

Bladder Cancer

Cystectomy in Patients with High Risk Superficial Bladder Tumors Who Fail Intravesical BCG Therapy: Pre-Cystectomy Prostate Involvement as a Prognostic FactorJ. Huguet^{a,*}, M. Crego^a, S. Sabaté^b, J. Salvador^a, J. Palou^a, H. Villavicencio^a^aUrology Service, Fundació Puigvert, C/ Cartagena, 340, 08025 Barcelona, Spain^bAnaesthesiology Service, Fundació Puigvert, Barcelona, Spain

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Abstract

Purpose: To review understaging and outcome of patients who underwent radical cystectomy (RC) for high risk superficial bladder cancer after bacillus Calmette-Guérin (BCG) failure.

Patients and methods: We carried out a retrospective study of 62 cases in which RC was indicated for clinical stage Tis, Ta, T1 transitional cell bladder tumors that failed transurethral resection (TUR) and BCG treatment. We used BCG (81 mg/Connaught BCG) in patients with superficial grade 3 tumors and CIS. We considered BCG failure a high-grade recurrence at 3 months of the first BCG course or after 2 courses. RC indications, correlation between their clinical and pathological stage and the ensuing progress were analyzed. We assessed the existence of any pre-cystectomy clinical or pathological factor related to understaging and survival.

Results: RC was performed in 22 patients with carcinoma in situ (CIS) (35%), 7 with Ta (11,2%), 31 with T1 (50%), and 2 with Tx tumors (3%). All 62 but one were high-grade tumors (grade 3 and/or CIS). Tumor was clinically understaged with stages pT2 or greater on the RC specimen in 17 patients (27%). The presence of tumor in the prostatic urethra at the moment of endoscopic staging before RC was the only factor associated with clinical understaging ($p = 0.003$) and shorter survival ($p < 0.0002$).

Five-year disease-specific survival rate was significantly lower in understaged (38%) as compared with not-understaged patients (90%) after a median follow-up of 40-months (range 1–142) ($p = 0.006$). Overall five-year disease-specific survival was 79%.

Conclusions: RC should be performed prior to progression in high risk superficial tumors that fail after TUR and BCG. In patients with clinical and pathological nonmuscle invasive disease, RC provides an excellent disease-free survival. One third of patients with HRSBT who underwent RC after BCG failure were understaged and had a shorter survival. Tumor in the prostatic urethra at endoscopic staging was the only factor associated to understaging and shorter survival.

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1. Introduction

High grade stage Ta, T1 and CIS have been associated with increased risk of recurrence and progression and are considered high-risk superficial bladder tumors (HRSBT) [1]. Transurethral resection (TUR)

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and adjuvant bacillus Calmette-Guérin (BCG) therapy is accepted as the optimal treatment for most patients with HRSBT [2]. BCG has proved effective in lowering the risk of recurrence and progression especially when maintenance is used [3]. Radical cystectomy (RC) may be considered as initial therapy if the tumors are large, if they are located in a poorly accessible site for complete resection, and if the patient has symptomatic diffuse disease [4,5].

Ten to 15% of BCG-treated HRSBTs progress, but in series with a long-term follow-up progression and mortality the percentage may be as high as 53% and 34% respectively [3,6]. RC performed in HRSBT that progressed showed extravesical disease in 40–60% of cases [7,8], and survival was lower than 30% at 15 years [9]. Thus, tumor progression should not be awaited to undertake radical treatment in HRSBT that fails BCG [7,9,10].

The controversy lies on what do we consider BCG failure and when to perform a RC for HRSBT that recurs after BCG but without progressing. In general, RC is recommended for patients with carcinoma in situ (CIS) or high-grade T1 that persisted or recurred after initial BCG treatment [4]. Other authors consider RC if CIS or high grade tumor recurs less than 3–6 months after BCG [11,12]. Some patients may benefit from a second course of BCG, but when this fails a RC should be considered [13].

