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Impact of carcinoma *in situ* of bladder at transurethral resection and radical cystectomy on survival: Retrospective multicenter study

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Purpose: Carcinoma *in situ* (CIS) of the bladder is a high-grade, non-invasive lesion known to increase the risk of recurrence and progression. However, the prognostic significance of CIS identified at transurethral resection of bladder tumor (TURB) versus radical cystectomy (RC) remains controversial. This study aimed to evaluate the impact of CIS at different treatment stages on recurrence-free survival (RFS) and cancer-specific survival (CSS).

Materials and Methods: A retrospective multicenter study was conducted using data from 2,553 patients who underwent TURB followed by RC between 2010 and 2019 across eleven Korean institutions. Kaplan–Meier survival curves and Cox proportional hazards models were used to assess the association of CIS at TURB and RC with RFS and CSS, adjusting for clinicopathological variables.

Results: CIS was identified in 731 TURB specimens (28.6%) and 821 RC specimens (32.2%). Patients with CIS at TURB had significantly higher RFS (p<0.001) and CSS (p=0.002) compared to those without. In multivariate analysis, CIS at TURB was independently associated with better RFS (hazard ratio [HR] 0.787, p=0.001) but not CSS (HR 0.989, p=0.905). CIS at RC showed no significant association with either RFS or CSS. Independent predictors of poor survival included advanced stage, lymph node involvement, lymphovascular invasion, and positive surgical margins. Adjuvant therapy was associated with improved CSS.

Conclusions: CIS at TURB is associated with a lower recurrence risk following RC, whereas CIS in RC specimens has limited prognostic impact. These findings suggest CIS at TURB may carry different prognostic implications than traditionally assumed, warranting careful clinical interpretation.

Keywords: Bladder cancer; Carcinoma *in situ*; Radical cystectomy; Survival; Transurethral resection of bladder tumor

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INTRODUCTION

Carcinoma *in situ* (CIS) of the bladder is an intraepithelial, high-grade, non-invasive malignant lesion that exhibits the same degree of anaplasia as high-grade urothelial carcinoma [1]. CIS in non-muscle invasive bladder cancer (NMIBC) is regarded as high-risk because it is estimated that approximately 54% of cases will progress to muscle invasive bladder cancer (MIBC) if left untreated [2-4]. The presence of CIS in specimens from transurethral resection of bladder tumor (TURB) and radical cystectomy (RC) is considered as an adverse pathological feature associated with a poor prognosis [5].

Understanding the prognostic implications of CIS is essential for the management of BC. CIS cannot be cured by an endoscopic procedure alone. In patients with NMIBC without very high-risk features, intravesical Bacillus Calmette–Guérin (BCG) therapy is strongly recommended in the presence of CIS to reduce the risk of both recurrence and progression [3]. Patients with persistent or recurrent high-risk disease despite intravesical BCG therapy should be considered for early RC [1,3]. Meanwhile, the presence of CIS in RC specimens also has potential prognostic implications. It has been associated with an increased risk of urethral involvement and a reduced pathological complete response (pCR) rate to neoadjuvant chemotherapy (NAC) [6,7]. Furthermore, CIS in RC specimens has been linked to a higher risk of recurrence after RC, and in patients with organ-confined disease (pT0–T2), CIS is associated with worse cancer specific survival [8].

Despite the accumulation of evidence, the precise role of CIS in predicting survival outcomes remains unclear. Although some studies have reported that CIS is associated with unfavorable oncological outcomes, including decreased cancer-specific survival (CSS) and recurrence-free survival (RFS) [8,9], other investigations have failed to demonstrate a consistent adverse impact [10,11]. Thus, the prognostic significance of CIS in bladder cancer (BC), whether identified in TURB or RC specimens, remains controversial. This study aims to elucidate the impact of CIS identified during TURB and RC on oncological outcomes.

MATERIALS AND METHODS

In June 2024, after the Korean Bladder Cancer Study Group of the Korean Urological Oncology Society systematically planned a web-based electronic database, a single dedicated database manager collected and verified all information. The present study received approval from the Institutional Review Board of Yonsei University Severance Hospital (approval number: 4-2023-1509), and the requirement for informed consent was waived owing to the study's retrospective nature. Data were obtained from medical records, and patient identifying information was anonymized before analysis. All methods were performed in accordance with the relevant guidelines and regulations, and the principles enshrined in the Declaration of Helsinki.

