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CARCINOMA IN SITU OF URINARY BLADDER: INCIDENCE, TREATMENT AND CLINICAL OUTCOMES DURING TEN-YEAR FOLLOW-UP

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SUMMARY – Bladder carcinoma in situ (CIS) is a rare, high-grade intraepithelial neoplasm with a high tendency of progression and unpredictable clinical course. The aim of this study was to evaluate the incidence, treatment and clinical outcome of patients with CIS during a 10-year period. Medical records of 1062 patients with primary bladder cancer and 847 patients with recurrent bladder cancer that underwent tumor resection at Department of Urology, Split University Hospital Center, Split, Croatia, between January 2001 and December 2010, were analyzed. Among all treated patients with primary bladder neoplasms, 51 (4.8%) had CIS. Primary CIS was diagnosed in 18 (1.7%) and concomitant CIS in 33 (3.1%) patients. In the same period, 847 patients with recurrent tumors were treated by transurethral resection (TUR), 12 (1.4%) of them with secondary CIS. Clinical course was followed-up in 15 patients with primary CIS and 21 patients with concomitant (TaT1) CIS. BCG immunotherapy was applied in 12 patients with primary and 17 patients with concomitant CIS. After median follow-up of 50 months, 9 patients with primary CIS had no sign of disease, 4 progressed, 1 had recurrence and 1 died. After median follow-up of 37 months, 13 (62%) patients with concomitant CIS had complete response, 3 progressed (14%), 1 had recurrence (4%) and 4 patients died, however, only 2 (10%) of these due to bladder cancer. Of all patients receiving BCG immunotherapy, 8 (27%) had significant side effects. The incidence and treatment of patients with CIS of urinary bladder in our institution is comparable to other recent literature reports.

Key words: *Bladder neoplasm; Carcinoma in situ; BCG vaccine; Treatment outcome*

Introduction

Carcinoma in situ (CIS) of urinary bladder is defined as a noninvasive, flat, and high-grade cancerous lesion confined to the superficial lining of the bladder, composed exclusively of poorly differentiated, anaplastic cells. According to clinical manifestations and compared to papillary urothelial carcinomas, CIS can be primary, secondary and concomitant[1]. Primary tumor is a lesion in the plane of mucosa in patients who previously had no urothelial malignancy. Secondary tumor occurs during evolution of previously treated urothelial cancer, while concomitant tumors are those that persist simultaneously with other forms of urothelial cancer at the time of setting the initial diagnosis. It is estimated that 5%-10% of patients with urothelial cancer have some form of CIS[1,2]. Although CIS is a rare entity, it is important for two reasons. First, it is difficult to make the diagnosis of CIS because it is an intraepithelial lesion that can exist in the macroscopically normal mucosa. Another reason is the high malignant potential of untreated CIS, which progresses in 80%-100% of cases[3,4]. CIS is considered a precursor of muscle-invasive bladder tumors[5,6].

Relevant literature provides a significant number of articles analyzing CIS from various aspects. It should be pointed out that those were mainly retrospective

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studies with a relatively small number of patients and that a relatively small number of patients with CIS are recruited through multicenter studies.

The aim of this study was to analyze the incidence, methods and results of treatment in patients with CIS of urinary bladder during a 10-year period at Department of Urology, Split University Hospital Center, Split, Croatia.

Methods

Study design

In this retrospective clinical study, we analyzed the incidence, methods and results of treatment in patients with CIS of urinary bladder during a 10-year period.

Setting

The study was conducted at Department of Urology, Split University Hospital Center, Split, Croatia, between January 2001 and December 2010.