We report 62 patients who underwent RC for non-muscle invasive urothelial carcinoma that recurred after BCG treatment. Our study provides a review of the indications, rates and factors regarding understaging and outcome in these patients.

2. Material and methods

Eight hundred and sixty-four RCs were performed at our Center between January 1989 and May 2002 for transitional cell bladder cancer. We carried out a retrospective study of 62 (7%) RCs for clinical stage Tis, Ta, and T1 tumors that failed both TUR and BCG treatment. All patients received at least one course of endovesical instillations of BCG (81 mg/Connaught BCG/weekly/six weeks). Our patients did not receive maintenance BCG. We used BCG in patients with superficial grade 3 disease and CIS in the bladder or prostatic urethra. We did not perform a restaging TUR in T1 tumors before BCG treatment.

Follow-up was performed by means of cystoscopy every 3 months over the first 2 years, and subsequently every 6 months. After BCG, all patients with previous CIS underwent multiple random cold cup biopsies including prostatic urethra.

We first considered BCG failure a high-grade recurrence (grade 3 or CIS) after 2 BCG courses. Intravesical Mytomicin C was administered in low grade recurrences. Over the last years we also established that high-grade recurrence 3 months after the first BCG course was also a failure. Large tumor size, solid appearance,

multifocal disease, local toxicity after BCG, severe micturitional syndrome due to multiple TUR were also contributory to the RC indications, especially after 1 BCG course.

The study did not include RC for superficial tumors without a previous BCG treatment, patients treated with BCG and clinical diagnosis of invasive disease (\geq T2) and retracted bladders (pT0).

To study the correlation between clinical (T) and pathological (P) stage we compared the histology of the last TUR prior to RC with the histology of the RC specimen.

Clinical endoscopic staging was performed by means of cystoscopy, TUR of the tumor, and 6 cold cup biopsies of normal-looking mucosa, one of them including prostatic urethra near the verumontanum. If there were any macroscopic tumor in the prostatic urethra, we performed TUR and the histologic study was made separately from the bladder. Four possibilities of prostatic tumor involvement were considered: superficial papillary tumor, CIS, prostatic duct involvement (superficial prostatic involvement) and stromal invasion (invasive prostatic involvement). Those cases with infiltration of prostatic stroma in the clinical stage were excluded. Two patients were included who had no *muscularis propria* in the transurethral resection specimen (Tx).

The median interval between the last TUR (clinical endoscopic stage) and cystectomy was 80 days (range 25–240).

We considered understaged patients with tumors in clinical stages Tis, Ta and T1 who presented with infiltrating bladder tumor (\geq pT2) or with prostatic stromal invasion in the RC specimen. We did not classify stromal invasion as intraurethral or extravesical.

Post-cystectomy follow-up was performed every 4 months over the first year, and subsequently every 6 months. Physical exploration, blood tests, abdominal ultrasound scan and chest x-ray were performed. The upper urinary tract was evaluated by urography or loopography 4 months postoperatively and then annually. CT and bone gammagraphy were carried out during follow-up, particularly when local recidivation or metastatic disease was suspected.

We evaluated pre-cystectomy clinical and pathological prognostic factors related to understaging and survival. *Clinical factors*: sex, early BCG failure (recurrence 3 months after treatment), failure of one or more BCG courses, number of TURs prior to RC (more or less than three), interval between tumor diagnosis and RC, interval between BCG treatment initiation and RC, time between initial presentation and second course of BCG, time between the last TUR and RC. *Pathological factors*: single or multiple tumor, tumor size (larger or smaller than 3 cm), macroscopic appearance of the tumor (papillary or solid), tumor grade, stage, presence of CIS, single or multiple CIS, tumor location in the bladder neck or in the prostatic urethra.

The statistical analysis was carried out with SPSS 11.5 (SPSS Inc).

The understage dichotomous variable was used as a dependent variable. Bivariate analysis was performed using X2 test for categorical independent variables, and the logistic regression test for continuous numerical independent variables. $p < 0.05$ values were considered significant.

