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Clinical Outcome of Primary versus Secondary Carcinoma in Situ of the Bladder

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Abstract

Purpose—Differences in clinical outcomes between primary and secondary bladder carcinoma is situ (CIS) are still unclear. We sought to compare the clinical outcomes of primary versus secondary CIS and to identify predictive factors.

Materials and Methods—A retrospective analysis of 476 patients with high grade cTis (221 primary and 255 secondary CIS) from 1990 to 2008 in a high-volume cancer center after transurethral resection (TUR) and intravesical bacillus Calmette-Guérin (BCG) therapy. Our endpoints were time to progression to invasive disease (≥cT1) or radical cystectomy (RC) before progression, and progression to muscle-invasive disease (≥cT2) or RC before progression. Cox proportional hazards regression models were used.

Results—Patients with primary CIS responded significantly more within 6 months of BCG therapy than secondary CIS (65% vs 39%; p<0.001). The 5-year cumulative incidence of progression to ≥cT1 was 43% (95% CI, 36%–51%) and 32% (95% CI, 27%–39%) in the primary and secondary CIS groups, respectively; progression to ≥cT2 was 17% (95% CI, 12%–23%) and 8% (95% CI, 5%–13%), respectively. In multivariable analyses, primary CIS was significantly more likely to progress to ≥cT1 or RC (HR: 1.38; 95% CI, 1.05–1.81; p=0.020), and to ≥cT2 or RC (HR: 1.72; 95% CI, 1.27–2.33; p=0.001). We found no significance for age, gender, or response to BCG therapy as predictors of outcome. The median follow-up time was 5.1 years.

Conclusions—Patients presenting with primary CIS have a worse outcome compared to those with secondary CIS, suggesting a need to differentiate these two entities in the treatment decision process.

Keywords

Bladder; Bladder Neoplasms; Carcinoma in situ; BCG

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Introduction

Since 1952, when Melicow first described the importance of bladder carcinoma in situ (CIS) in the recurrence and progression rates of urothelial bladder carcinoma (UBC), the understanding of this disease has evolved greatly, allowing improvements in patient care.[1, 2] The pathologic finding of CIS implies a worse prognosis in non-muscle-invasive UBC patients, despite a widely variable outcome in the long term.[3] Although the clinical and biological impact of CIS continues to be controversial, it has been suggested that CIS represents a distinct entity.[4] More recently, authors have begun to distinguish between primary CIS (isolated CIS with no prior or concomitant papillary tumors—de novo CIS) and secondary CIS (diagnosed concomitantly to or after a papillary tumor).[3, 5, 6]

However, it still remains unclear whether primary or secondary CIS represents a worse prognosis.[7] Moreover, the distinction between primary and secondary CIS has not yet been shown to be clinically relevant or associated with particular oncologic outcomes after receiving intravesical bacillus Calmette-Guérin (BCG) therapy. Although many authors have addressed the issue of the clinical significance of primary or secondary CIS, studies have shown that conclusions have been drawn from cohorts with a small number of patients from each of these categories or inadequate patient selection in mixed stages, not allowing a thorough understanding of the natural history of this disease.[3, 8–11]

In this context, we sought to compare the clinical outcomes of a large cohort of patients presenting with primary or secondary CIS at a tertiary referral cancer center.

Patients and Methods

A retrospective analysis of our institutional database was performed with the approval of the institutional review board. The diagnosis of CIS was based on urine cytology, cystoscopy with biopsy or transurethral resection (TUR), bimanual examination, as well as pathologic evaluation by a dedicated genito-urinary pathologist at MSKCC. We excluded patients whose pathology slides had been unavailable for review. Patients were followed every 3 months with urine cytology and cystoscopy. Random biopsies and repeat TUR were performed in all suspicious cases. Positive **cytology** was considered as a recommendation for random biopsies and upper tract imaging, even when cystoscopy was not suspicious. A negative cytology was acceptable, since all cases required random biopsies and pathologic confirmation of CIS. BCG therapy consisted of an induction course of 6 weekly intravesical instillations.

The study comprised a consecutive cohort of 476 patients diagnosed with primary or secondary CIS from 1990 to 2008 (221 primary CIS and 255 secondary CIS). Primary CIS was defined as an isolated high-grade cTis on the first transurethral resection (TUR) without any prior or concomitant papillary tumor, and secondary CIS as high grade cTis diagnosed concomitantly to or after a prior papillary cTa tumor. Patients with CIS concomitant to ≥cT1 were not included.

For the analysis of response to BCG therapy, patients who progressed before receiving BCG therapy (48) or were missing the date they received BCG therapy (36) were excluded, leaving 392 patients for analysis (182 primary CIS and 210 secondary CIS).

