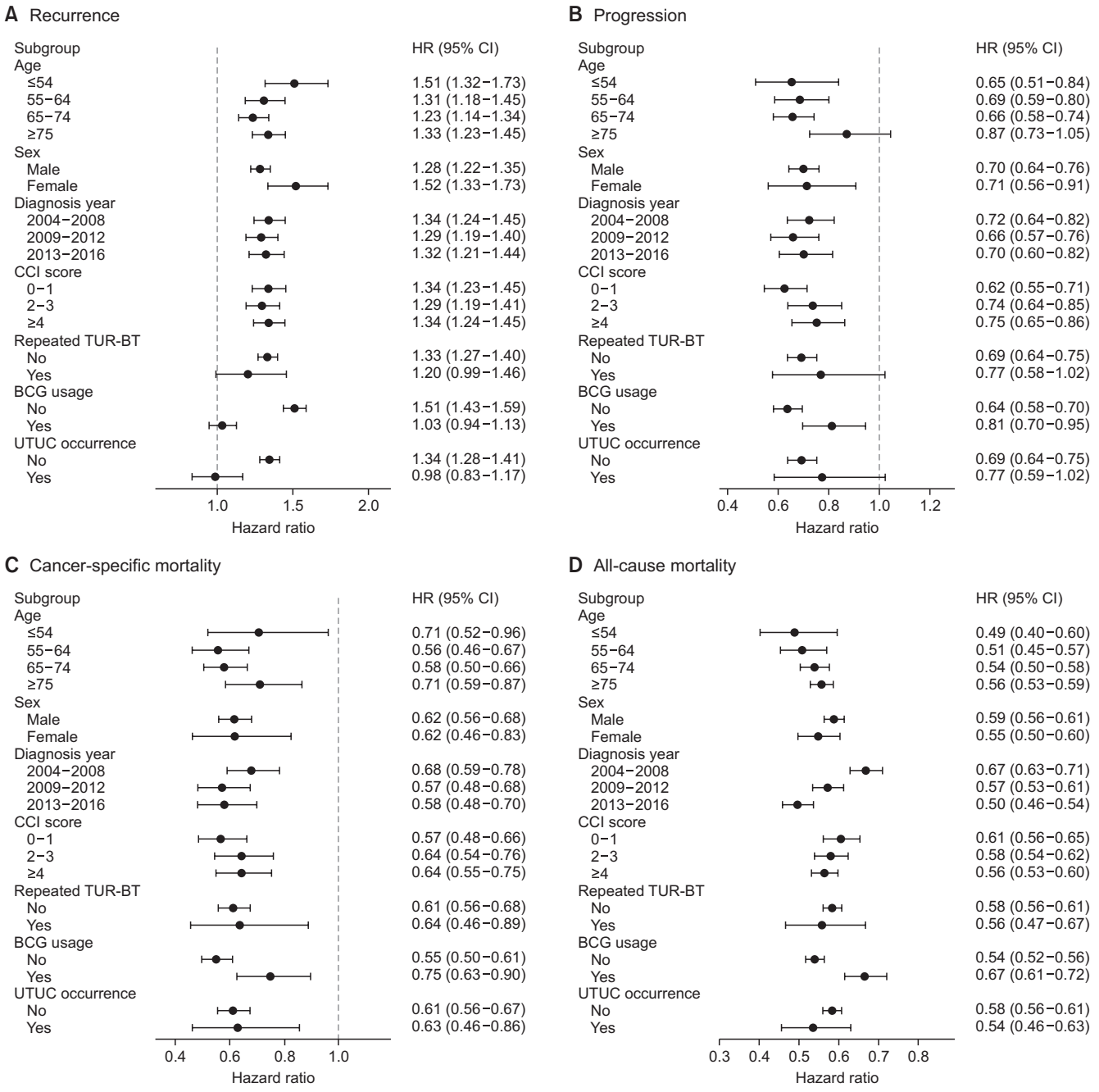

Fig. 3. Forest plots of HR (95% CI) according to subgroups based on age, sex, CCI score, repeat TUR-BT, and BCG usage. HR, hazard ratio; CI, confidence interval; CCI, Charlson comorbidity index; TUR-BT, transurethral resection of bladder tumors; BCG, bacillus Calmette–Guérin; UTUC, upper tract urothelial cancer.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Se Young Choi and Jooyoung Lee. Data acquisition: Chung Un Lee and Jeong-Soo Kim. Statistical analysis: Jeong-Soo Kim and Jooyoung Lee. Data analysis and interpretation: Jeong-Soo Kim, Se Young Choi, and Jooyoung Lee. Drafting of the manuscript: Se Young Choi and Jeong-Soo Kim. Critical revision of the manuscript: Tuan Thanh Nguyen. Obtaining funding: Se

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