A multivariate analysis was also carried out through a forward stepwise logistic regression analysis. The most significant variables in the bivariate analysis were incorporated into the multivariate study. The independent variables were included in the model when p was < 0.05 based on the probability of a log likelihood test ratio. The variables were excluded when $p > 0.10$.

Table 1
Number of BCG courses administered and histology of last TUR prior cystectomy

Stage	Grade	N°	BCG failure			Other cystectomy indications
			1 Course	2 Courses	3 Courses	
CIS		22	8 (3)	13	1	1 SMS 2 BCG int
Ta	G1 + Cis	1			1	
	G3	2		2		
	G3 + Cis	4	1	3		
T1	G2	1			1	
	G2 + Cis	4	2 (1)	2		1 SMS
	G3	19	13 (8)	5	1	2 BCG Int
	G3 + Cis	7	4 (3)	2	1	1 SMS 1 BCG Int
Tx	G3	2		2		
Total		62	28 (15)	29	5	

() BCG early failure. SMS: Severe Micturitional Syndrome. BCG Int: Intolerance of BCG.

The survival analysis was performed with the Kaplan–Meyer test.

3. Results

Sixty-two RCs for clinical stages Tis, Ta and T1 transitional bladder tumor were performed in 56 men and 6 women with a mean age of 65 (range 46–79). The median interval between the first evidence of tumor and RC was 31 months (range 5–156). During this time a mean 3.7 TURs (range 2–18, median 3) were performed per patient. The median interval between BCG treatment and RC was 16 months (range 4–125).

Histology of last TUR prior to RC was CIS in 22 patients (35%), Ta in 7 (11,2%), T1 in 31 (50%) and Tx in 2 (3%). All of the tumors but one were high-grade tumors (grade 3 and/or CIS). RC was indicated in 29 cases (46%) following failure of 2 BCG courses, and in 28 (45%) following one course. In 15 cases (53%) of the last group the indication was early BCG failure.

Only 5 patients (8%) received more than 2 BCG courses. (Table 1).

No tumor was identified in 13 (21%) RC specimens (pT0). The clinical stage was the same as the pathologic stage in 29% of the cases, and in 32% the clinical stage was higher. Seventeen patients (27%) were understaged, they presented with infiltrating bladder tumor (≥pT2) or with prostatic stromal invasion in the RC specimen (Table 2).

Four patients (6%) had lymph node metastasis.

The only factor associated with clinical understaging both at the bivariate and the multivariate study was the presence of tumor at the prostatic urethra at the moment of endoscopic staging ($p = 0.003$). (Table 3).

Understaging was verified in 7 (53%) out of 13 cases with prostatic urethra tumor at endoscopic staging. Their five-year disease-specific survival was lower (20%) than in patients without prostatic urethra tumor (78%) ($p < 0.0002$). Five out of 9 patients with macroscopic tumor and superficial prostatic involvement after TUR, had stromal invasion in the RC specimen. Cold cup biopsies in normally appearing prostatic

Table 2
Correlation between clinical stage (TUR prior to cystectomy) and pathological stage (cystectomy specimen)

Clinical stage (TUR prior to cystectomy)	Pathological stage (cystectomy specimen)					Total
	pTo	pTis	pTa	pT1	pT2–T4 N+	
Tis	5	9	1	3	4	22
Ta	–	–	1	2	4	7
T1	8	5	2	8	8	31
Tx	–	1	–	–	1	2
Total	13	15	4	13	17	62

Table 3
Multivariable analysis of clinical-pathological factors related to understaging

Variable	Hazard ratio	95% CI	p-Value
Tumor in prostatic urethra	12.2	2.2–65.5	0.003
No tumor	0.4	0.07–2.5	0.3
Size	2.3	0.4–12.01	0.3
Grade	0.7	0.1–3.4	0.6
Presence of CIS	0.3	0.08–1.7	0.2
Sex	0.1	0.01–1.5	0.1

Only the most significant variables in the bivariate analysis are included.