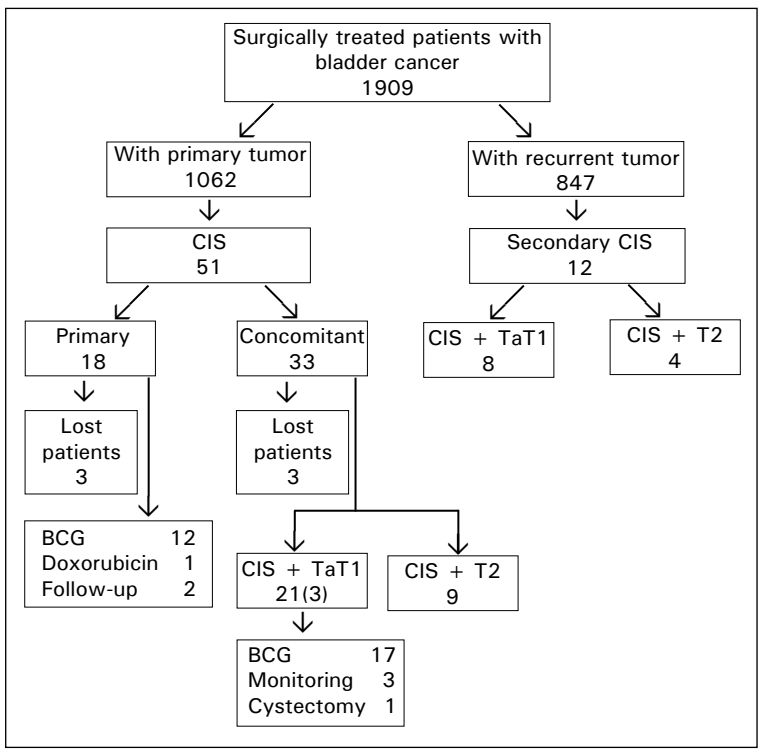

Fig. 1. Flow chart: surgically treated patients with bladder cancer

CIS = carcinoma in situ; BCG = bacille Calmette-Guérin; TaT1 = non-muscle invasive bladder cancer; T2 = muscle invasive bladder cancer

Patients

We analyzed medical records of 1909 patients operated for primary and recurrent bladder cancer (Fig. 1). There were 1062 patients with primary bladder tumors who underwent tumor resection. Out of 847 patients with recurrent tumors, 726 underwent transurethral resection (TUR) biopsy for primary and recurrent bladder tumors during the study period, whereas 121 patients were treated by TUR for primary tumor before the study period. Painless, unprovoked hematuria was the most common indication for conducting diagnostic work-up. Information on the attributes of the tumor (number, size, localization, appearance, degree of malignancy and stage) were recorded from the history of the disease and surgical and histopathologic findings.

Diagnosis and therapy of CIS

Diagnosis of primary CIS was made in patients with persistent irritation disorders of urination, dysuria, and asymptomatic microscopic hematuria. The standard preoperative procedure included intravenous pyelography (IVP), urinary tract ultrasonography, urethrocystoscopy and cytologic analysis of urine sediment. The degree of malignancy was determined according to the World Health Organization classification from 1998, and stage of disease according to TNM classification from 1997[7,8].

Primary, secondary, concomitant CIS and non-muscle invasive bladder tumors were an indication for BCG immunotherapy. We applied Stamm-strain Cannaught Immucyst (Cannaught Laboratories Ltd., Ontario), 27 mg/mL, $3x10^8$ mL of live mycobacteria in 1 mL vaccine. Before instillation, urinary tract infection was excluded and the catheter was introduced in an atraumatic way. Suspended vaccine (3 mL of the vaccine in 50 mL of saline) was administered through catheter into the bladder. Patients retain the fluid within the bladder for 2 h (30 min prone, 30 min supine and 30 min on each side) to ensure that all bladder mucosa comes into contact with

BCG. We began therapy in the 3rd or 4th week after TUR.

Patient follow-up

The course of disease was determined by the recurrence, progression (defined as muscle invasion) and lethal outcome. Patients were followed-up with cystoscopy and cytologic analysis of urine sediment every 3 months during the first year after TUR. Later, the interval was successively extended to 6 months or 1 year and IVP every 2-3 years, depending on the initial histopathologic findings.

Statistical methods

Descriptive statistics was used for data presentation. Data were presented as frequencies and percentages, and medians where appropriate.

Results

During the 10-year study period, 1062 patients (819 men, 77%) with primary bladder cancer and 847 patients (620 men, 73%) with recurrent tumors were operated on. In 1062 patients with primary urothelial cancers, CIS was noted in 51 (4.8%) patients. Primary CIS was diagnosed in 18 (1.7%) and concomitant CIS in 33 (3.1%) patients. Among 33 patients with concomitant CIS, there were 24 concomitant CIS with TaT1 tumors and 9 concomitant CIS with T2 tumors. In 847 patients with recurrent urothelial tumors, secondary CIS was recorded in 12 (1.4%) patients (Fig. 1).

Three of 18 patients with primary CIS failed to present for regular check-ups after surgery. We treated and followed-up 15 patients. In 12 patients, we applied intravesical BCG immunotherapy. We prefer Southwest Oncology Group (SWOG) schedule in which after the induction dose of BCG instillation once weekly for 6 weeks, patients receive further courses of BCG as maintenance therapy: BCG instillations once a week for three weeks at 3, 6, 12, 18, 24, 30 and 36 months after the initial course of BCG[9].