The diagnosis was based on the TNM system of the International Union Against Cancer and graded according to the World Health Organization/International Society of Urological Pathology (WHO/ISUP) 1998 grading system of urothelial neoplasms of the urinary bladder.[12] The medical records were reviewed for clinical information related to patient characteristics.

Statistical Methods

In order to compare the clinical outcomes of primary versus secondary CIS, we analyzed the time to separate endpoints: progression to invasive disease, defined as cT1 or higher (≥cT1); and progression to muscle-invasive disease, defined as cT2 or higher (≥cT2). Because radical cystectomy (RC) is an adverse outcome that may be related to disease severity, we considered the earlier of either RC or progression as a single endpoint in our analyses. As many patients underwent RC before progression to invasive disease, we plotted the risk of progression using the cumulative incidence function in the presence of a competing risk.

We created separate multivariable Cox regression models for each of the endpoints, as follows: (a) progression to ≥cT1 or RC before progression; and (b) progression to ≥cT2 or RC before progression. We used as predictors: CIS presentation (primary vs secondary), age, gender, and response to intravesical BCG therapy. We defined ‘responders’ as those whose disease did not recur within 6 months of receiving BCG therapy, and ‘non-responders’ as those whose disease recurred within 6 months of BCG therapy.

All analyses were conducted using SPSS 16.0 (SPSS Inc, Chicago, IL) and R (R Foundation for Statistical Computing, http://www.R-project.org) with the cmprsk package.

Results

A total of 476 patients received BCG therapy after presenting with CIS. The majority of patients were male (n=389; 82%), white (n=446; 94%), and current or former smokers (n=341; 72%)(Table 1). Gross hematuria was more frequently diagnosed in the secondary CIS group (51% vs 31%), while voiding symptoms (irritative or obstructive), were more commonly reported by the patients diagnosed with primary CIS (29% vs 10%; $p<0.001$). Overall, the median follow-up time was 5.1 years (IQR:2.5, 8.2).

Sixty-five percent of the patients in the primary CIS group and 39% in the secondary CIS group responded to BCG therapy within 6 months ($p<0.001$) (Table 2). In total, 179 patients progressed to invasive disease and 57 patients progressed to muscle-invasive UBC. The median time to progression to ≥cT1/RC was 3.4 years (IQR: 2.4, 4.5) and 5.8 years (IQR: 3.7, 7.8), and to ≥cT2/RC was 5.2 years (IQR: 3.2, 7.4) and 9.9 years (IQR: 5, 12.7) in the primary and secondary CIS groups, respectively. The median follow-up for patients in the primary CIS group was 3.4 years (IQR: 2.4, 4.5) and in the secondary CIS group was 5.7 years (IQR: 3.7, 7.8). Median follow-up for patients who did not experience disease

progression was 3.9 years (IQR: 1.2, 6.7). Direct progression from CIS to cT2 occurred in 27 patients in the primary CIS group and in 17 patients in the secondary CIS group. Overall, 173 patients underwent RC (92 primary CIS and 81 secondary CIS). RC before progression was performed in 132 patients (67 primary CIS vs 66 secondary CIS). The pathology stage at RC did not differ between the two groups (p=0.26). In the primary CIS group, 31 patients (34.5%) had ≥pT2 at RC, while in the secondary CIS group, 23 patients (29.2%) had ≥pT2 at RC. Disease specific-survival at 10 years was 82% and 96% in the primary and secondary CIS groups, respectively.

In multivariable analyses, primary CIS had a significantly higher risk of progression to ≥cT1/RC (HR: 1.38; 95% CI, 1.05–1.81; p=0.020), or to ≥cT2/RC (HR: 1.72; 95% CI, 1.27–2.33; p=0.001) compared to secondary CIS (Table 3). Age, gender and response to BCG therapy were not significantly associated with disease progression or RC.

Figure 1 shows a higher cumulative incidence of progression to ≥cT1 in patients with primary CIS. RC before progression to ≥cT1 was similar in the two groups. In Figure 2, progression to ≥cT2 is shown to be consistently higher in the primary CIS group, despite the higher incidence of RC before progression to ≥cT2 in this group. The competing risk of RC before progression was greater than the cumulative incidence of progression to ≥cT2 in both groups. This inversion is related to the higher recommendation of RC before progression for cT1 than for CIS.

