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Association of initial transurethral resection staging on survival in radical cystectomy patients

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Purpose: Muscle-invasive bladder cancer (MIBC) is highly aggressive and presents complex treatment challenges. This study aimed to determine if the stage found during the initial transurethral resection of bladder tumor (TURBT) significantly impacts the prognosis of patients undergoing subsequent radical cystectomy (RC).

Materials and Methods: We retrospectively analyzed a multi-institutional database of 3,258 RC patients treated between January 2010 and December 2019, with confirmed survival data. The analysis included 68 variables such as baseline characteristics, initial and highest TURBT pathology, and final pathology. Patients were categorized into four groups based on initial T stage: pTa, pT1, pT2, and Tis (carcinoma *in situ*).

Results: The mean follow-up was 46.6±38.7 months. There were no significant differences in demographic variables between the groups. Overall survival (OS) rates differed significantly across the four groups (p=0.017). Crucially, the Tis group demonstrated the most favorable long-term outcomes, with an OS rate over 60% at 150 months. The initial pTa, pT1, and pT2 groups did not show significant OS differences among themselves.

Conclusions: The initial TURBT stage is associated with the prognosis of patients undergoing RC for bladder cancer. Patients with carcinoma *in situ* (Tis) is associated with more favorable outcomes from earlier cystectomy, leading to markedly improved long-term survival. For patients with more advanced initial stages (pT1, pT2), however, final pathology and lymph node status are more predictive of survival than the initial TURBT findings.

Keywords: Bladder cancer; Carcinoma *in situ*; Cystectomy

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INTRODUCTION

Bladder cancer is the 10th most common cancer worldwide, with approximately 549,000 new cases and 200,000 deaths annually in 2018 [1]. Among its types, muscle-invasive bladder cancer (MIBC) is particularly aggressive, with a high recurrence rate and a strong propensity for metastasis. These factors make early detection and precise staging critical for effective management.

Radical cystectomy (RC), with pelvic lymph node dissection (LND) and urinary diversion, is considered the gold-standard surgical treatment for MIBC and high-risk non-MIBC (NMIBC) [2]. Optimal preoperative staging is critical for determining the most effective treatment pathways. Recent advancements in artificial intelligence-driven digital pathology offer promising tools for enhancing the precision of these diagnostic processes, potentially reducing the inter-observer variability inherent in conventional staging [3]. Despite the widespread use of RC, survival outcomes vary widely, depending on factors such as tumor stage, lymph node involvement, and the presence of comorbidities.

A key area of debate in bladder cancer management is the role of transurethral resection of bladder tumors (TURBT) as a staging tool for MIBC [4]. TURBT is a crucial procedure performed to remove bladder tumors and obtain tissue for histopathological analysis. European Association of Urology guidelines emphasize its importance for accurate staging, recommending a thorough inspection of the entire urethra and bladder, en-bloc resection when possible, and biopsies of abnormal-looking urothelium [5].

Carcinoma *in situ* (CIS) is a high-grade, flat lesion confined to the bladder mucosa, with a gene expression profile resembling that of MIBC [6]. CIS is an aggressive form of NMIBC, for which early cystectomy has been suggested as a treatment option. In the absence of adjuvant bacillus Calmette-Guérin (BCG) therapy after TURBT, up to 50% of CIS cases progress to MIBC [7]. For patients with high-grade T1 lesions, it has also been suggested that early cystectomy may benefit patients, as the recurrence and progression rates to MIBC exceed 60% and 35%, respectively [4].

Our study investigates whether initial TURBT data influence survival outcomes in patients undergoing RC for bladder cancer. We aim to clarify the impact of early detection and appropriate staging on patient prognosis by analyzing a large cohort from multiple urologic centers in Korea.

MATERIALS AND METHODS

This study included 3,258 patients between January 2010 and December 2019 at 11 major urologic centers in Korea. Inclusion criteria were patients undergoing RC for MIBC or high-risk NMIBC (including BCG-unresponsive cases). Exclusion criteria were patients with incomplete pathological data or lost to follow-up. In June 2024, the Korean Bladder Cancer Study Group of the Korean Urological Oncology Society established a web-based electronic database, while a dedicated database manager collected and validated the data.