Table 1. Patients with primary carcinoma in situ

Gender	n	Age (years)	Follow-up (months)
Female	1	54	90
Male	14	68 (42-80)	48 (6-114)

This intense and prolonged schedule was fully applied in three patients and in a reduced form (due to side effects or lack of cooperation) in five patients. Two patients received only 6 induction doses, whereas in two patients we used our original schedule: 6 weekly + 6 monthly instillations[10]. In one patient, we applied doxorubicin (6 weekly doses) intravesically, while two patients refused BCG immunotherapy and were just followed-up.

After an average follow-up of 50 months, complete favorable response was recorded in nine (60%) patients, progression in four (26%) patients, and relapse and death in one (6%) patient each (Table 2).

Table 2. Outcome in treated patients with primary carcinoma in situ

	n	CR	P	R	Death
BCG	12	9	1	1	1
Doxorubicin	1		1		
Just followed	2	1	1		

BCG = bacille Calmette-Guérin; CR = complete response; P = progression; R = recurrence

Concomitant CIS with TaT1 tumors were documented in 24 patients, but three of these patients failed to present for follow-up after the surgery, so we followed-up 21 patients (Table 3).

Table 3. Patients with concomitant carcinoma in situ

Gender	n	Age (years)	Follow-up (months)
Female	2	65.5	18.5
Male	19	65 (46-79)	39 (12-92)

BCG immunotherapy was applied in 17 patients, three were followed-up, and in one patient radical cystectomy was performed. SWOG schedule was used in 11 patients (complete in 3 and reduced form in 8 patients), whereas 6 weekly doses and 6 weekly + 6 monthly instillations were administered in 3 patients each. After an average follow-up of 37 months, complete favorable response was recorded in 13 (62%) patients, progression in three (14%) patients, relapse in one (4%) patient, while four patients died (2 from bladder cancer, 10%) (Table 4).

Significant side effects that warranted withdrawal of BCG immunotherapy were recorded in eight (27%)

Table 4. Outcome in treated patients with concomitant carcinoma in situ

	n	CR	P	R	Death
BCG	17	11	3		1+2*
Just followed-up	3	1		1	1
Cystectomy	1	1			

BCG = bacille Calmette-Guérin; CR = complete response; P = progression; R = recurrence; *fatal outcome due to other reasons

patients. Seven patients experienced fever with dysuria, frequency and hematuria for several days. This condition was alleviated with supportive measures (adequate hydration, antipyretics, bed rest). Another patient became highly febrile after 15 instillations (SWOG scheme) and was hospitalized for hemodynamic instability and threatening sepsis. Gram-negative bacteria were isolated from urine and blood and the patient was treated according to the antibiotic sensitivity report. After 7-day therapy that failed to produce any effect, we introduced *ex juvantibus* antituberculous drugs: isoniazid, rifampicin and ethambutol. This therapy led to clinical improvement and patient recovery. The patient continued taking isoniazid and rifampicin for 3 months after leaving the hospital and at the time of the last follow-up did not exhibit clinical problems.

Of 12 patients with secondary CIS, in four patients CIS occurred during the evolution of primary muscle-invasive tumors, while in another eight patients CIS was recorded during monitoring of patients with TaT1 tumors, who had previously received BCG immunotherapy. These patients were not included in the analysis.

Table 5. Literature data on the number of patients with primary carcinoma in situ

Author	Number of patients	Patient recruitment (years)	Number of institutions
Jakse *et al.*, 2001[21]	19	4	5
Losa *et al.*, 2000[22]	21	8	1
Gofrit *et al.*, 2009[26]	38	18	1
Takenaka *et al.*, 2008[25]	69	6	16
Griffiths *et al.*, 2002[27]	23	10	1

Discussion

Unlike other organs (testis, prostate) where CIS is considered a premalignant lesion, CIS of the urinary bladder is a clinically and histopathologically clearly defined entity[11]. It is featuring often unpredictable clinical course, with a significant malignant potential[12]. Since our patient cohort was small, with a total of 1183 patients operated on for bladder cancer, the absolute number of patients with CIS in our study was also small, especially those with primary CIS, which is relatively uncommon as a primary entity. However, we believe that this study adds useful data on the incidence, treatment and clinical outcome of urinary bladder CIS in Split, Croatia. In Croatian urological literature, there are very few papers dealing with any aspect of urinary bladder CIS[13].