The 5-year cumulative incidence of progression to ≥cT1 was 43% (95% CI, 36%–51%) in the primary CIS group and 32% (95% CI, 27%–39%) in the secondary CIS group. In patients with primary CIS, RC for <cT1 was 15% (95% CI, 10%–21%) and for <cT2 was 32% (95% CI, 26%–39%) at 5 years. In patients with secondary CIS, RC for <cT1 was 12% (95% CI, 7%–19%) and for <cT2 was 25% (95% CI, 20%–32%) at 5 years. The 5-year cumulative incidence of progression to ≥cT2 was 17% (95% CI, 12%–23%) in the primary CIS group and 8% (95% CI, 5%–13%) in the secondary CIS group.

Discussion

In this large cohort of patients with primary or secondary CIS, we compared the oncologic outcomes of patients after intravesical BCG failure and identified evidence that primary CIS represents a higher risk for progression than secondary CIS. We found that primary CIS was significantly associated with higher progression to invasive disease or RC and muscle-invasive disease or RC.

The mechanism of progression from CIS to a life-threatening disease may be related to the pattern of invasion. Historical studies have introduced the concept of divergent routes for flat and papillary tumors, and presumably, these patterns behave differently.[2, 13, 14] Therefore, if we consider secondary CIS an initiation for the papillary type of tumor—that is, if two patterns of invasion actually coexist—then distinct clinical outcomes might be expected from the different patterns of invasion. Recent evidence showed genomic alterations related to CIS carcinogenesis that further distinguishes flat and papillary lesions by giving support to the presence of two separate biological pathways in bladder tumors.

Zieger et al found a series of chromosomal instability characterized by gains of chromosomes (5p, 6p22.3, 10p15.1) and losses of heterozygosity (5q, 13q13-q14) associated with CIS lesions, while FGFR3 mutations were associated with papillary tumors.[6]

Despite not clearly defining the impact of CIS on oncologic outcomes, results from several previous studies have identified the presence of CIS as a poor prognostic factor because it is associated with increasing both the risk of progression to muscle-invasive disease and the risk of death from bladder cancer.[3, 15–17] However, very few authors aimed at comparing the outcomes of primary versus secondary CIS patients and consequently could not determine whether the use of this classification holds any importance to the management of this disease.[8, 18]

Previously, no study has been able to clearly demonstrate significant differences in outcomes between primary and secondary CIS in a homogenous cohort of non-muscle-invasive UBC. Most have suggested similar rates of disease progression or have shown confounding results by favoring primary CIS as a better biological behavior, mostly due to small samples or mixed stage groups.

A landmark study by Orozco et al compared patients with primary CIS versus patients with CIS associated with UBC at any level of invasion, of which more than 50% had muscle-invasive disease at initial diagnosis.[19] Not surprisingly, the mixed secondary CIS group had a worse outcome, leading to a misleading conclusion that primary CIS may be a less aggressive disease. More recently, however, Cheng et al found in a small cohort that patients with primary CIS had a lower progression-free survival at 15 years than secondary CIS, although not statistically significant (54% vs 65%; p=0.34).[20] Gofrit et al studied 104 patients with CIS (primary and secondary combined), showing no significant difference between pure and concomitant CIS.[8] Takenaka et al published findings based on small number of patients, also showing no difference between type of CIS. Although reporting a sample of 185 patients with CIS, the analysis included primary, secondary, and concomitant disease in a same risk-group.[21]

In our study, the higher cumulative incidence of progression to invasive and to muscle-invasive disease at 5 years, adjusting for the competing risk of RC before progression, underscores the aggressiveness of primary CIS. If we would consider at risk patients with primary CIS who underwent RC before progression to cT2, the 5-year cumulative incidence of progression to muscle-invasive UBC could be as high as 49% in the absence of RC before progression. Moreover, with RC being recommended more frequently in the primary CIS group with the goal of avoiding progression, one could expect a reduced incidence of progression in this group, contrary to our findings in this cohort. Therefore, our results support recommending surgery in presumably higher-risk patients and even suggest that more frequent recommendations for surgical treatment could benefit patients with primary CIS.

Radical cystectomy before progression is an acceptable recommendation in patients with non-muscle-invasive UBC after BCG therapy failure.[22–24] In our study, the relatively high incidence of RC before progression to muscle-invasive UBC demonstrates a trend towards

considering these patients at high risk. Moreover, similar rates of RC before progression to ≥cT1 in both CIS groups and a higher RC rate before progression to ≥cT2 in the primary CIS group suggest that the poorer outcome in the primary CIS group is reliable because it is not biased by the surgical treatment that could preclude this group from progressing in an even higher rate. However, several other factors may influence the timing of RC, which could also have affected the results.