This retrospective study included data from 3,258 patients who underwent RC for MIBC between January 2010 and December 2019 at eleven major urologic centers across Korea. After excluding patients with non-pure urothelial carcinoma (n=270), previous or concurrent upper tract urothelial carcinoma (n=271), and incomplete clinical or pathological data (n=164), a total of 2,553 patients were included in the final analysis (Fig. 1). Demographic, clinicopathological, treatment, and follow-up data were collected, including age, sex, CIS status at TURB and RC, perioperative treatment, tumor grade and stage, lymphovascular invasion, surgical margin status, and lymph node involvement.

RFS and CSS were compared using Kaplan–Meier analyses according to CIS status at TURB and RC. Survival time for recurrence and cancer-specific death was calculated from the date of RC. Cox proportional hazards models were then applied to assess the association between CIS and survival outcomes. Hazard ratios (HR) and 95% confidence intervals

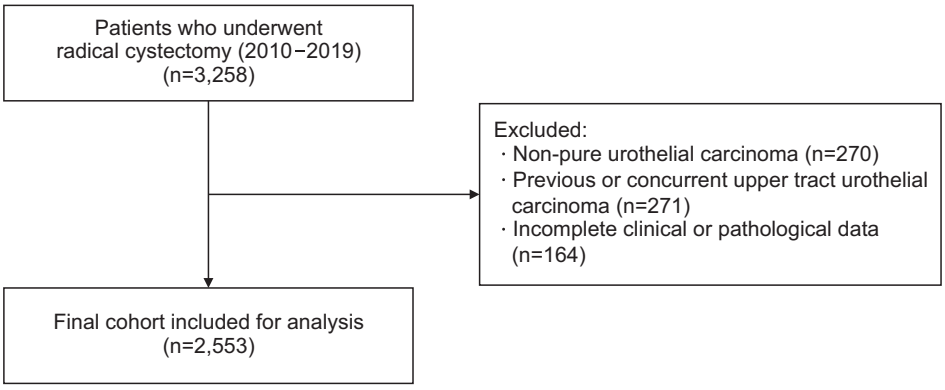

Fig. 1. Flow chart for study inclusion.

(CI) were reported, with statistical significance set at p<0.05.

Survival was estimated within each subgroup using the Kaplan–Meier method. Cox regression analysis was performed to identify prognostic factors for survival. The level of significance was set at 0.05 for all analyses. All statistical analyses were performed using IBM SPSS version 26.0 (IBM Corp.). This study was reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

RESULTS

Baseline patient characteristics are presented in Table 1. Of 2,553 patients, with a median age of 68 years (interquartile range [IQR] 60–74), and 2,317 (90.8%) were male. CIS was identified in 731 of TURB specimens (28.6%) and in 821 of RC specimens (32.2%). Metastatic disease was observed in 91 patients (3.6%), and 603 (23.6%) received NAC. Pathological findings showed that 2,222 patients (87.0%) had high-grade BC, 1,359 (53.2%) had organ-confined disease (≤pT2), and 664 (26.0%) had pathologic lymph node involvement. Lymphovascular invasion was found in 977 patients (38.3%), and positive surgical margins were noted in 247 patients (9.7%). A total of 702 patients (27.5%) received adjuvant therapy. The median follow-up duration was 36 months (IQR 13–65). During this period, recurrence occurred in 977 patients (38.3%), and 622 patients (24.4%) died of BC. The median RFS time was 25 months (IQR 8–60), and the median CSS time was 38 months (IQR 14–67).