Indications for RC included muscle-invasive disease, high-grade T1, or Tis unresponsive to intravesical therapy. LND was categorized as: standard (up to the common iliac bifurcation), extended (including common iliac and presacral nodes), and super-extended (up to the aortic bifurcation). The study population comprised patients in the following initial TURBT stages: Ta (non-invasive papillary carcinoma), T1 (tumor invading subepithelial connective tissue), T2 (tumor invading the muscle layer), and Tis (CIS). Data on patient demographics, tumor characteristics, and treatment details (including neoadjuvant chemotherapy, final pathology, and LND) were systematically collected.

To maintain the accuracy of staging and survival outcomes, patients with incomplete pathological or overall survival (OS) data were excluded from the primary analysis. For the 68 variables systematically collected from the multi-institutional database, variables with more than 10% missingness were excluded for their impact on the overall cohort.

Patients were grouped based on their initial TURBT staging, and survival outcomes, including OS, were tracked over a mean follow-up period of 46.6±38.7 months. We analyzed whether the patient's initial stage influences OS after RC, along with related variables. Kaplan–Meier survival curves were generated to compare survival outcomes across the staging groups. Univariate and multivariate Cox proportional hazards models were used to identify independent predictors of survival, with a focus on the role of initial TURBT staging. All statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp.). A p-value of <0.05 was considered statistically significant.

The study was approved by the Institutional Review Board of Chung-Ang University Gwangmyeong Hospital (approval number: 2503-227-044) and conducted in accordance with the Declaration of Helsinki. Data confidentiality was ensured in compliance with the Data Protection Act 2016/679 (Spanish Government). Written informed consent was waived due to the retrospective nature of the study.

RESULTS

The study cohort comprised 3,258 patients, with 248 clas-

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sified as Ta, 1,450 as T1, 1,501 as T2, and 59 as Tis, based on initial TURBT staging (Table 1). The mean follow-up for cystectomy patients was 46.6±38.7 months (mean±standard deviation). There were no significant differences in baseline sex, American Society of Anesthesiologists (ASA) score, or pathology type between the groups (all p>0.05). Significant differences were observed in pre-cystectomy T and N stages, with the Tis group showing the lowest cT1 (60.7%, p<0.001 and cN0 (91.2%, p=0.002).

Table 2 and Supplementary Table 1 outlines the cystectomy procedures. Among all patients, 73.1% underwent open surgery (2,380/3,258), and 24.6% had robot-assisted cystectomies (803/3,258). Robotic procedures were most common in the pT2 group (26.6%) and least common in the Tis group (15.3%, p=0.009). Conduit diversion was performed in 52.4% (1,708/3,258) of patients, and neobladder reconstruction in 38.4% (1,250/3,258), with no statistically significant differences between the groups (p>0.999). The Tis group had the lowest rate of neoadjuvant chemotherapy (8.5%, p<0.001). LND was mostly performed using the standard template in all patients (77.6%, p<0.001), with no significant differences in diversion type or blood transfusion rates (p>0.999).

OS differs significantly among the four groups, with no significant differences between other groups. However, the Tis group showed notably favorable outcomes, with over 60% OS at 150 months (p=0.017, Fig. 1). In univariate analysis, patients with clinical Tis had a significantly lower risk of mortality compared to those with the Ta group, exhibiting a hazard ratio (HR) of 0.52 (95% confidence interval [CI] 0.30–0.91, p=0.022). In contrast, clinical T1 and T2 stages did not show a statistically significant difference in survival outcomes compared to the Ta group (p=0.978 and p=0.508, respectively). In multivariate analysis, statistical significance was attenuated, the Tis group continued to show a point estimate suggesting a lower risk of death compared to the reference (HR 0.71, 95% CI 0.33–1.52, p=0.378).

Multivariate analysis revealed that a final T stage of T2 or higher was independently associated with worse OS rates (HR=1.32, p<0.001). Other significant influential factors included high ASA scores, diabetes, and preoperative T and N staging (Table 3).

