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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Prognosis of carcinoma in situ according to the presence of papillary bladder tumors after bacillus Calmette–Guérin immunotherapy

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Abstract

Purpose This study aimed at determining the relationship between classification according to the papillary tumor pattern of carcinoma in situ (CIS) of the bladder and prognosis, as this has not yet been well established.

Methods This study comprised a consecutive cohort of 254 patients (primary CIS: 66 patients, stage Ta-CIS: 52 patients, and stage T1-CIS: 136 patients) with CIS-associated bladder cancer. We classified CIS according to the pathological pattern of papillary tumors and analyzed prognostic factors, including CIS classification, for progression. We evaluated progression using two endpoints: infiltrative tumors detected at stage T1 or higher or at stage T2 or higher. Bacillus Calmette–Guerin (BCG) immunotherapy response was defined as no recurrence within 6 months.

Results Both the BCG immunotherapy response and CIS classification were significant prognostic factors for both the endpoints. Patients with CIS-associated stage Ta urinary bladder cancer had better prognosis for both the endpoints than those with stage T1 cancer or those with primary CIS. BCG immunotherapy response ($p < 0.001$) and age ($p = 0.007$) were also significant prognostic factors for the progression of stage T2 or higher infiltrative tumors. The prognosis of patients with recurrent primary CIS (12/26, 46.2%) and T1-CIS (25/45, 55.6%) was poor for progression; distant metastasis occurred in approximately 40% of these patients.

Conclusions Clinicians should consider radical surgery for poor prognosis in patients with recurrent CIS-associated T1 cancer or primary CIS. The CIS classification according to the tumor pattern reflects the prognosis.

Keywords Bacillus Calmette–Guérin · Carcinoma in situ · Classification · Urinary bladder · Neoplasms

Introduction

Carcinoma in situ (CIS) is a high-grade mucosal urothelial cancer of the bladder. CIS is often found with papillary tumors, and the concomitant occurrence of CIS increases the risk of recurrence and progression (Sylvester et al. 2006). Without treatment, 54% of patients with CIS experience progression to muscle-invasive disease, and 90% of patients experience recurrence (Lamm 1992). CIS cannot be treated by endoscopic surgery alone; hence, additional

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treatment is necessary. Since Morales et al. introduced the empirical 6-week bacillus Calmette–Guérin (BCG) immunotherapy for urothelial carcinoma in 1976 (Morales et al. 1976), BCG has been the standard treatment for CIS.

The most widely used CIS classification system is composed of three clinical types described in the 2016 European Association of Urology (EAU) guidelines (Babjuk et al. 2017). This classification of patients with CIS is based on the clinically detectable manifestations. Primary CIS (P-CIS) is CIS detected in patients without previously diagnosed bladder cancer and who exhibit no concomitant papillary tumors at the time of CIS diagnosis. Secondary CIS (S-CIS) is CIS detected in patients during follow-up for previously diagnosed bladder cancer without CIS. Concurrent CIS (C-CIS) is detected in patients diagnosed with CIS associated with papillary tumors but who do not have any previous history of bladder cancer (Fig. 1).

This clinical classification is advantageous in that it can intuitively classify the bladder tumor according to the detected pattern. However, according to this classification, both S-CIS and C-CIS are associated with papillary tumors, in line with the World Health Organization's (WHO) pathological classification of Ta and T1, albeit these two types display different aggressiveness. Under this clinical classification, some authors have reported that P-CIS patients have a better prognosis than S-CIS or C-CIS patients (Griffiths et al. 2002; Witjes 2004). However, other authors have reported that P-CIS patients have a worse prognosis than S-CIS or C-CIS patients (Takenaka et al. 2008; Gofrit et al. 2009).

The relationship between the classification of CIS according to the detected pattern (Babjuk et al. 2017) and prognosis has not been well established. The aim of this study was to analyze the prognostic value of the classification system in relation to the progression and mortality of patients with CIS. The categorization was based on the pathological pattern of papillary tumors that coexisted with CIS.

Materials and methods

This study was performed after obtaining approval and insight from the Asan Medical Center Institutional Review Board, Seoul, Republic of Korea (IRB No. S2018-0561-0001). The medical records of patients diagnosed as having CIS with or without papillary tumors between January 1999 and January 2014 were reviewed retrospectively. All enrolled patients had a pathology consistent with CIS based on the first transurethral resection of bladder tumor (TURBt) specimen. We excluded patients who had a stage pT2 tumor according to the analysis of the first TURBt. Patients who underwent radical cystectomy after the initial TURBt without any other treatment were also excluded. Patients who were unable to be treated with BCG therapy or who were not expected to experience a general effect, for example, immunocompromised patients, those who were receiving immunosuppressants, and those who had uncontrolled urinary