Patients with CIS at TURB demonstrated better survival outcomes than those without CIS, with higher 5-year RFS (63.7% vs. 53.2%) and CSS (75.0% vs. 70.0%). Consistently, Kaplan–Meier analysis showed significantly improved RFS (p<0.001; Fig. 2A) and CSS (p=0.002; Fig. 3A) in the CIS-positive TURB group. In contrast, CIS in RC specimens was not associated with differences in survival outcomes. The 5-year RFS was 56.4% in both CIS-positive and CIS-negative patients, and 5-year CSS was 71.6% and 71.5%, respectively. Kaplan–Meier analysis confirmed no significant differences

Table 1. Patients characteristics (n=2,553)

Characteristic	Value
Age (y)	68 (60–74)
Sex	
Male	2,317 (90.8)
Female	236 (9.2)
CIS at TURB	731 (28.6)
Metastasis	91 (3.6)
Neoadjuvant chemotherapy	603 (23.6)
Pathologic results	
Grade	
No residual tumor	203 (8.0)
Low	128 (5.0)
High	2,222 (87.0)
Organ-confined (≤pT2)	1,359 (53.2)
Positive lymph node	664 (26.0)
CIS at RC	821 (32.2)
Lymphovascular invasion	977 (38.3)
Positive surgical margin	247 (9.7)
Adjuvant therapy	702 (27.5)
Follow-up duration (mo)	36 (13–65)
Recurrence	977 (38.3)
Overall mortality	1,051 (41.2)
Cancer-specific mortality	622 (24.4)

Values are presented as median (interquartile range) or number (%).
CIS, carcinoma *in situ*; TURB, transurethral resection of bladder tumor; RC, radical cystectomy.

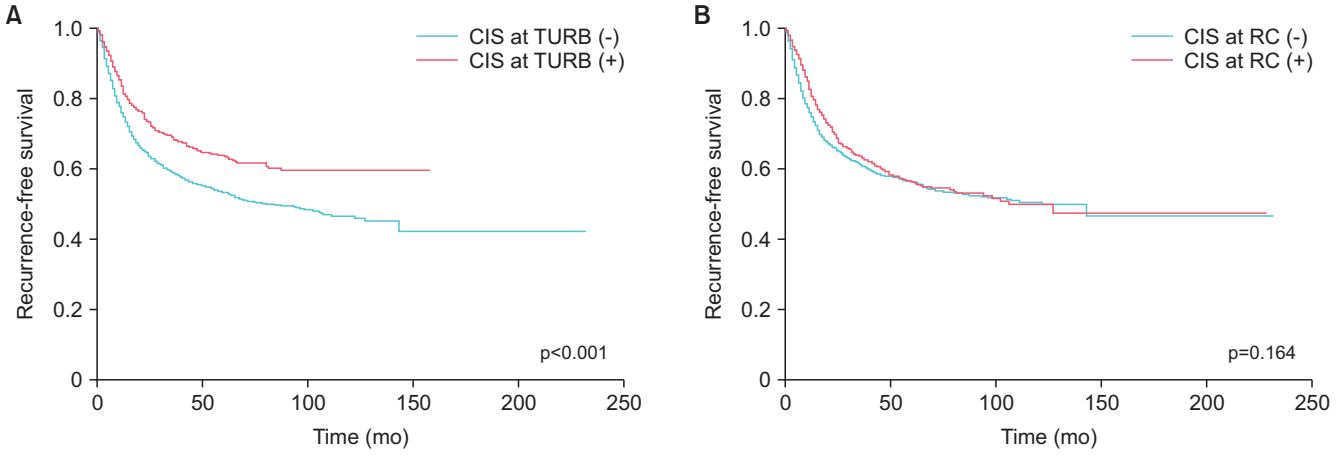

Fig. 2. Kaplan–Meier curve of recurrence-free survival. (A) Carcinoma *in situ* (CIS) at transurethral resection of bladder tumor (TURB). (B) CIS at radical cystectomy (RC).

