

The Effect of Restaging Transurethral Resection on Recurrence and Progression Rates in Patients with Nonmuscle Invasive Bladder Cancer Treated with Intravesical Bacillus Calmette-Guérin

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Purpose: We determined whether restaging resection before initiating induction intravesical bacillus Calmette-Guérin improves the recurrence-free rate in patients with high risk nonmuscle invasive bladder cancer.

Materials and Methods: We retrospectively analyzed data on 1,021 patients treated at our institution with intravesical bacillus Calmette-Guérin for non-muscle invasive high risk bladder cancer. All patients underwent a second resection except those already receiving bacillus Calmette-Guérin at the time of initial consultation and those who refused restaging resection. All patients were assessed every 3 to 12 months for a minimum of 5 years. Univariate and multivariate regression was used to identify predictors of 5-year recurrence.

Results: Restaging transurethral resection was performed in 894 patients (87.5%). At restaging resection viable tumor was found in 496 patients (55.5%). At 3 months patients with a single resection had a 44.3% recurrence rate compared to 9.6% in those with restaging resection ($p < 0.01$). On multivariate analysis a single transurethral resection was the only predictor of recurrence at 5 years (OR 2.1, 95% CI 1.3–3.3, $p = 0.01$). Time to recurrence in patients with a single resection was significantly shorter than in those with restaging resection (median 22 vs 36 months, $p < 0.001$).

Conclusions: Failure to repeat resection before initiating intravesical bacillus Calmette-Guérin therapy for high risk nonmuscle invasive bladder cancer significantly increases the risk of recurrence. Therefore, we believe that restaging resection should be performed before initiating bacillus Calmette-Guérin therapy in all patients with high risk nonmuscle invasive bladder cancer.

Key Words: urinary bladder; carcinoma; BCG vaccine; neoplasm recurrence, local; reoperation

RANDOMIZED trials in patients with high risk NMIBC show the benefits of BCG therapy compared to TUR alone or with intravesical chemotherapy.^{1–4} TUR with intravesical BCG is the standard of care and it has been incorporated into treatment guidelines.^{5,6} However, despite BCG

treatment most patients experience tumor recurrence and a small percent experience disease progression. TUR quality is directly associated with more favorable recurrence and progression rates,⁷ and the response to BCG therapy.⁸ Restaging TUR also decreases the incidence of recurrence

Abbreviations and Acronyms

BCG = bacillus Calmette-Guérin

CIS = carcinoma in situ

NMIBC = nonmuscle invasive bladder carcinoma

TUR = transurethral resection

Accepted for publication August 9, 2013.

Study received institutional review board approval.

Supported by the Sidney Kimmel Center for Prostate and Urologic Cancers, and National Institutes of Health T32-CA82088 (JPS).

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and progression, and facilitates a more accurate pathological diagnosis.^{9–12} The improved staging associated with restaging TUR allows patients to receive more appropriate therapy. Therefore, according to the most recent European Association of Urology guidelines⁵ restaging TUR for NMIBC has become the standard of care but the practice is not universally accepted.

In a recent review Vianello et al identified persistent tumor on restaging TUR in 39% and 47% of patients initially diagnosed with Ta and T1 disease, respectively.¹² Because we believe that having minimal tumor in the bladder before the initiation of intravesical BCG is important for treatment efficacy, restaging TUR may be important before BCG instillation. We evaluated our NMIBC data set to determine whether restaging TUR before initiating intravesical BCG improved recurrence-free and progression-free rates compared to only a single TUR before BCG.

MATERIALS AND METHODS

After receiving institutional review board approval we retrospectively analyzed a prospectively maintained NMIBC (Ta, Tis and T1) database of patients treated at our institution. We identified 1,021 patients in whom bladder cancer was treated with intravesical BCG by a total of 4 high volume urologists at our institution from January 1994 to December 2006. All patients received 6 weekly instillations of Connaught strain (81 mg) BCG therapy. Patients with low grade NMIBC were considered at high risk and were treated with intravesical BCG if they had positive cytology, or multifocal or high volume disease. All patients underwent restaging resection before the initiation of intravesical BCG except those who were already receiving BCG treatment at initial consultation and those who refused restaging resection. Restaging resection included aggressive resection and fulguration of all visible and suspected tumors, including mucosa involved with CIS, and adequate sampling of muscle deep to suspected invasive tumors within 2 to 6 weeks after the initial diagnostic TUR.⁸

Patients were assessed 3, 6 and 12 months after the completion of induction BCG using office cystoscopy, cytology and bladder tumor resection, as indicated. After 12 months patients were assessed every 6 to 12 months for a minimum of 5 years. A complete response was defined as negative cystoscopy and urine cytology at followup. Patients with positive urine cytology or a visible tumor on cystoscopy were considered to have recurrence. Patients with low grade-appearing recurrence on followup cystoscopy were treated with fulguration in the office while those with high grade tumors were taken to the operating room for TUR. Progression was defined as an increase in pathological stage (Ta to T1 or T1 to T2) on restaging resection or the development of metastatic disease. Patients with recurrent nonmuscle invasive disease were eligible to receive another course of 6 weekly instillations of BCG. No study patient received maintenance BCG.