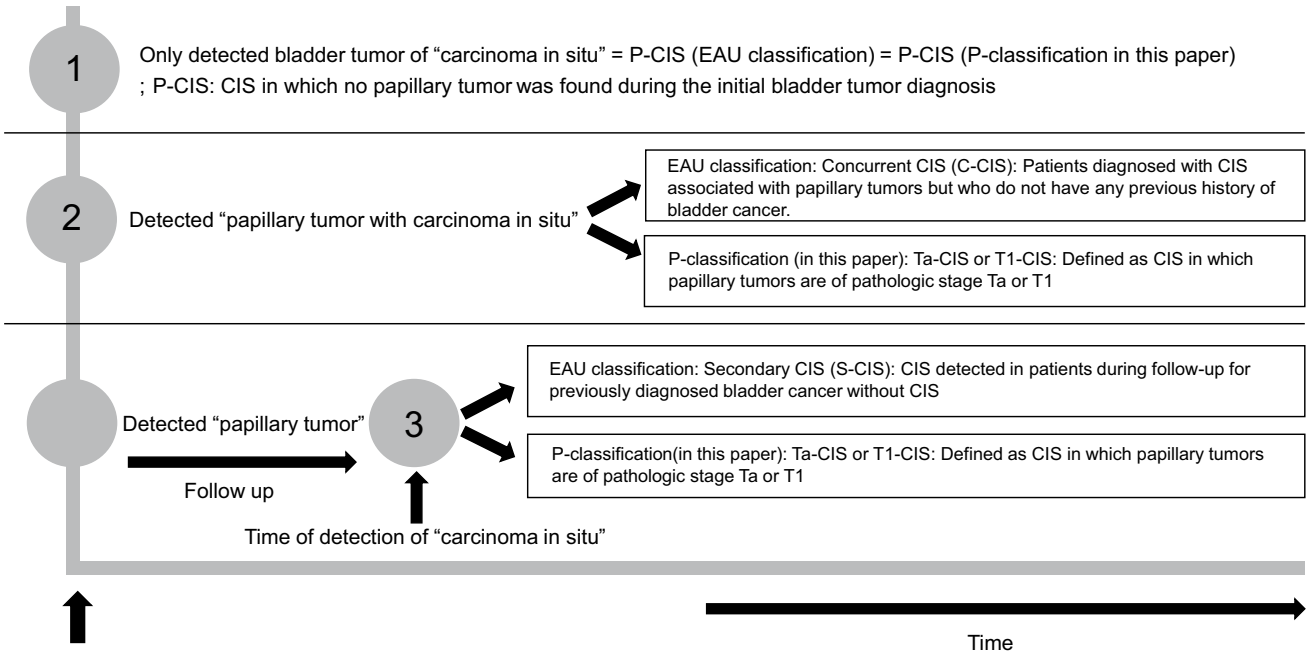

Fig. 1 Classification of carcinoma in situ (EAU classification and pathological classification)

tract infections, were excluded. All the enrolled patients were followed up for > 6 months and were evaluated for the recurrence of bladder cancer.

Pathological classification of CIS (P-classification)

We classified bladder CIS according to the pathological T stage of papillary tumors and investigated whether this classification reflected the prognosis. P-CIS was defined as CIS in which no papillary tumor was found during the initial bladder tumor diagnosis. Ta-CIS and T1-CIS were defined as CIS in which papillary tumors of pathologic stage Ta or T1, respectively, were found previously or at the time of CIS diagnosis (Fig. 1).

Endpoints

Clinical T1 stage or higher (cT1 or higher) was defined as progression to a detectable pathologic T1-stage or higher infiltrative tumor in the bladder or the occurrence of extravesical metastasis. Similarly, clinical T2 stage or higher (cT2 or higher) was defined as the progression to a detectable pathologic T2-stage or higher infiltrative tumor in the bladder or the occurrence of extravesical metastasis. Other therapeutic options (radical cystectomy, radiation therapy, chemotherapy) are considered for advanced bladder cancer presenting with pathologic T2-stage or higher infiltrative tumors. To compare the clinical outcome of P-CIS with Ta-CIS, we used cT1 and higher as the first endpoint of progression. We used cT2 or higher as the second endpoint of progression to compare the clinical outcome of each EAU classification (P-CIS vs. S-CIS vs. C-CIS) and P-classification (P-CIS vs. Ta-CIS vs. T1-CIS). We divided the patients according to the BCG response. BCG responders were defined as patients who had no recurrence on cystoscopy and who had negative urine cytology within 6 months.