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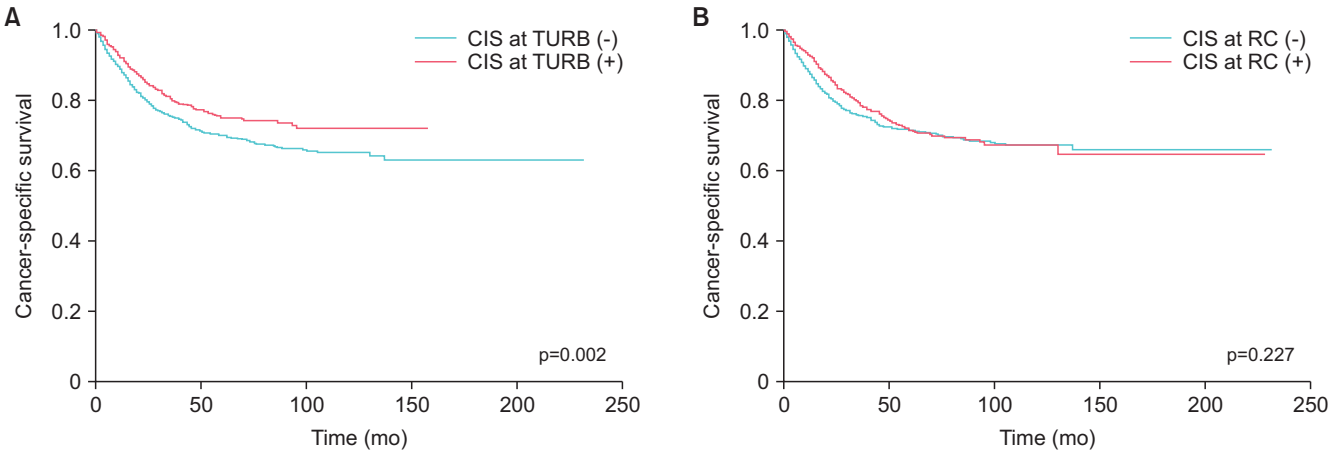

Fig. 3. Kaplan–Meier curve of cancer-specific survival. (A) Carcinoma *in situ* (CIS) at transurethral resection of bladder tumor (TURB). (B) CIS at radical cystectomy (RC).

Table 2. Cox regression analysis of predictors of recurrence-free survival

	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.005	0.998–1.011	0.161	-	-	-
Sex						
Male		Reference		-	-	-
Female	1.009	0.813–1.252	0.938	-	-	-
CIS at TURB	0.698	0.603–0.808	<0.001	0.787	0.679–0.911	0.001
Metastasis	2.569	1.942–3.399	<0.001	1.791	1.351–2.375	<0.001
Neoadjuvant chemotherapy	1.116	0.963–1.292	0.145	-	-	-
Grade						
No residual tumor		Reference			Reference	
Low	3.419	2.069–5.650	<0.001	2.130	1.281–3.541	0.004
High	4.751	3.140–7.186	<0.001	2.212	1.446–3.385	<0.001
Organ-confined (≤pT2)	3.100	2.718–3.535	<0.001	1.799	1.538–2.105	<0.001
Positive lymph node	3.258	2.864–3.706	<0.001	1.875	1.605–2.192	<0.001
CIS at RC	0.909	0.795–1.041	0.167	-	-	-
Lymphovascular invasion	3.190	2.809–3.624	<0.001	1.732	1.483–2.023	<0.001
Positive surgical margin	1.952	1.621–2.350	<0.001	1.345	1.113–1.627	0.002
Adjuvant therapy	2.164	1.905–2.459	<0.001	0.902	0.776–1.048	0.177

HR, hazard ratio; CI, confidence interval; CIS, carcinoma *in situ*; TURB, transurethral resection of bladder tumor; RC, radical cystectomy.

in either RFS (p=0.164; Fig. 2B) or CSS (p=0.227; Fig. 3B).

Multivariate Cox regression analysis identified CIS at TURB as an independent predictor of better RFS (HR 0.787, 95% CI 0.679–0.911, p=0.001). Significant predictors of lower RFS included presence of metastasis (HR 1.791, 95% CI 1.351–2.375, p<0.001), high tumor grade (HR 2.212, 95% CI 1.446–3.385, p<0.001), lymph node involvement (HR 1.875, 95% CI 1.605–2.192, p<0.001), lymphovascular invasion (HR 1.732, 95% CI 1.483–2.023, p<0.001), and positive surgical margin (HR 1.345, 95% CI 1.113–1.627, p=0.002). Furthermore, patients with non-organ-confined disease (≥pT3) had worse RFS compared to those with organ-confined disease (≤pT2) (HR 1.799, 95% CI 1.538–2.105, p<0.001). CIS in RC specimens was not a significant predictor of RFS in univariate analysis (p=0.167), and therefore not included in the multivariate model (Table 2).