The chi-square test was used to analyze associations between categorical variables and the Student t-test was used for continuous variables. We applied univariate and multivariate logistic regression to assess each variable as a predictor of recurrence at 3, 6 and 12 months. Multivariate logistic regression was also used to identify possible predictors of overall progression and recurrence. Since all study patients had a minimum 5-year followup, recurrence and progression were treated as categorical variables. Kaplan-Meier curves were constructed for recurrence-free and progression-free survival. Differences in recurrence and progression were assessed by the log rank test. All statistical analysis was done using SPSS® 20.0.

RESULTS

Restaging TUR was performed in 894 (87.5%) of the 1,021 patients. Of our patients 756 (75.3%) were male with a mean \pm SD age of 63 ± 11.5 years. No difference was found between the 2 treatment cohorts in gender ($p = 0.19$) or age ($p = 0.75$). Diagnostic resection revealed T1 disease in 409 patients (40.1%) and Ta disease in 612 (59.9%) with no difference in stage between the 2 treatment cohorts ($p = 0.42$). Overall 769 patients (75.3%) had high grade disease and 629 (61.6%) had concomitant or primary Tis. Patients who underwent a single TUR were significantly more likely to have high grade tumors than those with restaging TUR (93% vs 73%, $p < 0.001$) and those with CIS (77% vs 59%, $p < 0.001$). Residual tumor was present in 496 patients (55.5%) with residual Tis found at the highest frequency (18.8%) (table 1).

At 3 months 43.3% of patients who underwent a single TUR had evidence of disease recurrence compared to only 9.6% who underwent restaging TUR ($p < 0.001$). In patients treated with a single TUR the recurrence rate increased to 44.8% and 58.3% at 6 and 12 months, respectively. Patients who underwent restaging TUR had a significantly lower recurrence rate of 16.6% and 28.2% at 6 and 12 months, respectively (each $p < 0.001$). At 5 years patients treated with a single TUR had a 77.2% recurrence rate compared to 61.6% in those who underwent restaging TUR ($p < 0.001$). When excluding patients in whom disease recurred at 3 months, which may have indicated persistent rather than recurrent disease, the recurrence rate at 5 years in those with a single TUR and those with restaging TUR was 58.3% and 57.5%, respectively ($p = 0.84$, fig. 1).

On univariate analysis tumor grade (OR 6.4, 95% CI 3.1–13.2, $p < 0.001$), CIS (OR 2.2, 95% CI 1.4–3.2, $p < 0.001$) and a single TUR (OR 7.2, 95% CI 4.7–10.9, $p < 0.001$) were predictors of recurrence at 3 months. Similarly, grade (OR 3.9, 95% CI 2.4–6.4, $p < 0.001$), CIS (OR 1.7, 95% CI 1.2–2.3,

Table 1. Baseline patient characteristics

	Overall	Restaging TUR	Single TUR	p Value (Fisher exact test)
No. pts (%)	1,021	894 (87.5)	127 (12.5)	
Mean \pm SD age at surgery	63.0 \pm 11.5	62.8 \pm 10	63.1 \pm 11.7	0.75
No. female (%)	265 (26.0)	238 (27)	27 (21)	0.19
No. male (%)	756 (74.0)	656 (73)	100 (78)	
No. grade (%)				<0.001
Low	252 (24.7)	243 (27)	9 (7)	
High	769 (75.3)	651 (73)	118 (93)	
No. initial stage (%):				0.42
Ta	612 (59.9)	525 (59)	87 (69)	
T1	409 (40.1)	369 (41)	40 (31)	
No. CIS (%)	629 (61.6)	532 (59)	97 (77)	<0.001
No. stage at restaging TUR:	—		—	
T0		398 (44.5)		
Papilloma		104 (11.6)		
CIS		168 (18.8)		
Ta		114 (12.8)		
T1		110 (12.3)		

$p = 0.003$) and a single TUR (OR 4.1, 95% CI 2.8–6.1, $p < 0.001$) were predictors of recurrence at 6 months. On multivariate analysis grade (OR 4.9, 95% CI 2.2–11.1, $p < 0.001$) and a single TUR (OR 5.9, 95% CI 3.8–9.1, $p < 0.001$) were predictors of recurrence at 3 months. Grade (OR 3.7, 95% CI 2.1–6.7, $p < 0.001$) and a single TUR (OR 3.5, 95% CI 2.4–5.3, $p < 0.001$) were also predictors of recurrence at 6 months.