Patient follow-up and monitoring

Patients were followed up with cystoscopy every 3 months; urine cytology testing was used in cases of biopsies with suspicious lesions. After 1 year, patients were followed up every 6 months for 3 years. Yearly imaging (computed tomography urography, ultrasonography) was performed for evaluating extravesical metastases. The time of recurrence was defined as the first time of detection of the gross lesion on cystoscopy or imaging after pathologic confirmation or imaging surveillance. Abnormal cytology findings during follow-up were considered to represent recurrence after confirming the causative lesion. Pathologic classification of the analyzed samples was performed according to the WHO 1973 classification of urothelial carcinoma.

Statistical methods

We used analysis of variance to compare each group by age in this study (Table 1). We analyzed the patients to compare clinical features according to BCG instillation and CIS type in each group using either the Chi squared test or Fisher's exact test, as appropriate (Tables 1 and 2). Univariate and multivariate Cox proportional hazard models were used to analyze the significance of factors related to disease progression. We generated a Cox proportional hazard model that could predict each endpoint by selecting a variable by the forward selection method. We generated survival curves using the Kaplan–Meier method and obtained p values using the log-rank test. Statistical significance was obtained when the p value was < 0.05. Statistical analyses were performed using SPSS software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

Results

The study comprised a consecutive cohort of 254 patients (P-CIS: 66 patients, Ta-CIS: 52 patients, and T1-CIS: 136 patients) among 931 patients diagnosed with CIS-associated bladder cancer after excluding 5014 patients who were diagnosed with bladder cancer without CIS. Of the 931 patients diagnosed with CIS, 677 were excluded, as indicated in Fig. 2. There were no differences in the mean age at the initial diagnosis of urothelial cancer or in the male:female ratio (Table 1). Overall, 38 (73%, 38/52) patients with Ta-CIS and 123 (90.4%, 123/136) patients with T1-CIS were diagnosed with CIS-associated papillary tumors without a previous history of urothelial cancer. Initial presenting symptoms were investigated for these patients; lower urinary tract symptoms (LUTs) included symptoms of frequency, urgency, weak stream, residual urine sensation, and dysuria.

In cases of more advanced papillary tumors, a higher proportion of patients complained of gross hematuria [P-CIS: 23/66 (34.8%) patients, Ta-CIS: 21/38 (55.3%) patients, and T1-CIS: 87/123 (70.7%) patients]. The initial presenting symptoms of urothelial cancer were significantly related to the P-classification ($p < 0.001$). Half of the patients with P-CIS (50%, 33/66) were initially investigated because of the complaints of LUTs; furthermore, LUTs were more common symptoms in P-CIS than in other categories ($p = 0.000$). Compared to patients with Ta-CIS, patients with P-CIS had a more frequent tendency for the initial symptoms to be LUTs [50.0% (33/66) vs. 4.7% (2/38), $p < 0.001$] and a less frequent tendency for gross hematuria [34.8% (23/66) vs. 55.3% (21/38), $p = 0.042$; Table 1].

Most patients with T1-CIS had a papillary tumor grade of 3 (93.3%, 127/136); moreover, the incidence of grade 3

Table 1 Characteristics and clinical manifestations of the patients treated with bacillus Calmette–Guerin immunotherapy

	Total	Primary CIS	Ta-CIS	T1-CIS	*p*
Number of patients, *n* (%)	254 (100)	66 (26.0)	52 (20.5)	136 (53.5)	
Age, year ± SD	64.6 ± 9.6	64.3 ± 7.8	63.44 ± 11.5	65.27 ± 9.6	0.485
Sex, *n* (%)					
Male	219 (86.2)	60 (90.9)	44 (84.6)	115 (84.6)	0.438
Concurrent papillary tumor		–	38 (73.0)	123 (90.4)	
Presenting symptoms		66 (100)	38 (100)	123 (100)	< 0.001
Gross hematuria		23 (34.8)	21 (55.3)	87 (70.7)	
Microscopic hematuria		3 (4.5)	4 (10.5)	6 (4.9)	
LUTs		33 (50.0)	2 (5.3)	14 (11.4)	
Incidental		4 (6.1)	7 (18.4)	7 (5.7)	
Unknown		3 (4.5)	4 (10.5)	9 (7.3)	
Initial CIS description		66 (100)	38 (100)	123 (100)	0.002
Focal		16 (24.2)	14 (36.8)	27 (22.0)	
Diffuse		14 (21.2)	3 (7.9)	27 (22.0)	
Multifocal		24 (36.4)	9 (23.7)	11 (8.9)	
Unknown		12 (18.2)	12 (31.6)	58 (47.2)	
Papillary tumor			52 (100)	136 (100)	< 0.001
pTxG1-2		–	23 (44.2)	9 (6.6)	
pTxG3		–	27 (51.9)	127 (93.3)	
Unknown			2 (3.8)	1 (0.7)	
Tumor number			38 (100)	123 (100)	0.802
1			10 (19.2)	26 (19.1)	
2–4			15 (28.8)	50 (36.8)	
5			11 (21.2)	28 (20.6)	
Unknown			2 (16.3)	19 (7.3)	
Tumor size			38 (100)	123 (100)	0.077
1 cm			14 (36.8)	24 (19.5)	
1–3 cm			16 (42.1)	47 (38.2)	
> 3 cm			5 (13.1)	31 (25.2)	
Unknown			3 (7.8)	21 (17.0)	
Follow-up period, months		46.1 [23.4; 89.3]	30.6 [17.8; 48.9]	38.8 [16.9; 78.3]	< 0.001