CIS in TURB specimens was not independently associated with CSS in multivariate analysis (HR 0.989, 95% CI 0.824–1.187, p=0.905). Similar to the RFS analysis, CIS in RC specimens was not identified as a significant predictor of CSS in the univariate analysis (p=0.229). Other variables were identified as independent predictors of worse CSS. These included older age (HR 1.020, 95% CI 1.011–1.028, p<0.001), presence of metastasis (HR 1.757, 95% CI 1.258–2.454,

Table 3. Cox regression analysis of predictors of cancer-specific survival

	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.021	1.013–1.030	<0.001	1.020	1.011–1.028	<0.001
Sex						
Male		Reference		-	-	-
Female	0.982	0.749–1.286	0.892	-	-	-
CIS at TURB	0.753	0.628–0.902	0.002	0.989	0.824–1.187	0.905
Metastasis	2.568	1.841–3.582	<0.001	1.757	1.258–2.454	0.001
Neoadjuvant chemotherapy	1.005	0.833–1.212	0.960	-	-	-
Grade						
No residual tumor		Reference			Reference	
Low	2.224	1.090–4.540	0.028	0.897	0.435–1.851	0.769
High	5.060	2.921–8.767	<0.001	1.541	0.872–2.723	0.136
Organ-confined (≤pT2)	3.797	3.193–4.515	<0.001	2.206	1.792–2.714	<0.001
Positive lymph node	3.053	2.603–3.581	<0.001	1.533	1.265–1.860	<0.001
CIS at RC	0.901	0.761–1.068	0.229	-	-	-
Lymphovascular invasion	3.071	2.616–3.605	<0.001	1.242	1.019–1.514	0.032
Positive surgical margin	2.292	1.843–2.850	<0.001	1.452	1.162–1.815	0.001
Adjuvant therapy	1.674	1.423–1.969	<0.001	0.639	0.531–0.768	<0.001
Recurrence	6.561	5.453–7.894	<0.001	5.014	4.126–6.092	<0.001

HR, hazard ratio; CI, confidence interval; CIS, carcinoma *in situ*; TURB, transurethral resection of bladder tumor; RC, radical cystectomy.

p=0.001), non–organ-confined disease (≥pT3) (HR 2.206, 95% CI 1.792–2.714, p<0.001), lymph node involvement (HR 1.533, 95% CI 1.265–1.860, p<0.001), lymphovascular invasion (HR 1.242, 95% CI 1.019–1.514, p=0.032), and positive surgical margin (HR 1.452, 95% CI 1.162–1.815, p=0.001). Additionally, recurrence was the strongest predictor of worse CSS (HR 5.014, 95% CI 4.126–6.092, p<0.001), whereas adjuvant therapy was associated with improved CSS (HR 0.639, 95% CI 0.531–0.768, p<0.001) (Table 3).

Although NAC was not identified as a significant predictor in the Cox regression analyses, stratified analyses were performed given its well-established favorable impact on survival outcomes. Based on CIS status at TURB, NAC was administered to 221 of 731 patients (30.2%) in the CIS-positive group and to 382 of 1,822 patients (21.0%) in the CIS-negative group, representing a significant difference between groups (p<0.001). According to CIS status at RC, NAC was administered to 208 of 821 patients (25.3%) in the CIS-positive group and to 395 of 1,732 patients (22.8%) in the CIS-negative group (p=0.175) (Supplementary Table 1). Five-year RFS and CSS stratified by CIS status and NAC are provided in Supplementary Table 2. For RFS, patients with CIS at TURB had significantly better outcomes than those without CIS in both the no–NAC and NAC groups (both p<0.001). For CSS, CIS at TURB was associated with improved outcomes in patients who did not receive NAC (p=0.007), whereas no significant difference was observed among those who received NAC (p=0.117). In contrast, when stratified by CIS status at RC, no significant differences in either RFS or CSS were observed according to NAC status.

DISCUSSION

Our multicenter retrospective study demonstrated that the presence of CIS at TURB was associated with more favorable oncologic outcomes. Patients with CIS at TURB showed higher 5-year RFS and CSS compared with those without CIS, and CIS at TURB remained an independent predictor of improved RFS in multivariate analysis, although it was not independently associated with CSS. In contrast, CIS in RC specimens was not associated with RFS or CSS in either univariate or multivariate analyses, suggesting that its prognostic role may be limited. These findings contrast with the conventional view of CIS at TURB as a high-risk feature.