On multivariate analysis a single TUR (OR 2.1, 95% CI 1.3–3.3, $p = 0.01$) was the only significant predictor of any recurrence during the 5-year followup (table 2). We also identified stage (OR 2.5, 95% CI 1.76–3.45, $p < 0.001$), grade (OR 18.7, 95% CI 5.71–61.11, $p < 0.001$) and a single TUR (OR 2.1, 95% CI 1.38–3.28, $p = 0.01$) as predictors of progression at 5 years.

On Kaplan-Meier analysis median time to recurrence was significantly shorter in patients who underwent a single TUR than in those who also

underwent restaging TUR (22 vs 36 months, $p < 0.001$, fig. 2, A). At 5 years significantly shorter progression-free survival was seen in patients with a single vs restaging TUR (67.2% vs 81.7%, $p < 0.001$, fig. 2, B).

DISCUSSION

Accumulating evidence supports the importance of restaging TUR for NMIBC.^{9,10,12,13} We report our findings in 1,021 patients who underwent TUR before intravesical BCG. Patients treated with a single TUR had a 43.3% recurrence rate at 3 months compared to only 9.6% in those with restaging TUR before intravesical BCG therapy. The relationship between restaging TUR and recurrence continued to be significant at 12 months with recurrence in 58.2% of patients with a single TUR compared to only 28.3% of those with restaging TUR. The high disease rate at 3 months in patients with a single TUR was most likely due to persistent rather than

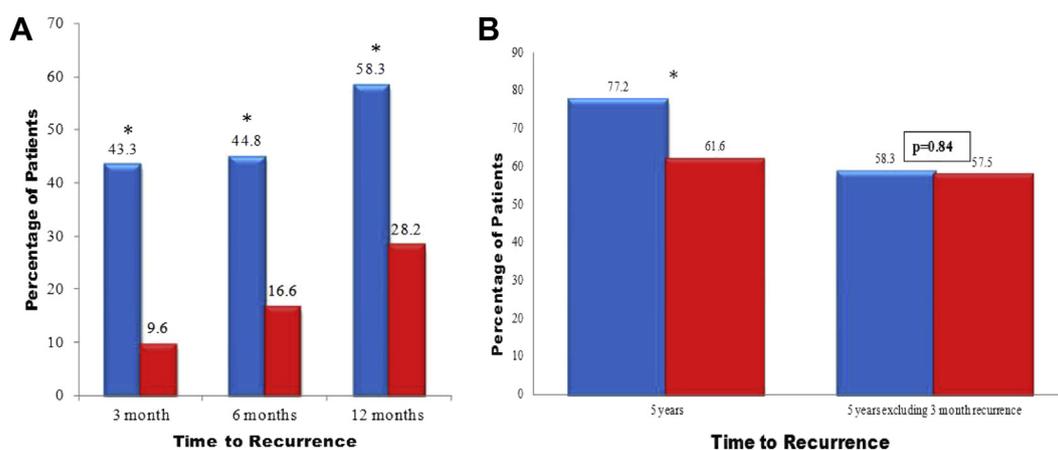


Figure 1. Recurrence rates in patients treated with single (blue bars) or restaging (red bars) TUR. A, at 3, 6 and 12 months. B, at 5 years and at 5 years excluding 3-month recurrence. Asterisk indicates $p < 0.001$.

Table 2. Multivariate logistic regression analysis for any recurrence during 5-year followup

	OR (95% CI)	p Value
Single TUR	2.1 (1.3–3.3)	0.01
Initial pathological finding (pTa vs pT1)	1.1 (0.82–1.43)	0.6
Grade (high vs low)	1.2 (0.81–1.80)	0.4
pTis on initial resection	1.18 (0.83–1.68)	0.4

recurrent disease. When we excluded patients with recurrence at 3 months, we found an almost identical recurrence rate at 5 years. These findings show the importance of having minimal viable disease before intravesical BCG treatment to achieve the optimal response.