Table 4

Correlation between clinical stage (TUR prior to cystectomy) and pathological stage (cystectomy specimen) in patients with prostate involvement

Endoscopic clinical prostatic stage prior cystectomy		Pathological prostatic stage (cystectomy specimen)				
		Stromal invasion	Ductal inv	CIS	PT0	
Macroscopic tumor (TUR)	Ta-T1	6	2	2	–	2
	Ductal inv	3	3	–	–	–
No macroscopic tumor	CIS	4	2	1	–	1
Cold cup biopsy	No tumor	43	3	2	1	37
Total		56	10	5	1	40

TUR: Transurethral resection, Stromal inv: Prostatic Stromal invasion, Ductal inv: Prostatic ductal involvement.

urethra detected 4 CIS, and 2 of them had stromal invasion in the RC specimen, and 6 cases with prostatic tumor at RC were not detected, 3 of them with stromal invasion. (Table 4).

Six of these last 10 cases with prostatic urethra involvement and without macroscopic tumor had multifocal disease, and 6 had bladder CIS. Six patients had previous tumor in the bladder neck or trigone, and 4 had previous CIS in the prostatic urethra.

Table 5 shows the characteristics of the understaged cases. Prostatic stroma invasion was found in 10 (58%) of the 17 understaged cases.

Table 5

Tumor characteristics of understaged patients

TUR (n°)	BCG courses (n°)	Time BCG - cystectomy (months)	Clinical stage (TURB prior to cystectomy) Bladder/prostatic urethra (pu)	Pathological stage (cystectomy specimen)	Progress at follow up (months)
2	1	4	Cis	G3 pT3b + Cis	Alive (33)
3	2	20	Cis	G3 pT2b/pu: Cis	Alive (83)
4	2	27	G3 Tx	G3 pT2b + Cis	Alive (43)
6	2	110	G3 Ta + Cis	G3 pTa + Cis + N1	Dead (36)
2	1	9	G3 T1	G3 pT2b	Alive* (40)
3	2	18	G3 T1	G3 pT2b	Alive (24)
5	2	15	G3 T1 + Cis	G3 pT2a + Cis	Alive (36)
3	1	6	Cis	G3 stromal inv + Cis	Alive (35)
2	1	9	G3 T1	G3 stromal inv + Cis + N1	Dead (17)
2	1	6	G3 T1	G3 stromal inv	Alive (2)
3	2	50	pu: Cis	G3 stromal inv + Cis	Dead (70)
2	1	22	G3 Ta/pu: Cis	G3 stromal inv + Cis	Alive (16)
3	2	12	Cis/pu: G3 Ta	G3 stromal inv + Cis	Dead (9)
2	2	12	G3 T1/pu: G3 T1	G3 stromal inv + N1	Dead (6)
17	1	9	G2 T1/pu: G2 ducts	G2 stromal inv + N2	Dead (2)
3	2	40	G3 T1/pu: ducts	G3 stromal inv + Cis	Alive (44)
4	2	9	G3 Ta/pu: ducts	G3 stromal inv	Alive (31)

Tumors in clinical stages Tis, Ta, T1 that presented with infiltrating bladder tumor (>pT2) or with prostatic stromal invasion on the cystectomy specimen. TUR: Transurethral resection, Pu: prostatic urethra, Stromal inv: Prostatic stromal invasion.

* Alive with disease.