The clinical behavior of CIS at TURB needs further attention. CIS is a flat, high-grade urothelial lesion often widespread or even inconspicuous with no definite demarcation of the tumor margins [1]. These characteristics make complete resection difficult and may contribute to residual disease [12]. CIS at TURB may represent a biologically aggressive or multifocal disease with a high propensity for

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recurrence, despite subsequent definitive treatment [2-4]. Despite this aggressive potential, a significant association with CSS was not identified. In another multicenter study in patients with NAC for cT2-T4aN0-3M0 followed by RC, the presence of CIS at TURB did not affect pCR rate (17.9% with CIS vs. 21.9% without CIS; p=0.16) and was not associated with overall survival (OS) (p=0.70) [11]. Piszczek et al. [13] evaluated 301 patients with BC and CIS who received at least seven instillations of BCG. The 5-year CSS rates were 83.1% for primary CIS, 81.9% for concomitant CIS, and 90.1% for secondary CIS, with no statistically significant differences among the groups.

Several prior studies have reported findings that contradict the presumed aggressiveness of CIS at TURB. A 2022 Chinese cohort study restricted to 236 RC patients who did not receive NAC found no significant association between CIS at TURB and disease-free survival (p=0.395) [14]. A retrospective analysis published in 2015 evaluated 189 patients with MIBC treated with NAC followed by RC. Although patients with CIS at TURB demonstrated a lower pCR rate compared with those without CIS (10.7% vs. 26.3%; p=0.02), CIS at TURB was not associated with differences in recurrence-free (11.4 months vs. 7.3 months; p=0.80), cancer-specific (11.4 months vs. 12.0 months; p=0.99), or OS (10.5 months vs. 11.8 months; p=0.94) [6]. Similarly, Thomas et al. [15] retrospectively analyzed 137 MIBC patients who underwent NAC followed by RC. While the pCR rate was lower in patients with CIS at TURB compared with those without (9.5% vs. 23.2%; p=0.07), there were no significant differences in progression-free survival (27.6 months vs. 18.2 months; p=0.669) or OS (47.6 months vs. 29.4 months; p=0.819) [15]. Thus, based on the three studies discussed above, CIS at TURB was not associated with RFS regardless of NAC status.

Although neither of the two U.S.-based studies demonstrated statistical significance, both showed a trend toward longer RFS in patients with CIS at TURB compared with those without. Our study included a substantially larger cohort and confirmed the same trend of better RFS in patients with CIS at TURB, with the association reaching statistical significance. Although earlier studies were predominantly composed of White patients (86.2%–93.4%), whereas our cohort consisted entirely of Korean patients, prior evidence indicates no meaningful differences in disease-free or OS between White and Asian/Pacific Islander patients with BC [16,17]. Therefore, it is reasonable to compare our findings with those reported in earlier Western cohorts.

The prognostic impact of CIS in RC specimens is controversial. Moschini et al. [8] analyzed 1,128 patients with non-metastatic BC who were treated with RC and found that, among those with organ-confined disease (≤pT2), CIS in RC specimen was associated with worse CSS (HR 1.82, 95% CI 1.01–3.29, p=0.04), but not with RFS (HR 1.31, 95% CI 0.76–2.27, p=0.30). In another study with 410 patients with non-metastatic BC who were treated with RC, concomitant CIS in pure urothelial carcinoma was significantly associated with poor RFS (HR 2.1, 95% CI 1.19–3.58, p=0.01), while the association with CSS did not reach statistical significance (HR 1.7, 95% CI 0.92–3.00, p=0.09) [18]. More recently, meta-analyses have reported conflicting results. A meta-analysis of 23 studies including 20,647 patients showed that concomitant CIS in RC specimen was not associated with either RFS (pooled HR 1.06, 95% CI 0.99–1.13, p=0.459) or cancer-specific mortality (pooled HR 1.00, 95% CI 0.93–1.07, p=0.380) [19]. Another meta-analysis of 24 studies involving 18,845 patients also demonstrated no significant association between CIS in RC specimen and either CSS (pooled HR 1.06, 95% CI 0.97–1.16, p=0.186) and RFS (HR 1.05, 95% CI 0.99–1.11, p=0.098) [5]. Our results align with those of recent meta-analysis, indicating that CIS in RC specimens was not significantly associated with either RFS or CSS.