The Tis group had favorable pathologic T and N stages (54.2% <pT2), which means early cystectomy, and the lowest incidence of lymph node involvement (8.4%, p=0.002). Also, Tis group had the lowest rate of neoadjuvant chemotherapy (8.5%, p<0.001), likely due to the lower initial clinical stage compared to the T1 and T2 groups. In contrast, the T1 and T2 groups had more advanced disease, with higher rates of lymph node involvement (Table 4).

DISCUSSION

This study highlights the prognostic association of initial TURBT staging, particularly for patients with CIS (Tis group) who demonstrated markedly better survival rates, likely attributed to timely RC. Early cystectomy is essential in CIS management, as factors such as tumor grade and stage, prior recurrences, tumor size, multifocality, and the presence of CIS can all help guide treatment decisions [8]. In contrast, patients with higher initial T stages (T1 and T2) had more advanced disease, often associated with heterogeneity, poorer outcomes, and higher rates of lymph node involvement, requiring more aggressive surgical approaches and adjuvant therapies [9].

CIS differs from papillary tumors in its immunological landscape, marked by higher levels of PD-1–positive cells in CIS lesions, which may contribute to its aggressive phenotype [10]. Additionally, CIS patients have a higher incidence of upper tract urothelial carcinoma, compared to other bladder cancer types, ranging from 1.7% to 2.9% [7]. The BCG response rate in CIS is 76.7%, with 17.4% undergoing RC [11]. Our study reports favorable outcomes for CIS patients who undergo early cystectomy.

The KEYNOTE-057 trial demonstrated the efficacy of pembrolizumab in patients with BCG-unresponsive, high-risk NMIBC who were either ineligible for or refused RC. However, its median disease-free survival (DFS) of 7.7 months and 12-month DFS rate of 43.5% make RC the gold-standard option for most patients [12]. Alternative treatments, such as nadofaragene firadenovec, nogapendekin alfa inbakicept plus BCG, pembrolizumab, and atezolizumab have been explored along with CG0070, CAD-05, and gemcitabine-docetaxel sequential therapy [13]. To date, pembrolizumab has shown the best 1-year progression-free survival (PFS) rate of 97% (95% CI 86.0%–99.2%) [14].

Early diagnosis of CIS has been associated with better therapeutic responses and reduced tumor progression. This is consistent with recent findings emphasizing that structured surveillance protocols in NMIBC significantly correlate with improved long-term survival by facilitating timely interventions [15]. For BCG-unresponsive CIS, the median PFS is nine months (interquartile range, 5–15 months) with RC as the primary treatment option [16]. The relatively low rate of neoadjuvant chemotherapy in the Tis group may reflect their lower T stage before cystectomy and favorable outcomes for RC alone. However, in a previous study, 45.6%, 25.4%, and 60.6% of CIS, NMIBC, and MIBC cases, respectively were missed by TURBT, emphasizing the need for thorough detection [17].

Table 1. Baseline demographic and clinical characteristics stratified by initial clinical T stage