CIS carcinoma in situ, *BCG* bacillus Calmette–Guerin therapy, *SD* standard deviation, *LUTs* lower urinary tract symptoms

Table 2 Response to bacillus Calmette–Guerin immunotherapy and clinical outcomes related to prognosis

	Total	Primary CIS	Ta-CIS	T1-CIS	*p*
Number of patients, *n* (%)	254 (100)	66	52	136	
BCG immunotherapy					
BCG responder		57 (86.4)	48 (92.3)	121 (89.0)	0.592
Recurrence, *n* (%)		26 (39.4)	14 (26.9)	45 (33.1)	0.359
Progression to					
T1 or higher, *n* (%)		15 (22.7)	3 (5.8)	–	0.004
T2 or higher, *n* (%)		12 (18.2)	2 (3.8)	25 (18.4)	0.035
Distant metastasis, *n* (%)		5 (7.6)	0 (0)	10 (7.4)	0.128
Death, *n* (%)		12 (18.2)	4 (7.7)	14 (10.3)	0.155
Bladder cancer		3 (4.5)	0 (0)	4 (2.9)	
Other cause		7 (10.6)	3 (5.8)	7 (5.1)	
Unknown		4 (6.0)	1 (1.9)	3 (2.2)	

BCG bacillus Calmette–Guerin therapy, *CIS* carcinoma in situ

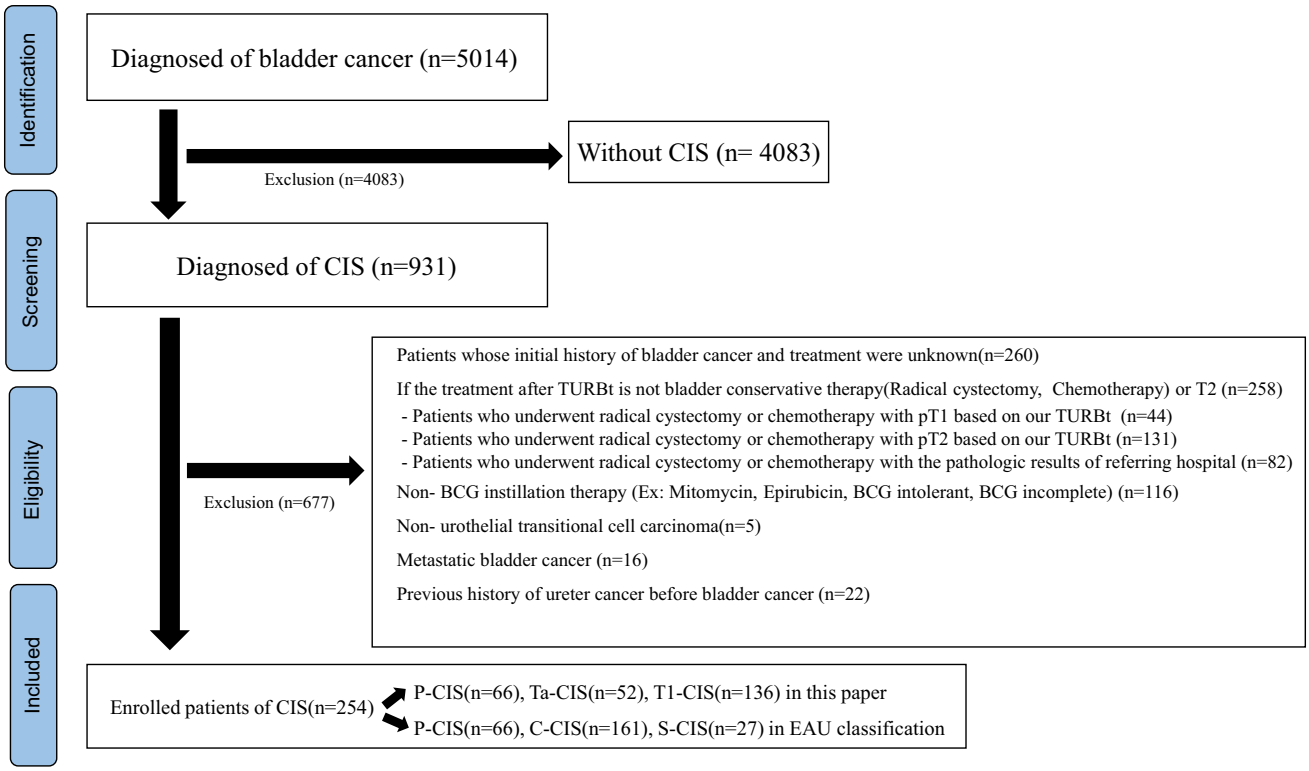

Fig. 2 Flow diagram of patient identification

papillary tumors in patients with T1-CIS was higher than that in patients with Ta-CIS (51.9%, 27/52). In contrast, the number of papillary tumors associated with CIS was not different across the categories. Additionally, there was a higher incidence of large papillary tumors (> 3 cm) in patients with T1-CIS than in patients with Ta-CIS, but the difference did not reach statistical significance (Table 1).

The median follow-up period for patients with bladder cancer was 35.9 months [P-CIS: 46.1 (23.4; 89.3), Ta-CIS: 30.6 (17.8; 48.9), T1-CIS: 38.8 (16.9; 78.3)]. Responses to the initial BCG instillations were not different based on the type of CIS (Table 2). Furthermore, there was no difference in recurrence rates between P-CIS [39.4% (26/66)], Ta-CIS [26.9% (14/52)], and T1-CIS [33.1% (45/136); Table 2].

When patients with P-CIS and Ta-CIS were analyzed using univariate and multivariate Cox hazard models based on whether they had pT1 or higher progression, response to BCG ($p = 0.005$) and presence of Ta-CIS ($p = 0.032$) were significantly favorable prognostic factors (Table 3). Moreover, age as a continuous variable, non-response to BCG, and having T1-CIS were significantly prognostic factors for progression to pT2 or higher ($p = 0.007$, $p < 0.001$, $p = 0.043$, and $p = 0.010$, respectively; Table 4). However, the EAU classification of CIS (P-CIS, C-CIS, or S-CIS) was not a significant prognostic factor for T2 or higher progression. When patients with P-CIS and Ta-CIS were analyzed using the Kaplan–Meier model with regard to the pT1 progression-free survival rate, patients with Ta-CIS had a higher 5-year