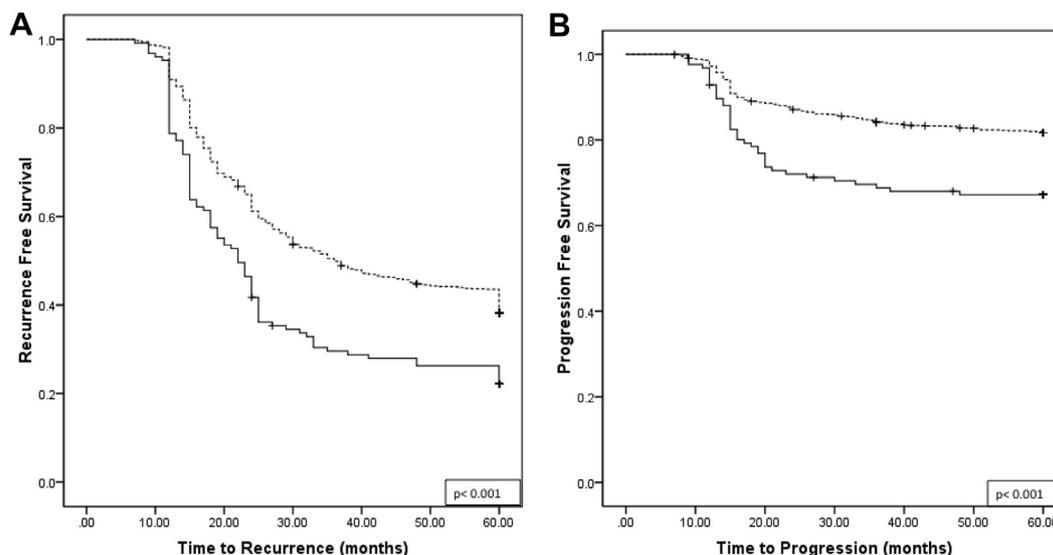
The tumor rate at the time of a second TUR varies in the literature from 20% to 81.5%.¹⁴ In our series we found residual tumor in 55.5% of the patients who underwent restaging TUR. Thus, we strongly encourage restaging TUR not only for a more accurate pathological confirmation but also for its therapeutic effect.^{15,16}

In a retrospective study of patients treated with induction and maintenance BCG at first followup resection Guevara et al noted a recurrence rate of 11.4% in patients without residual tumor and 27.7% in those with residual tumor before treatment.¹⁷ These findings along with our results led us to believe that BCG therapy has improved efficacy when the tumor burden is minimal.

To achieve the minimal tumor burden it is important that the highest quality TUR be performed in all patients for the initial diagnosis as well as for restaging. Quality control guidelines for

TUR put forward by our group include inspecting the macroscopic resection of the surgeon to ensure that no visible tumor remains, identifying muscle in the final specimen and monitoring by each urologist of the recurrence rate at first followup.¹¹ Using these guidelines would allow operating urologists to gauge the quality of TUR and optimize the effects of BCG therapy.

Furthermore, we found that a single TUR was associated with a twofold increased risk of recurrence at 5 years with the greatest risk (4.5-fold) at 3 months. We also found a 14-month shorter median time to recurrence in patients who underwent only a single TUR before BCG. These findings suggest that patients treated with a single TUR are inappropriately staged and, thus, they receive inadequate treatment or undergo inadequate resection. Our findings are similar to the findings of Divrik et al.⁹ In a prospectively randomized trial of patients with only T1 disease who underwent a single and a second TUR they found a 5-year recurrence-free survival rate of 32% and 59%, respectively ($p < 0.001$). In that study a second TUR referred to resection performed after appropriate, complete initial TUR. Even when using this definition, 33% of the patients had residual tumor at the time of the second TUR. The inclusion of Tis and Ta cases in our study is the likely reason for the difference in the recurrence-free rates. However, in each series there are large differences in recurrence-free survival between patients who underwent a single TUR vs those who underwent a second or restaging TUR. These findings suggest that patients with a single TUR are inappropriately staged and, thus, they

**Figure 2.** Kaplan-Meier plot of survival in patients treated with single (solid curve) vs restaging (dashed curve) TUR. A, recurrence-free survival. B, progression-free survival.

receive inadequate treatment or undergo inadequate resection.

While we strongly encourage restaging TUR for its therapeutic effect, another strategy in these patients includes therapy for the tumors at the first followup cystoscopy after BCG therapy. While this is an option, at 3 months we found a 4.5-fold increase in recurrence between our 2 treatment groups. Therefore, repeating TUR before BCG instillation may decrease the recurrence rate. In addition, the initial response to BCG therapy is a strong predictor of the cancer outcome, as shown in previous studies.^{10,18} This further adds to the importance of resecting all possible tumor before initiating intravesical immunotherapy.