Herr has shown that aging was significantly associated with recurrence in a large cohort of 805 patients with non-muscle-invasive disease (Ta or T1 with concomitant CIS in 78% of patients).[25] In the present study, age was not associated with progression to muscle-invasive disease or RC before progression. This may possibly be related to a higher cumulative incidence of RC before progression in the younger population in the primary CIS group.

Although response to BCG therapy was significantly higher in the primary CIS group than in the secondary (65% vs 39%; $p<0.001$), we found that it did not impact on progression rates when controlled for age, gender, and CIS group. This may due to the higher rate of RC before progression in the primary CIS group. Recent studies have also shown no significant association of response to BCG with outcome.[8] Andius et al, however, found that the first cystoscopy had a predictive value for progression, BCG failure, and death in a cohort of 173 patients, but no difference between type of CIS.[9]

There are several limitations to our study. It is retrospective in nature. Patients treated at our tertiary referral hospital may differ from bladder cancer patients treated at community centers. And also, the cohort covered a 19-year period, during which a trend towards earlier RC occurred. Although the indication of earlier RC has only recently gained more support, this treatment option had been part of our recommendation during this time interval, which may have prevented a greater impact on our series.[22]

Conclusion

Our results suggest that primary CIS represents a more aggressive tumor than secondary CIS and that these two types of tumor are distinct. Although primary CIS patients respond better to BCG therapy, we found no association with progression. Although RC before progression was recommended more frequently in the primary CIS group, it was not enough to reduce the progression rates close to the secondary CIS group. Even though additional data is required to validate these findings, the distinction between these two entities may influence the clinical management of this disease, on decision-making for RC before progression, and on prognostic models.

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Abbreviations

CIS	carcinoma is situ
TUR	transurethral resection
RC	radical cystectomy
UBC	urothelial bladder carcinoma
BCG	bacillus Calmette-Guérin

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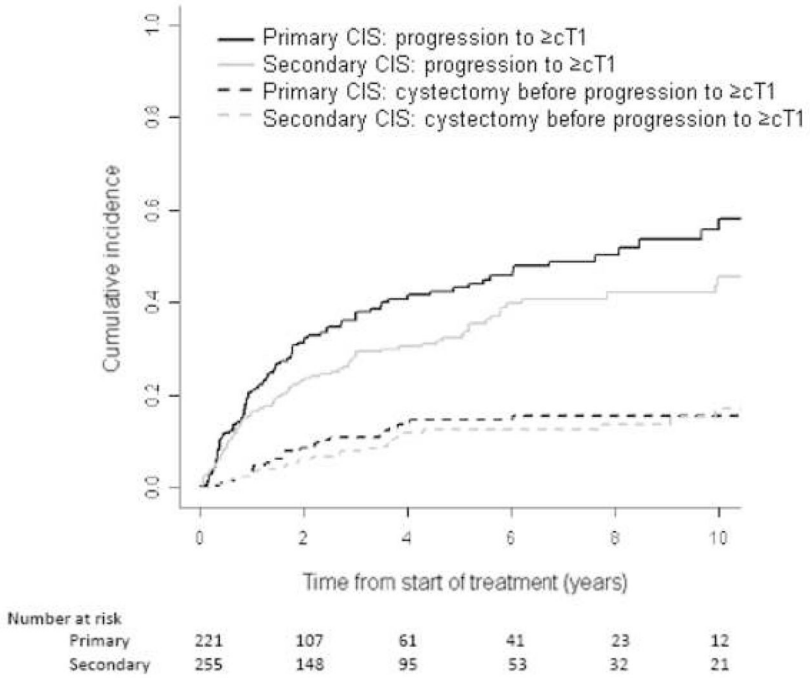

Figure 1.

Cumulative incidence of progression to invasive disease (≥cT1; solid lines) or radical cystectomy before progression (dashed lines) in primary or secondary CIS