progression-free survival rate (94.2%) than did patients with P-CIS (77.2%; $p = 0.021$; Fig. 3). In terms of the pT2 progression-free survival rate, patients with Ta-CIS had a statistically higher 5-year progression-free survival rate (96.2%) than did patients with P-CIS (81.8%) or T1-CIS (81.6%; $p = 0.018$; Fig. 4). There was no difference regarding pT2 progression-free survival rate between patients with P-CIS and T1-CIS.

After the patients were divided according to the P-classification, the ratio of BCG responders to the recurrence rate was not different in each group (Table 2). Among patients with recurrence, 46.2% (12/26) of P-CIS patients, 14.2% (2/14) of Ta-CIS patients, and 55.6% (25/45) of T1-CIS patients progressed to pT2 or higher disease. Among these patients, distant metastasis was the form of progression in 19.2% of P-CIS (5/26) patients and 22.2% of T1-CIS (10/45) patients. For all the patients regardless of recurrence, Ta-CIS had a favorable prognosis for any progression, and patients with Ta-CIS had no distant metastasis or cancer-specific death (Table 2).

Among 123 patients who were classified as having T1-CIS in this study, 58 (47.1%, 58/123) underwent repeated TURBt restaging and 49 (39.8%, 49/123) were classified without repeated TURBt restaging, but the muscularis

Table 3 Univariate and multivariate analyses of tumor progression to pT1 or higher

	Univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age	1.050 (0.996–1.107)	0.069		
Sex		0.447		
Women	Reference			
Men	2.188 (0.290–16.506)			
BCG response				
Responder	Reference		Reference	
Non-responder	4.380 (1.548–12.394)	0.005	4.513 (1.587–12.834)	0.005
P-classification				
Ta-CIS	Reference		Reference	
P-CIS	3.896 (1.126–13.482)	0.032	3.967 (1.147–13.725)	0.030
Presenting symptoms				
Gross hematuria	Reference			
Microscopic hematuria	1.006 (0.111–9.111)	0.996		
LUTs	3.388 (0.300–38.212)	0.324		
Incidental	2.597 (0.323–20.885)	0.370		
CIS description				
Focal	Reference			
Diffuse	0.918 (0.265–3.178)	0.892		
Multifocal	1.765 (0.470–6.636)	0.400		

HR hazards ratio, *CI* confidence interval, *BCG* bacillus Calmette–Guerin therapy, *LUTs* lower urinary tract symptoms, *CIS* carcinoma in situ, *P-CIS* primary CIS

propria layer was included in the specimen. Overall, 107 patients were diagnosed with T1-CIS with the muscularis propria layer included in the specimens (82.8%, 107/123). No patient with Ta-CIS underwent repeated TURBt restaging. Of the patients, 25 (65.7%, 25/38) were diagnosed with Ta-CIS with the muscularis propria layer included in the specimens.