Initial T stage	Ta (n=248)	T1 (n=1,450)	T2 (n=1,501)	Tis (n=59)	p-value
Sex					0.075
Male	220 (88.7)	1,298 (89.5)	1,378 (91.8)	56 (94.9)	
Female	28 (11.3)	152 (10.5)	123 (8.2)	3 (5.1)	
BMI (kg/m^2)	23.8±3.5	23.7±3.2	23.9±3.1	24.1±3.8	0.303
HTN	124 (50.0)	650 (44.8)	696 (46.4)	29 (49.2)	0.430
DM	59 (23.8)	344 (23.7)	326 (21.7)	16 (27.1)	0.501
ASA score					0.133
1	39 (15.7)	206 (14.2)	197 (13.1)	11 (18.6)	
2	171 (69.0)	978 (67.4)	1,031 (68.7)	28 (47.5)	
≥3	38 (15.3)	266 (18.3)	273 (18.2)	20 (33.9)	
Grade					<0.001
Low	86 (36.8)	131 (9.3)	54 (3.7)	5 (15.6)	
High	148 (63.2)	1,282 (90.7)	1,399 (96.3)	27 (84.4)	
Pathology type					0.536
Urothelial carcinoma	204 (95.3)	1,181 (91.3)	1,134 (90.6)	56 (96.6)	
Squamous carcinoma	1 (0.5)	4 (0.3)	4 (0.3)	0 (0.0)	
Adenocarcinoma	9 (4.2)	107 (8.3)	113 (9.0)	2 (3.4)	
Etc.	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	
CIS	63 (26.0)	354 (25.0)	408 (28.4)	56 (100.0)	<0.001
Variant					<0.001
None	234 (98.3)	1,225 (87.6)	1,087 (78.5)	59 (100.0)	
Squamous	2 (0.8)	47 (3.4)	102 (7.4)	0 (0.0)	
Glandular	1 (0.4)	23 (1.6)	45 (3.3)	0 (0.0)	
Micropapillary	0 (0.0)	63 (4.5)	69 (5.0)	0 (0.0)	
Nested	0 (0.0)	8 (0.6)	34 (2.5)	0 (0.0)	
Plasmatoid	0 (0.0)	9 (0.6)	10 (0.7)	0 (0.0)	
Sarcomatoid	1 (0.4)	18 (1.3)	30 (2.2)	0 (0.0)	
Etc.	0 (0.0)	5 (0.4)	7 (0.5)	0 (0.0)	
T stage					<0.001
cT1	99 (41.1)	523 (37.5)	128 (8.8)	34 (60.7)	
cT2	66 (27.4)	385 (27.6)	638 (43.9)	12 (21.4)	
cT3	56 (23.2)	378 (27.1)	557 (38.3)	3 (5.4)	
cT4	20 (8.3)	109 (7.8)	130 (8.9)	7 (12.5)	
N stage					0.002
cN0	224 (92.2)	1,195 (86.0)	1,217 (83.6)	52 (91.2)	
cN1	8 (3.3)	95 (6.8)	147 (10.1)	3 (5.3)	
cN2	8 (3.3)	84 (6.0)	68 (4.7)	2 (3.5)	
cN3	3 (1.2)	16 (1.2)	24 (1.6)	0 (0.0)	
M stage					0.651
cM0	233 (97.1)	1,345 (96.3)	1,399 (95.9)	58 (98.3)	
cM1	7 (2.9)	52 (3.7)	60 (4.1)	1 (1.7)	

Values are presented as number (%) or mean±standard deviation.
Missing values with unidentified variables were excluded.
Ta, non-invasive papillary carcinoma; T1, tumor invading subepithelial connective tissue; T2, tumor invading the muscle layer; Tis, carcinoma *in situ*.
BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; ASA, American Society of Anesthesiologists; CIS, carcinoma *in situ*.

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Table 2. Operative and perioperative characteristics according to initial T stage

Initial T stage	Ta (n=248)	T1 (n=1,450)	T2 (n=1,501)	Tis (n=59)	p-value
Neoadjuvant chemotherapy	47 (19.0)	257 (17.7)	465 (31.0)	5 (8.5)	<0.001
Cystectomy type					0.009
Open	190 (76.6)	1,064 (73.4)	1,076 (71.7)	50 (84.7)	
Laparoscopic	9 (3.6)	41 (2.8)	25 (1.7)	0 (0.0)	
Robot	49 (19.8)	345 (23.8)	400 (26.6)	9 (15.3)	
Diversion type					>0.999
Ileal conduit	130 (52.4)	767 (53.6)	772 (52.4)	39 (66.1)	
Neobladder	94 (37.9)	534 (37.3)	609 (41.3)	13 (22.0)	
Ureterocutaneostomy	19 (7.7)	122 (8.5)	89 (6.0)	7 (11.9)	
Etc.	3 (1.2)	6 (0.4)	2 (0.1)	0 (0.0)	
Corporeal type					0.006
Open	150 (71.8)	902 (71.3)	771 (65.2)	49 (84.5)	
Extracorporeal	37 (17.7)	190 (15.0)	231 (19.5)	2 (3.4)	
Intracorporeal	22 (10.5)	174 (13.7)	181 (15.3)	7 (12.1)	
Lymph node dissection					<0.001
None	23 (9.7)	110 (7.9)	87 (6.0)	6 (10.3)	
Limited	14 (5.9)	101 (7.2)	53 (3.7)	3 (5.2)	
Standard	133 (55.9)	814 (58.1)	844 (58.6)	45 (77.6)	
Extended	54 (22.7)	304 (21.7)	311 (21.6)	3 (5.2)	
Super extended	14 (5.9)	72 (5.1)	145 (10.1)	1 (1.7)	
Blood transfusion	73 (31.5)	516 (39.2)	483 (37.6)	21 (36.2)	>0.999

Values are presented as number (%).
Missing values with unidentified variables were excluded.
Ta, non-invasive papillary carcinoma; T1, tumor invading subepithelial connective tissue; T2, tumor invading the muscle layer; Tis, carcinoma *in situ*.