We found that the diagnosis of primary CIS was established in patients whose symptoms were identical with benign conditions, such as interstitial cystitis and chronic prostatitis. In these cases, diagnosis can only be made if suspicion of a malignant disease arises. Diagnosis of CIS, including urine cytology, biopsy of bladder mucosa, is quick and easy.

Diagnosis of concomitant CIS depends on how resection of bladder tumors is performed and on competence of the pathologists. Properly performed resection of the tumor involves resection of tumor above the base, then the base of the tumor, and eventually the surrounding apparently normal mucosa (fractioned resection)[14]. Taking biopsy material from apparently normal mucosa in different quadrants of the bladder is not considered obligatory, but there are divergent opinions about this[15,16].

Until 2000, CIS was diagnosed (primary or concomitant) at our department sporadically. Since 2000, we insist on fractioned resection (although not all urologists accept this way of tumor resection). Also, we intensified and improved communication with pathologists.

With regard to the character, i.e. multifocal, intraepithelial lesions that can persist on the macroscopically normal urothelium, CIS is a surgically unresectable disease. Therefore, TUR alone is not adequate for control of the disease

and results in progression in 80%-100% of cases and specific mortality of 39%[3,4,17].

Since 1976, when Morales *et al*. first demonstrated that intravesical BCG vaccine could be applied to reduce the rate of recurrence of non-muscle invasive tumors, BCG immunotherapy has established itself as an effective method in preventing recurrence and progression of non-muscle invasive tumors[18]. The indications for BCG immunotherapy are primary aggressive forms of non-muscle invasive tumors: T1G2-3, multiple, large, recurrent TaG2 tumors and CIS. Before the era of BCG immunotherapy, radical cystectomy was the method of choice in the treatment of CIS of the bladder[19]. According to the recommendations of the European Association of Urology (EAU) from 2011, BCG immunotherapy is considered the treatment of choice for primary CIS[20]. However, this recommendation is based on only two studies with a relatively small number of patients[21,22]. Jakse *et al*. applied 6 weekly doses in 17 patients with primary CIS with an average follow-up at 7 years; complete response to therapy was recorded in 82% of patients, with no fatal outcome[16,19,21]. Losa *et al*. treated 21 patients with primary CIS; they applied the scheme with additional instillations (6 weekly + 12 monthly doses), but in a reduced manner. However, in their analysis, results were expressed for all forms of CIS (primary, secondary and concomitant). At 6-year follow-up, complete response was recorded in 93% of patients, but from these results we cannot read the results of treatment in patients with primary CIS only[22].

Although accepted, the division of CIS into primary, secondary and concomitant is ignored in the vast majority of research publications and the results on all types of CIS are displayed together. Concomitant CIS with T2 tumors is exempted, where muscle-invasive tumor determines the course of treatment. We believe that the division of CIS is not only didactic and formal, but patients with different forms of CIS do not have the same likelihood of successful disease control. When TUR was the only treatment provided to patients with primary CIS, progression was observed in 28% of cases, and in patients with concomitant and secondary CIS in 59% cases[23,24].

Since primary and concomitant CIS are histopathologically identical lesions, it is logical to assume that patients with concomitant carcinoma will have less favorable clinical course, which is significantly affected by the attributes of tumor, such as stage, grade, number and size. In some studies, there is no difference in the response to BCG immunotherapy without maintenance between patients with different forms of CIS who had complete response in 63%-86% of cases, depending on the length of follow-up[25,26]. Griffiths *et al*. applied 6 weekly doses and noted a statistically significantly greater rate of progression in patients with concomitant CIS (T1) compared to those with primary or concomitant CIS with Ta tumors[27]. In this study, the number of patients with concomitant CIS (T1) was significantly higher than in the previously mentioned works. Losa *et al*. also noted a higher rate of progression in concomitant CIS (T1) in comparison to other forms[22].

In our patients, we preferred the scheme with additional instillations, referring to the meta-analysis of Sylvester *et al*. in which they showed that only a scheme with additional instillations could reduce the rate of progression in non-muscle invasive bladder cancer. This meta-analysis also clearly points out the superiority of BCG immunotherapy against intravesical chemotherapy in treating non-muscle invasive urothelial bladder cancer[28].