The discordance between the clinical perception of CIS as a high-risk lesion and the lack of survival impact at RC prompts further consideration. One possible explanation is that CIS at RC may represent residual or previously treated disease with diminished aggressive potential. CIS at TURB typically reflects the initial manifestation of high-grade urothelial dysplasia within a dynamic and potentially progressive disease environment. In contrast, CIS at RC follows prior therapeutic interventions, including NAC, which may have altered its pathological features or clinical behavior. This hypothesis is supported by findings from Gabrielson et al. [20], who demonstrated that patients with CIS-only in RC specimens after NAC had survival outcomes comparable to those with pCR. Another study also reported that the presence of CIS did not significantly influence survival outcomes in patients treated with NAC. Although concomitant CIS in RC specimens has been associated with decreased RFS, it has shown no impact on OS. Moreover, multivariate analysis has demonstrated that it is not an independent predictor of oncologic outcomes [21]. These findings collectively support the notion that CIS at RC may not be an aggressive factor associated with poor prognosis.

CIS at TURB is traditionally regarded as a high-risk feature, and we expected that it would be associated with worse oncologic outcomes. However, patients with CIS at TURB in our cohort demonstrated higher RFS and CSS compared with those without CIS. A potential explanation for the more favorable survival observed in the CIS at

TURB-positive group may relate to baseline clinical differences between the cohorts. Specifically, a greater proportion of patients in the CIS at TURB-positive group had ≤cT2 disease (65.7% vs. 60.1%, p=0.010) and more frequently received NAC (30.2% vs. 21.0%, p<0.001). However, in Cox regression analyses, NAC was not identified as a significant predictor of either RFS or CSS, suggesting that its impact on survival outcomes in this cohort may be limited. Although our study lacked detailed information on prior intravesical therapy, most physicians are likely to have followed guideline recommendations advocating intravesical BCG therapy in the presence of CIS in NMIBC. In cases of BCG-unresponsive NMIBC, early RC is recommended [22], which may have contributed to the favorable survival outcomes observed. Taken together, these differences in stage distribution and preoperative treatment may have contributed to the unexpectedly favorable survival outcomes observed in patients with CIS at TURB.

Aside from CIS, our analysis reaffirmed well-established prognostic indicators in BC. Non–organ-confined disease (≥pT3), lymphovascular invasion, lymph node involvement, positive surgical margins, and presence of metastasis were all associated with poorer RFS and CSS. Conversely, adjuvant therapy conferred a protective effect on CSS, highlighting its role in postoperative management. Moreover, recurrence itself was the strongest predictor of cancer-specific mortality, underscoring the importance of effective close surveillance and timely intervention.

This study has several limitations. First, due to its retrospective design, selection bias cannot be excluded. In addition, inter-institutional variability in surgical techniques and pathological reporting may have affected the consistency of CIS diagnosis, as not all TURB and RC specimens were centrally reviewed. Although all participating institutions were tertiary referral centers, repeat TURB practices at referral were not standardized, which may have influenced the detection of CIS at TURB. Furthermore, as previously mentioned, the database lacked detailed information on prior intravesical therapy, limiting further analysis of its potential impact on oncologic outcomes. Despite these limitations, the large multicenter cohort provides clinically meaningful data. Our findings suggest that the prognostic impact of CIS may differ according to the timing of detection, indicating that CIS should be interpreted with caution and within its clinical context.

CONCLUSIONS

Despite traditional assumptions of poor prognosis, CIS at TURB was associated with a lower risk of recurrence but was not associated with CSS following RC, whereas CIS identified in RC specimens was not significantly associated with survival outcomes. Although CIS at TURB has been reported to adversely affect intravesical recurrence prior to RC, its prognostic significance after cystectomy remains incompletely understood. In this context, our analysis of a large multicenter RC cohort in Korea adds further data regarding the potential prognostic role of CIS at TURB in the post-cystectomy setting. These results indicate that the prognostic implications of CIS at TURB may differ from traditional assumptions and should be interpreted with caution.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20250455.

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