In contrast, patients with higher initial TURBT stages, such as T1, often present with more advanced disease and poor prognoses. While there have been debates regarding re-TURBT in these cases, large-scale studies have revealed 50% prevalence rates for residual tumors and 10% upstaging to invasive disease at re-TURBT in T1 patients [18]. Re-TURBT also plays a critical role in bladder preservation therapy for MIBC [19]. Prospective clinical evidence further reinforces that a repeat TURBT in T1 high-grade cases is a vital diagnostic step to identify patients who would benefit from immediate RC rather than continuing bladder-sparing approaches [20]. Additionally, more than 70% of CIS patients have concomitant CIS rather than CIS alone [11], necessitating the need for BCG treatment and maintenance therapy for high-risk patients [20]. However, only 16% of patients complete the full course, underscoring the need for accurate preoperative staging and tailored treatment strategies, such as early cystectomy, based on individual patient disease characteristics [21-23].

Despite the robust nature of our dataset, the study has several limitations. First, we lacked data on the number of recurrences before RC, clinical stage immediately before RC,

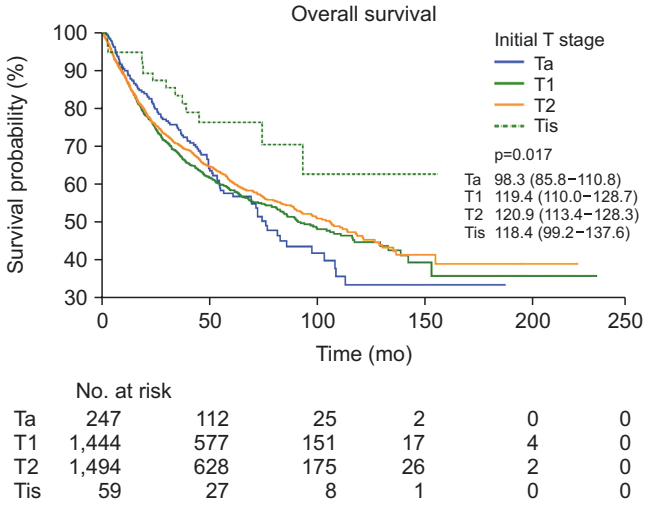

Fig. 1. Kaplan–Meier survival curves for overall survival based on initial transurethral resection of bladder tumor (TURBT) staging. Patients are categorized into four groups based on their initial TURBT stage. Ta, non-invasive papillary carcinoma; T1, tumor invading subepithelial connective tissue; T2, tumor invading the muscle layer; Tis, carcinoma *in situ*.

Table 3. Univariate and multivariate Cox regression analyses of risk factors associated with overall survival

	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Initial T stage				
Ta	Reference	-	-	-
T1	1.00 (0.81–1.23)	0.978	-	-
T2	0.93 (0.76–1.15)	0.508	-	-
Tis	0.52 (0.30–0.91)	0.022	0.71 (0.33–1.52)	0.378
Initial grade				
Low	Reference	-	-	-
High	0.82 (0.68–0.99)	0.043	0.82 (0.68–1.00)	0.048
Final T stage				
<T2	Reference	-	-	-
≥T2	1.32 (1.15–1.52)	<0.001	1.32 (1.15–1.52)	<0.001
ASA score				
1	Reference	-	-	-
2	1.14 (0.96–1.35)	0.143	-	-
3	1.27 (1.01–1.58)	0.038	-	-
4	1.98 (1.14–3.44)	0.015	1.72 (1.01–2.92)	0.046
Sex				
Male	Reference	-	-	-
Female	1.03 (0.84–1.26)	0.769	-	-
Diabetes	1.20 (1.05–1.38)	0.010	1.25 (1.09–1.43)	0.001
Preoperative T stage				
T1	Reference	-	-	-
T2	1.20 (1.01–1.44)	0.039	1.21 (1.02–1.44)	0.033
T3	1.32 (1.11–1.58)	0.002	1.35 (1.14–1.61)	0.001
T4	2.00 (1.59–2.51)	<0.001	2.10 (1.68–2.63)	<0.001
Preoperative N stage				
N0	Reference	-	-	-
N1	1.21 (0.98–1.48)	0.080	1.54 (1.22–1.96)	<0.001
N2	1.63 (1.29–2.08)	<0.001	-	-
N3	1.45 (0.96–2.19)	0.080	-	-