Discussion

We classified patients according to the P-classification proposed in this study and evaluated the usefulness of this classification as a prognostic factor for cT2 or higher progression using a multivariate model in patients with P-CIS, Ta-CIS, and T1-CIS. We found that the response to BCG therapy reflects prognosis in all models.

Previously, many studies have reported the prognosis of P-CIS compared to that of C-CIS and S-CIS. For instance, Orozco et al. reported a favorable prognosis for P-CIS with regard to cancer-specific survival compared with that of C-CIS and S-CIS, but half of patients with C-CIS and S-CIS exhibited muscle-invasive bladder cancer, and poor survival of these patients may have influenced the results (Orozco et al. 1994). Additionally, Cheng et al. reported low progression-free survival for patients with P-CIS compared to patients with other CIS classifications (54% vs. 65%), although the results did not reach statistical significance (Cheng et al. 1999). In contrast to the current results, according to the clinical classification, the type of CIS was not a significant prognostic factor (Takenaka et al. 2008; Gofrit et al. 2009; Andius et al. 2004). Moreover, in one study, the presence of papillary tumors was an independent prognostic factor for progression (Griffiths et al. 2002), but in another study, the presence of T1 papillary tumors was not a significant prognostic factor (Takenaka et al. 2008). However, similar to the present results, recent studies have shown a less favorable prognosis for P-CIS compared to that for Ta-CIS in C-CIS and S-CIS, after excluding T1-CIS (Chade et al. 2010).

The T-stage of bladder cancer is determined by the infiltration level, and the prognosis depends on the tumor stage. Stage Ta tumors are limited to the basement membrane and do not reach the lymphatic vessels; hence, the risk of metastasis is low. The progression of Ta tumors to T1 tumors occurs when the tumor invades the basement membrane, and high progression has been related to poor survival-related prognosis (Nieder et al. 2005; Cao et al. 2010). While the progression to muscle-invasive bladder cancer is an important parameter for determining a treatment plan and prognosis, the clinical significance of invading the basement membrane has not been clearly elucidated. In recent years, the International Bladder Cancer Group defined the progression of CIS from pTa to pT1 as being indicative of a high risk

Table 4 Univariate and multivariate analyses of tumor progression to stage pT2 or higher

	Univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age	1.059 (1.020–1.099)	0.002	1.056 (1.015–1.099)	0.007
Sex				
Men	Reference			
Women	1.586 (0.698–3.607)	0.271		
BCG response				
Responder	Reference		Reference	
Non-responder	5.442 (2.789–10.618)	< 0.001	5.457 (2.782–10.706)	< 0.001
P-classification				
Ta-CIS	Reference		Reference	
P-CIS	4.152 (0.929–18.561)	0.007	4.800 (1.049–21.961)	0.043
T1-CIS	6.113 (1.444–25.879)	< 0.001	6.848 (1.583–29.629)	0.010
Presenting symptoms				
Gross hematuria	Reference			
Microscopic hematuria	2.475 (0.820–7.470)	0.108		
LUTs	0.861 (0.332–2.232)	0.758		
Incidental	1.891 (0.627–5.700)	0.258		
CIS description				
Focal	Reference			
Diffuse	2.160 (0.822–5.676)	0.118		
Multifocal	0.781 (0.228–2.675)	0.694		
Tumor number	Reference	0.552		
1	1.444 (0.430–4.843)	0.177		
2–4	2.377 (0.676–8.358)			
5				
Tumor size				
1 cm	Reference			
1–3 cm	0.787 (0.279–2.219)	0.651		
>3 cm	0.628 (0.177–2.231)	0.472		
EAU classification				
P-CIS	Reference			
C-CIS	0.961 (0.471–1.961)	0.914		
S-CIS	0.327 (0.610–4.402)	0.327		

HR hazards ratio, *CI* confidence interval, *BCG* bacillus Calmette–Guerin therapy, *CIS* carcinoma in situ, *EAU* European Association of Urology, *P-CIS* primary CIS, *C-CIS* concurrent CIS, *S-CIS* secondary CIS

of advanced disease (Lamm et al. 2014). C-CIS and S-CIS include various T-stage tumors of different prognoses in the same category, and the overall prognosis may be associated with the T stage of the bladder tumor.