In our study, the incidence of urinary bladder primary CIS was low, only 1.7% of 1062 patients with primary urinary bladder cancer. This is in agreement with the current knowledge of bladder cancer and previous findings that primary CIS accounts for only 1%-3% of all urothelial neoplasms[29,30]. Our patient cohort was small, but comparable to other recent publications on the issue, as shown in Table 5. In multicenter studies, subjects are often recruited over a longer period of time, but the low number of patients with primary CIS certainly has an impact on the quality and credibility of statistical analysis. Our experience with BCG immunotherapy in the treatment of primary CIS is in agreement with literature data. After an average follow-up of 50 months, 94% of patients were alive, while 60% of patients had complete favorable response. These results confirm that BCG immunotherapy (schedules with additional instillations as maintenance therapy) is the method of choice in the treatment of primary CIS of urinary bladder.

According to the EAU recommendation from 2011, the treatment of concomitant CIS with TaT1

tumors is determined by therapeutic approach to TaT1 tumors[20]. The EAU formulation is partially inaccurate and incorrect. If we look at non-muscle invasive tumors, concomitant CIS is usually associated with high grade T1 tumors in which BCG immunotherapy is certainly indicated and the indication areas for both forms of the tumor are matched. However, concomitant CIS can be found, although rarely, with G2 differentiated Ta tumors, which can be monitored (small, solitary, primary) or we can indicate the use of intravesical chemotherapy. In these cases, the CIS is the form that determines the dominant therapy, which is the use of intravesical BCG immunotherapy.

The latest recommendations from EAU (June 2011) include BCG immunotherapy as the treatment of choice for CIS if there is an intention to preserve the bladder with complete positive response rate of 72%-93%[29,30]. This recommendation applies to all forms of CIS, which partially corrects the imprecision of previous guidelines. For now, there are no randomized, prospective studies comparing the effectiveness of BCG immunotherapy and early radical cystectomy in the treatment of CIS[31].

Despite the significant number and types of side effects that we recorded, we believe that our results justify the use of BCG immunotherapy in the treatment of CIS of urinary bladder, in particular this schedule with additional instillations (maintenance therapy). Follow-up of patients with urinary bladder CIS must be rigorous and lifelong because there is a significant risk of recurrence and progression in spite of appropriate treatment. In these cases, radical cystectomy is indicated, depending on patient age and comorbidity.

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Sažetak

KARCINOM IN SITU MOKRAĆNOG MJEHURA: INCIDENCIJA, LIJEČENJE I KLINIČKI ISHOD TIJEKOM DESETOGODIŠNJEG PRAĆENJA

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Karcinom in situ mokraćnog mjehura (CIS) je rijetka intraepitelijska neoplazija visokog stupnja s visokom tendencijom progresije i teško predvidljivog kliničkog tijeka. Cilj ovoga istraživanja bila je evaluacija incidencije, liječenja i ishoda liječenja bolesnika s CIS-om tijekom 10-godišnjeg razdoblja. Analizirane su povijesti bolesti 1062 bolesnika s primarnim tumorima mokraćnog mjehura koji su podvrgnuti transuretralnoj resekciji (TUR) na Odjelu za urologiju KBC Split između siječnja 2001. i prosinca 2010. godine. Od svih bolesnika s primarnim tumorom mokraćnog mjehura koje smo liječili, 51 (4.8%) ih je imalo CIS. Primarni CIS dijagnosticiran je u 18 (1.7%) bolesnika, a konkomitantni u 33 (3.1%) bolesnika. U istom razdoblju 847 bolesnika s recidivnim tumorima liječeno je TUR-om, njih 12 (1.4%) sa sekundarnim CIS-om. Pratili smo klinički tijek 15 bolesnika s primarnim CIS-om i 21 bolesnika s konkomitantnim (TaT1) CIS-om. BCG imunoterapija je primijenjena u 12 bolesnika s primarnim i u 17 bolesnika s konkomitantnim CIS-om. Nakon medijana praćenja od 50 mjeseci 9 bolesnika s primarnim CIS-om nije imalo znakove bolesti, u 4 je zabilježena progresija, u 1 recidiv i 1 bolesnik je umro. Nakon medijana praćenja od 37 mjeseci među bolesnicima s konkomitantnim CIS-om 13 (62%) ih je bilo bez znakova bolesti, 3 je progrediralo (14%), u 1 je zabilježen recidiv (4%), 4 bolesnika su umrla, ali samo 2 zbog karcinoma mokraćnog mjehura (10%). Od svih bolesnika liječenih BCG imunoterapijom 8 (27%) ih je imalo značajnije nuspojave. Incidencija i liječenje bolesnika s CIS-om mokraćnog mjehura u našoj ustanovi usporedivi su s rezultatima iz literature.

Ključne riječi: *Tumor mokraćnog mjehura; Karcinom in situ; BCG cjepivo; Ishod liječenja*