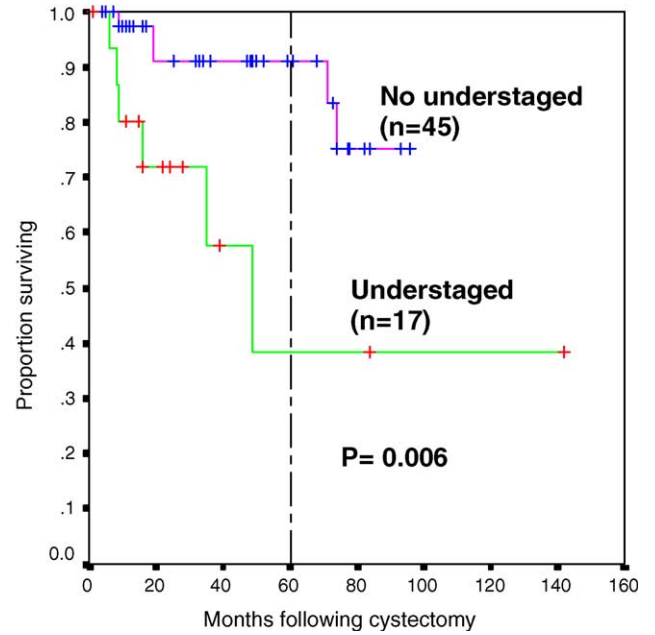


Fig. 1. Kaplan–Meier curves comparing survival in not-understaged cases (patients with clinical and pathological nonmuscle invasive disease) with understaged cases (pathological stage pT2 or greater).

Five-year disease-specific survival rate was significantly lower in patients who presented with understaging (38%) as compared with not-understaged patients (90%) after a 40-month follow-up median (range 1–142) ($p = 0.006$, Fig. 1). Overall five-year disease-specific survival was 79%.

4. Discussion

It is advisable to perform RC in HRSBT unresponsive to BCG before progression [7,9,10]. Which patients to operate and the optimum timing of surgery are controversial. The risk of over-aggressive treatment must be balanced against the potential to offer timely treatment with curative intent [14]. Even though our patients did not receive maintenance BCG, indications for RC followed the accepted guidelines in this group of patients [4,5]. Most were carried out on high-grade tumors that had failed 1 or 2 BCG courses. Following those indications, 5-year survival of patients with clinical and pathological nonmuscle invasive disease reached 90%, an outcome similar to others [7,8,15–17]. However, 17 cases (27%) were understaged. Those were tumors whose progression was detected neither during follow-up, nor at the time of clinical staging with TUR. Five-year survival in these patients was 38%, implying that in several instances RC was performed too late.

Understaging and progression, occasionally subclinical, of HRSBTs, are the factors responsible for BCG-treated patients to present with an unexpectedly poor outcome [18].

Understaging has been observed after a second TUR for primary bladder cancer in 4.7–29% of cases [19,20] and also in RC specimens of patients with Tis, Ta and T1 tumors (24 to 40%) [7,14–17]. Understaging tends to be higher in stage T1 tumors and for this reason some authors perform restaging TUR before BCG therapy [19–21]. In our series a 27% understaging after BCG failure is a low percentage in such a high risk population study and would amount to 13% not counting the understaged cases at a prostatic urethra level. To improve the understaging error we currently perform restaging TUR in TxG3 and in large and solid T1G3 tumors.

In 78 RCs for clinical stages T1 or less, Dutta et al. found more severe understaging in cases with suspicious radiography and with absence of muscle on the biopsy specimen [14]. Freeman et al. could identify no clinical characteristics predictive of understaging in 182 RC carried out in superficial bladder tumors [7].

We found that tumor involvement of the prostatic urethra at endoscopic staging was the only factor associated to understaging. TUR and cold cup biopsies were useful to diagnose the presence of a tumor at a prostatic urethra level, but not to establish a correct staging.

Series assessing prostatic involvement before RC have identified transurethral lateromontanal biopsy as

the most accurate method of determination. Wood et al. were 90% accurate in demonstrating the presence of prostatic tumor involvement, but only 2 of 5 cases (40%) of stromal invasion were detected [22]. Donat et al. detected prostatic involvement in 80 of 99 patients (81%) suffering from prostatic tumor but the specificity (77%), sensitivity (53%) and positive predictive value (45%) of the transurethral resection biopsy to predict prostatic stromal invasion at RC was low [23].