The initial presenting set of symptoms is a critical factor in deciding the type of evaluation for patients with suspected urologic disease (Singh et al. 2003). In one study, initial presentation with gross hematuria was associated with an advanced pathologic stage (Ramirez et al. 2016). In the present study, the initial presenting symptom of more than half of patients with P-CIS was dysuria. Many patients with P-CIS presented to our hospital with LUTs, and bladder cancer was often diagnosed after an interval following treatment for such symptoms. The diagnosis is delayed when the patient does not have symptoms typical of bladder cancer such as gross hematuria (Singh et al. 2003), and the delayed diagnosis could be related to the poor prognosis of P-CIS. Although a relationship with BCG response and non-response was not established, BCG response was a significant prognostic factor for progression, as reported by van Gils-Gielen et al. (1995). However, contrasting results have also been reported (Gofrit et al. 2009; Chade et al. 2010). Moreover, age was a significant prognostic factor for progression-free survival (Cheng et al. 1999).

There are compelling theories concerning dual pathways of bladder carcinogenesis, with different pathways for low-grade superficial papillary tumors and high-grade non-papillary tumors. Based on the CIS classification, only a

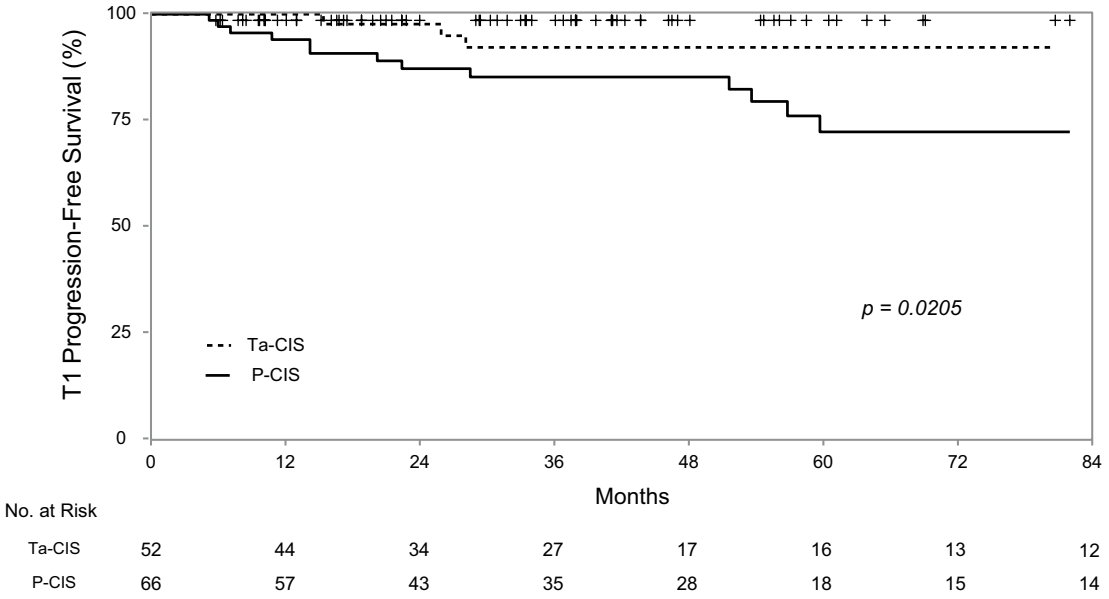

Fig. 3 Progression-free survival rate for T1-stage tumors according to the type of carcinoma in situ