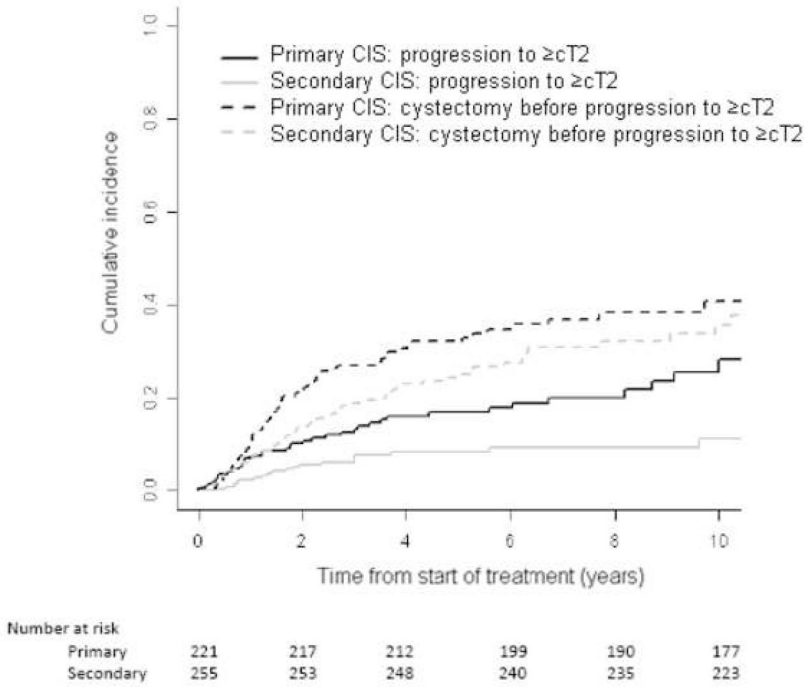

Figure 2.

Cumulative incidence of progression to muscle-invasive disease (≥cT2; solid lines) or radical cystectomy before progression (dashed lines) in primary or secondary CIS

Table 1

Clinical characteristics of patients who received BCG therapy for primary or secondary CIS. All values are median (interquartile range) or frequency (proportion).

	All Patients	Initial CIS Presentation		
	N=476	Primary n=221	Secondary n=255	P value
Age at first diagnosis of bladder cancer (years)	66.7 (13.1)	68.6 (11.8)	65.2 (14.6)	0.002***
Male	389 (81.7%)	185 (83.7%)	204 (80.0%)	0.342****
White	446 (93.7%)	210 (95.5%)	236 (92.9%)	0.329****
Smoking history				0.027****
None	111 (23.3%)	63 (28.5%)	48 (18.8%)	
Former	282 (59.2%)	125 (56.6%)	157 (61.6%)	
Current	59 (12.4%)	22 (10.0%)	37 (14.5%)	
Unknown	24 (5.0%)	11 (5.0%)	13 (5.1%)	
Initial symptoms				<0.001****
Asymptomatic*	101 (21.2%)	48 (21.7%)	53 (20.8%)	
Gross hematuria	198 (41.6%)	69 (31.2%)	129 (50.6%)	
Voiding symptoms (irritative or obstructive)**	88 (18.5%)	63 (28.5%)	25 (9.8%)	
Unknown	89 (18.7%)	41 (18.6%)	48 (18.8%)	

* Asymptomatic: includes incidental finding and microhematuria

** Other voiding symptoms: irritative, obstructive

*** Mann-Whitney U-test

**** Chi-square tests

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ

Table 2

Clinical outcomes of patients who received BCG therapy for primary or secondary CIS

	All Patients	Initial CIS	
	N=476	Primary n=221	Secondary n=255
Intravesical BCG therapy*			
Responders	243 (51%)	144 (65%)	99 (39%)
Non-responders	233 (49%)	77 (35%)	156 (61%)
Intravesical chemotherapy	79 (17%)	33 (15%)	46 (18%)
Recurrence	367	182	185
Progression to ≥T1	179	93	86
Progression to ≥T2	57	37	20
Direct progression to T2	44	27	17
Radical cystectomy			
RC for all stages	173	92	81
RC before progression	132	67	66
RC for CIS	57	27	30
RC for T1	75	40	36
Distant metastasis	51	28	23
Second primary urothelial carcinoma			
Upper tract	32	10	22
Urethral	25	8	17
Death	95	50	45
Bladder cancer	33	18	15
Upper tract urothelial carcinoma	6	0	6
Other causes	28	11	17
Unknown	28	21	7

* $p<0.001$

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; RC = radical cystectomy

Table 3

Multivariable analyses of progression to invasive disease (≥cT1) and to muscle-invasive disease (≥cT2), adjusting for RC before progression in 392 patients

Variables	Progression to invasive disease (≥cT1) or radical cystectomy*		Progression to muscle- invasive disease (≥cT2) or radical cystectomy*	
	HR (95% CI)	P	HR (95% CI)	P
Primary vs secondary CIS	1.37 (1.05–1.81)	0.020	1.72 (1.27–2.33)	0.001
Age	1.01 (0.99–1.02)	0.178	1.01 (0.99–1.02)	0.568
Gender	1.18 (0.86–1.63)	0.300	1.15 (0.80–1.65)	0.455
Response to BCG	1.12 (0.85–1.46)	0.421	1.03 (0.76–1.39)	0.865

(84 patients were excluded due to progression before BCG therapy or missing data)

* RC before progression to invasive disease

RC = radical cystectomy; CIS = carcinoma in situ; BCG = bacillus Calmette-Guérin