Therefore, if we want to detect prostatic involvement or we find macroscopic tumor at this level, it seems advisable to perform a TUR including transurethral lateromontanal biopsies, assuming that it will not always be possible to detect stromal involvement. This difficulty to perform an accurate endoscopic staging of the prostatic urethra implies that, even though patients with prostatic urethra affected by CIS, papillary tumor and even by duct infiltration may respond to BCG, those are tumors with high progression risk and needing a strict follow-up with repeated biopsies of the prostatic urethra [24,25].

Herr et al. found relapse in prostatic urethra in 72 (39%) of 186 consecutive men with superficial bladder tumors treated with TUR and followed over 15 years. Twenty-seven (38%) cases had stromal invasion. The authors considered that they had silent tumor progression within the prostate that escaped detection during the follow-up [26]. They did not systematically use transurethral lateromontanal loop biopsies and no surveillance policy for the detection of tumor involvement of the prostate was applied. In our series, 6 of 43 patients without macroscopic tumor and negative cold cup biopsies had tumor in the RC specimen.

The question as yet unanswered is when to perform TUR of the prostate in the absence of macroscopic tumor to detect silent prostatic invasion. Previous tumor at the bladder neck, trigone, or prostatic urethra [27] and suspicion of TIS of the bladder [4] have been suggested as potential indications.

The importance of tumor involvement of the prostate lies in that it is a poor prognostic factor, especially in stromal invasion, with 5-year survival between 16–55% [26,28,29].

Solsona et al. observed stromal invasion in 15 (34%) out of 45 RCs performed in HRSBT refractory to TUR and intravesical therapy. Extravesical recurrences were responsible for an unexpectedly poor outcome and RC came to late in some cases. Solsona et al. consider that in primary HRSBT it is necessary to identify progression predictive factors in order to find the optimum timing for RC. No response to intravesical therapy

evaluated at 3 or 6 months seems to be an important factor for the indication of an early RC [18].

Even though our patients are a selected group, having the indication for a cystectomy, in our study we observe that the presence of a post-BCG superficial tumor in the prostatic urethra is a poor prognostic factor, and that it probably is also an important factor for the indication of an early RC.

5. Conclusions

In HRSBTs unresponsive to BCG, RC should be performed before progression. In patients with clinical

and pathological nonmuscle invasive disease, RC provided excellent disease-free survival. One third of patients with HRSBT who underwent RC after BCG failure were understaged and had shorter survival. After BCG failure, tumor involvement of the prostatic urethra at endoscopic staging prior to RC was the only prognostic factor associated to understaging and a shorter survival. This is due to the fact that correct endoscopic staging of the prostatic urethra is difficult and in patients who have received BCG the prostatic urethra is a location in which a transitional tumor may progress silently. In those cases at risk of presenting with subclinical involvement, TUR biopsy of the prostatic urethra should be done.

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Editorial Comment

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Patients with high risk superficial bladder tumours who fail to respond or recur following BCG therapy are a relatively small, but nonetheless, highly significant and difficult group of patients to treat. BCG therapy has been initiated in the hope of eradicating disease and preserving normal bladder function and there is always the tension between attaining this goal and running the risk of being too late in offering radical ablative surgery (radical cystectomy).

This retrospective study from a well respected Urological Cancer Institute in Spain drives home this lesson, yet again emphasising in general terms the

effectiveness in obtaining cure by radical cystectomy but warning of the precarious path that we tread in showing that a third of the patients who had BCG failure were upstaged after radical cystectomy and therefore their survival was shorter indicating that radical cystectomy had been performed later than optimally, and adds yet a further adverse prognostic factor, the only one in their factor analysis to prove consistent, that tumour in the prostatic urethra at endoscopic stage was the only factor associated with understating and a shorter survival.

It reinforces the persistent message that sampling from the urethra in high risk patients is essential, that radical treatment in the presence of aggressive, even if apparently superficial disease within the prostatic urethra, emphasises the need for early radical cystectomy.