Clinical Outcome of Primary Versus Secondary Bladder Carcinoma In Situ

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Abbreviations and Acronyms

BCG = bacillus Calmette-Guerin

CIS = carcinoma in situ

RC = radical cystectomy

TUR = transurethral resection

UBC = urothelial bladder carcinoma

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Purpose: Differences in clinical outcome are still unclear between primary and secondary bladder carcinoma in situ. We compared the clinical outcomes of primary and secondary carcinoma in situ, and identified predictive factors.

Materials and Methods: We retrospectively analyzed the records of 476 patients with high grade cTis, including 221 with primary and 255 with secondary carcinoma in situ, from 1990 to 2008 at a high volume cancer center after transurethral resection and intravesical bacillus Calmette-Guerin therapy. End points were time to progression to invasive disease (cT1 or higher) or radical cystectomy before progression, and progression to muscle invasive disease (cT2 or higher) or radical cystectomy before progression. We used Cox proportional hazards regression models.

Results: Patients with primary carcinoma in situ responded significantly more within 6 months of bacillus Calmette-Guerin than those with secondary carcinoma in situ (65% vs 39%, $p < 0.001$). In the primary vs secondary groups the 5-year cumulative incidence of progression to cT1 or higher was 43% (95% CI 36–51) vs 32% (95% CI 27–39) and for progression to cT2 or higher it was 17% (95% CI 12–23) vs 8% (95% CI 5–13). On multivariate analysis primary carcinoma in situ was significantly more likely to progress to cT1 or higher (HR 1.38, 95% CI 1.05–1.81, $p = 0.020$) and to cT2 or higher, or radical cystectomy (HR 1.72, 95% CI 1.27–2.33, $p = 0.001$). We found no significance for age, gender or response to bacillus Calmette-Guerin as outcome predictors. Median followup was 5.1 years.

Conclusions: Patients presenting with primary carcinoma in situ have a worse outcome than those with secondary carcinoma in situ, suggesting a need to differentiate these 2 entities in the treatment decision process.

Key Words: urinary bladder, carcinoma, Mycobacterium bovis, carcinoma in situ, urinary bladder neoplasms

SINCE 1952, when Melicow first described the importance of bladder CIS for UBS recurrence and progression rates,[1] the understanding of this disease has evolved greatly, allowing improved patient care.[2] The pathological finding of CIS implies a worse prognosis in patients with nonmuscle invasive UBC despite widely variable outcomes in the long term.[3] The clinical and biological impact of CIS continues to be controversial but it was suggested that CIS represents a distinct entity.[4] More recently groups began to distinguish primary CIS (isolated CIS with no prior or concomitant papillary tumors, that is de novo CIS) from secondary CIS (that diag-

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nosed concomitantly with or after a papillary tumor).[3,5,6]

However, it remains unclear whether primary or secondary CIS carries a worse prognosis.[7] Also, to our knowledge the distinction between primary and secondary CIS has not yet been shown to be clinically relevant or associated with particular oncological outcomes after intravesical BCG therapy. Although many groups have addressed the issue of the clinical significance of primary or secondary CIS, studies show that conclusions have been drawn in a small number of patients in each category or in studies with inadequate patient selection at mixed stages, thus not allowing a thorough understanding of the natural history of this disease.[3,8–11] In this context we compared clinical outcomes in a large cohort of patients presenting with primary or secondary CIS to a tertiary referral cancer center.

PATIENTS AND METHODS

We retrospectively analyzed our institutional database with the approval of the institutional review board. The CIS diagnosis was based on urine cytology, cystoscopy with biopsy or TUR, bimanual examination and pathological evaluation by a dedicated genitourinary pathologist at our institution. We excluded patients with pathological slides unavailable for review. Patients were followed every 3 months with urine cytology and cystoscopy. Random biopsy and repeat TUR were done in all suspicious cases. Positive cytology was considered a recommendation for random biopsy and upper tract imaging even when cystoscopy was not suspicious. Negative cytology was acceptable since all cases required random biopsy and pathological 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 (221) or secondary (255) CIS from 1990 to 2008. Primary CIS was defined as isolated, high grade cTis at initial TUR without any prior or concomitant papillary tumor. Secondary CIS was defined as high grade cTis diagnosed concomitantly with or after a prior papillary cTa tumor. Patients with CIS concomitant to cT1 or higher were not included in analysis. To analyze the response to BCG we excluded from study 48 patients who progressed before BCG therapy and 36 missing the date of BCG therapy, leaving 182 with primary and 210 with secondary CIS available for analysis.

Diagnosis was based on the UICC TNM system and graded according to the 1998 WHO/International Society of Urological Pathology grading system of bladder urothelial neoplasms.[12] We reviewed the medical records for clinical information on patient characteristics.

To compare the clinical outcome of primary vs secondary CIS we analyzed time to separate end points, including progression to invasive disease, defined as cT1 or higher, and progression to muscle invasive disease, defined as cT2 or higher. Because RC is an adverse outcome that may be related to disease severity, we considered the earlier of RC or progression as a single end point. Since 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 multivariate Cox regression models for each end point, including 1) progression to cT1 or higher, or RC before progression and 2) progression to cT2 or higher, or RC before progression. As predictors, we used primary vs secondary CIS presentation, patient age, gender and response to intravesical BCG. We defined responders as patients in whom disease did not recur within 6 months of BCG therapy and nonresponders as those in whom disease recurred within 6 months of BCG therapy. All analysis was done using SPSS® 16.0 and R with the cmprsk package.

RESULTS

A total of 476 patients received BCG therapy after presenting with CIS. At initial bladder cancer diagnosis median patient age was 66.7 years (IQR 13.1) overall, including 68.6 (IQR 11.8) in those with primary CIS and 65.2 (IQR 14.6) in those with secondary CIS (Mann-Whitney U test $p = 0.002$). Of the patients 389 (82%) were male, 446 (94%) were white and 341 (72%) were current or former smokers (table 1).

Table 1. *Clinical characteristics in patients with primary or secondary CIS*

	No. Pts (%)	No. Primary (%)	No. Secondary (%)	p Value (chi-square test)
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)	
Irritative or obstructive voiding symptoms	88 (18.5)	63 (28.5)	25 (9.8)	
Unknown	89 (18.7)	41 (18.6)	48 (18.8)	

* Incidental finding and microhematuria.