We had planned a randomized trial to compare the effect of BCG after 1 or 2 TURs but the institutional review board denied our request to perform such a study. The reason given was our compelling data showing that restaging TUR often revealed persistent cancer and improved staging accuracy. Since some patients had already started weekly BCG instillations when they first consulted us, we

received permission to allow them to complete the induction course and then undergo the second TUR (our first TUR) about 6 weeks later.

This study is limited by its retrospective methodology. Also, since our institution is a tertiary referral center, many diagnostic TURs were not performed here. However, dedicated genitourinary pathologists reviewed all resections for grade and stage. The generalizability of our findings is limited by the fact that we do not perform maintenance BCG at our institution.

CONCLUSIONS

A single TUR was a strong predictor of recurrence as well as progression. Patients who underwent a single TUR before intravesical BCG treatment had a significantly shorter time to recurrence and decreased progression-free survival. The greatest difference was seen at 3 months, as we would expect if tumor were still present after the initial TUR. Therefore, we believe that restaging TUR should be performed before initiating BCG therapy for NMIBC.

REFERENCES

- Lamm DL, Thor DE, Harris SC et al: Bacillus Calmette-Guerin immunotherapy of superficial bladder cancer. *J Urol* 1980; **124**: 38.
- Herr HW, Pinsky CM, Whitmore WF Jr et al: Effect of intravesical Bacillus Calmette-Guerin (BCG) on carcinoma in situ of the bladder. *Cancer* 1983; **51**: 1323.
- Lamm DL, Blumenstein BA, Crawford ED et al: A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette-Guerin for transitional-cell carcinoma of the bladder. *N Engl J Med* 1991; **325**: 1205.
- Malmström PU, Wijkström H, Lundholm C et al: 5-Year followup of a randomized prospective study comparing mitomycin C and bacillus Calmette-Guerin in patients with superficial bladder carcinoma. Swedish-Norwegian Bladder Cancer Study Group. *J Urol* 1999; **161**: 1124.
- Babjuk M, Oosterlinck W, Sylvester R et al: EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder, the 2011 update. *Eur Urol* 2011; **59**: 997.
- Montie JE, Clark PE, Eisenberger MA et al: Bladder cancer. *J Natl Compr Canc Netw* 2009; **7**: 8.
- Brausi M, Collette L, Kurth K et al: Variability in the recurrence rate at first follow-up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies. *Eur Urol* 2002; **41**: 52.
- Herr HW: Restaging transurethral resection of high risk superficial bladder cancer improves the initial response to bacillus Calmette-Guerin therapy. *J Urol* 2005; **174**: 2134.
- Divrik RT, Sahin AF, Yildirim U et al: Impact of routine second transurethral resection on the long-term outcome of patients with newly diagnosed pT1 urothelial carcinoma with respect to recurrence, progression rate, and disease-specific survival: a prospective randomised clinical trial. *Eur Urol* 2010; **58**: 185.
- Herr HW and Donat SM: A re-staging transurethral resection predicts early progression of superficial bladder cancer. *BJU Int* 2006; **97**: 1194.
- Herr HW and Donat SM: Quality control in transurethral resection of bladder tumours. *BJU Int* 2008; **102**: 1242.
- Vianello A, Costantini E, Del Zingaro M et al: Repeated white light transurethral resection of the bladder in nonmuscle-invasive urothelial bladder cancers: systematic review and meta-analysis. *J Endourol* 2011; **25**: 1703.
- Dalbagni G, Herr HW and Reuter VE: Impact of a second transurethral resection on the staging of T1 bladder cancer. *Urology* 2002; **60**: 822.
- Ramirez-Backhaus M, Dominguez-Escrig J, Collado A et al: Restaging transurethral resection of bladder tumor for high-risk stage Ta and T1 bladder cancer. *Curr Urol Rep* 2012; **13**: 109.
- Mariappan P, Zachou A, Grigor KM et al: Detrusor muscle in the first, apparently complete transurethral resection of bladder tumour specimen is a surrogate marker of resection quality, predicts risk of early recurrence, and is dependent on operator experience. *Eur Urol* 2010; **57**: 843.
- Ali MH, Ismail IY, Eltobgy A et al: Evaluation of second-look transurethral resection in restaging of patients with nonmuscle-invasive bladder cancer. *J Endourol* 2010; **24**: 2047.
- Guevara A, Salomon L, Allory Y et al: The role of tumor-free status in repeat resection before intravesical bacillus Calmette-Guerin for high grade Ta, T1 and CIS bladder cancer. *J Urol* 2010; **183**: 2161.
- Grimm MO, Steinhoff C, Simon X et al: Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. *J Urol* 2003; **170**: 433.