Ta, non-invasive papillary carcinoma; T1, tumor invading subepithelial connective tissue; T2, tumor invading the muscle layer; Tis, carcinoma *in situ*.
HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists.

and detailed BCG response status, all of which are established prognostic determinants. Second, the Tis group (n=59) is relatively small and may represent a clinically selected subset, potentially introducing selection bias. Third, procedural factors like detrusor muscle presence or enhanced imaging (narrow band image/blue-light) were not consistently recorded. Fourth, significant upstaging was observed in our cohort (e.g., 27.4% of initial Ta staged as cT2), suggesting that initial TURBT may have been suboptimally performed in some cases. This highlights the inherent challenges and staging biases in real-world clinical practice. Our observations are consistent with established literature, which reports that approximately 30%–50% of patients with clinical NMIBC are understaged during initial TURBT and are subsequently upstaged to muscle-invasive or non–organ-confined disease at the time of RC [24]. These significant understaging rates underscore the limitations of TURBT as a definitive staging tool and emphasize the necessity for clinical caution when interpreting initial pathological findings to guide treatment intensity.

This study demonstrates that initial TURBT staging added insight to determining survival outcomes in patients undergoing RC for bladder cancer. Patients with CIS can benefit from early RC, with improved long-term survival rates. These findings underscore the need for precise preoperative staging and individualized treatment strategies, par-

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Table 4. Final pathological T and N stage distribution by initial clinical T stage

	Ta (n=248)	T1 (n=1,450)	T2 (n=1,501)	Tis (n=59)	p-value
Pathologic T stage					<0.001
T0 or Tx	26 (10.7)	173 (12.0)	201 (13.5)	6 (10.2)	
Ta	26 (10.7)	40 (2.8)	10 (0.7)	2 (3.4)	
Tis	21 (8.6)	126 (8.7)	86 (5.8)	12 (20.3)	
T1	50 (20.5)	279 (19.3)	123 (8.2)	12 (20.3)	
T2	46 (18.8)	256 (17.7)	301 (20.2)	14 (23.8)	
T3	48 (19.7)	382 (26.5)	580 (38.8)	7 (11.9)	
T4	27 (11.1)	186 (12.9)	192 (12.8)	6 (10.2)	
<pT2	123 (50.5)	618 (42.8)	420 (28.2)	32 (54.2)	<0.001
Pathologic N stage					0.002
N0 or Nx	206 (84.1)	1,103 (76.5)	1,057 (70.9)	54 (91.6)	
N1	11 (4.5)	121 (8.4)	158 (10.6)	3 (5.1)	
N2	21 (8.6)	186 (12.9)	221 (14.8)	2 (3.4)	
N3	7 (2.9)	32 (2.2)	56 (3.8)	0 (0.0)	

Values are presented as number (%).
Missing values with unidentified variables were excluded.
Ta, non-invasive papillary carcinoma; T1, tumor invading subepithelial connective tissue; T2, tumor invading the muscle layer; Tis, carcinoma *in situ*.

ticularly when detecting CIS lesions and improving patient prognosis.

CONCLUSIONS

The initial TURBT stage is associated with the prognosis of patients undergoing RC for bladder cancer. Specifically, patients with CIS (Tis) is associated with more favorable outcomes from earlier cystectomy, demonstrating improved long-term survival rates compared to those with more advanced stages. Further prospective studies are needed to confirm these findings and optimize preoperative staging protocols.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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SUPPLEMENTARY MATERIAL

Supplementary material can be found via https://doi.org/10.4111/icu.20250573.

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