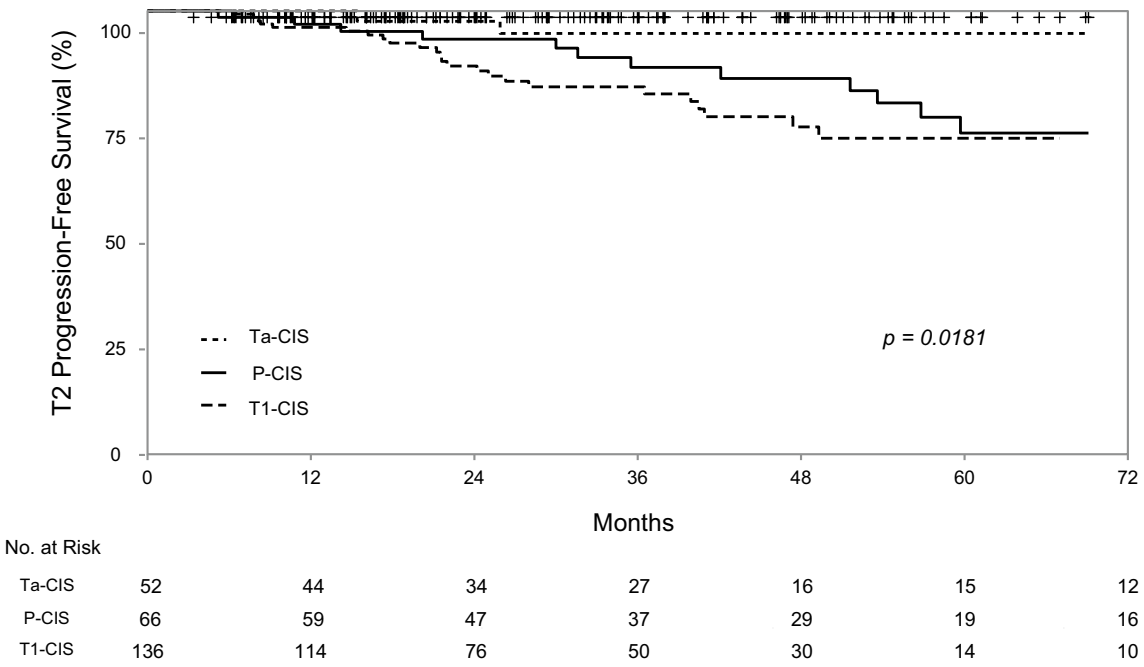

Fig. 4 Progression-free survival rate for T2-stage tumors according to the type of carcinoma in situ

fraction (10–15%) of low-grade superficial papillary tumors proved to be high-grade invasive bladder tumors (McConkey et al. 2010). When considering the grade of a papillary tumor apart from P-CIS, a high-grade papillary tumor associated with CIS was observed less frequently in patients with Ta-CIS than in patients with T1-CIS. Except for P-CIS, which accounts for the non-papillary high-grade pathway, high-grade T1-CIS results in more advanced genetic instability of the RB1/P53 papillary pathway than does low-grade Ta-CIS. Low-grade papillary tumors with CIS (44.2% of Ta-CIS) cannot be formed by the non-papillary pathway. In contrast, some components of T1-CIS can be formed by the non-papillary pathway. The rate of each pathway in a tumor differs depending on the percentage of low-grade tumors;

furthermore, each pathway exhibits different biological behaviors, may be related to the therapeutic response, and may influence prognosis (Chan et al. 2009).

The limitations of this study include its relatively low clinical application. This study was performed to evaluate the progression of papillary tumors associated with CIS in patients during follow-up for > 6 months for bladder preservation after BCG immunotherapy. We excluded patients who underwent radical cystectomy immediately after TURBt. This excluded patients who were diagnosed with T2, and clinically diagnosed with stage T1 but were at high risk of progression or had more aggressive malignant tumor features. This selection bias has reduced the range of patients in whom the classification can be applied in clinical practice, but it has the advantage that the patients in whom it can be applied are clear. Moreover, this study's results can be applied in predicting the prognosis of papillary bladder tumors of CIS.

Bladder conservative therapy in T1 + CIS was performed in patients whose papillary bladder cancers were adequately controlled by endoscopic surgery. The pathologic stage in radical cystectomy specimens of the 44 patients (Fig. 2) who underwent radical cystectomy after diagnosis of bladder cancer with TURBt T1 + CIS was as follows: pT0 + CIS ($n = 4$), pTa + CIS ($n = 5$), pT1 + CIS ($n = 16$), and pT2 ~ 4+CIS ($n = 19$). Only four patients underwent "early cystectomy" for radical cystectomy, although papillary tumors were well controlled [pT0 + CIS ($n = 4$)]. In the remaining patients, a radical cystectomy was considered for unresectable bladder cancer with TURBt rather than "early cystectomy". Four patients (pT0: 4), who may be included in this study, constituted a small number and the results of the study did not seem to have changed. Many patients included in this study were not in the period of repeated TURBt not being the gold standard treatment and about half of the patients had not undergone repeated TURBt restaging. This is a major limitation of this study. Bladder cancer treatment guidelines have changed over time, and the consensus for treatment may change following discussion between surgeons at each institution. Accordingly, this study is more reliable, as it is a single institutional study.

Conclusion

Response to BCG predicted progression and among CIS types, P-CIS and T1-CIS exhibited more aggressive progression than did Ta-CIS. Clinicians should perform radical surgery or curative treatment for patients with T1-CIS or P-CIS who experience relapse after BCG therapy. Although the pathologic classification of CIS reflects prognosis in this study, external validation is needed for widespread application of this classification.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Consent for publication Not applicable.

Data availability Data cannot be made available because of restrictions imposed by the Asan Medical Center Institutional Review Board (http://eirb.amc.seoul.kr). In case of further questions, the homepage of the IRB is "http://eirb.amc.seoul.kr" and the contact number for the person in charge of document access is "Tel: +82-2-3010-7165."

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