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No Added Benefit of Systematic Bladder Biopsies after BCG Induction in High-Risk Non-Muscle-Invasive Bladder Cancer Optimally Managed

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Research Article

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Abstract

Objectives: To evaluate the added detection benefit of routine transurethral biopsies after an induction course of intravesical Bacillus Calmette-Guérin (BCG) for high-grade NMIBC.

Methods: We retrospectively included all patients who underwent white and blue light TURB, subsequent adjuvant induction scheme of BCG, followed by post-instillation biopsies. We excluded patients in whom a prior BCG induction course failed those with synchronous upper tract urothelial carcinoma, and those who did not receive the full 6-week course. A total of 62 patients met inclusion criteria and their records were analyzed. Cystoscopy findings, urine cytology and pathological results of transurethral biopsy were evaluated. Sensitivity, specificity, positive predictive value, negative predictive value, positive and negative likelihood ratios and diagnostic accuracy were calculated for cystoscopy and cytology separately and in combination.

Results: After BCG, a total of 342 bladder biopsy were taken with a median of 5 (IQR 2) per case. The biopsy was positive in 13 patients (21%). The median number of positive biopsies was 2 (IQR 1) and the total number of positive biopsies was 27 (8%). The biopsy was positive at the initial tumor site in 8 patients (61.5%). No complications of Clavien III to V were reported. Out of 62 patients who underwent systematic transurethral biopsy, only 3 (5%) presented complications from grade I to II. We found a significant association of positive biopsy with positive urinary cytology ($p < 0.001$) and the presence of erythematous lesions ($p < 0.02$) or visible tumors ($p < 0.001$) at cystoscopy. The pre-BCG stage T ($p = 0.32$), the presence of CIS ($p = 0.71$), the multifocal tumor ($p = 0.41$) and the size ($p = 0.52$) were not associated with a positive biopsy occurrence. For normal bladder mucosa the predictive value of negative biopsy in cases with negative vs positive cytology was 98% vs 79% (p 0.001).

Conclusion: Routine transurethral bladder biopsies after a BCG induction course are not mandatory in the modern era of NMIBC management.

Keywords: Non Muscle Invasive Bladder Cancer; BCG, Biopsies; Recurrence

Abbreviations: NMIBC: Non-Muscle Invasive Bladder Cancer; BCG: Bacillus Calmette-Guérin; TURB: Transurethral Resection of Bladder Tumor.

Introduction

High-risk non-muscle invasive bladder cancer is an aggressive disease where an induction course of intravesical BCG is the standard adjuvant instillation therapy after TURB (with or without second-look) [1]. Despite optimal management, these patients may experience disease recurrence and/or disease progression to muscle-invasive bladder cancer [2]. Therefore, a stringent follow-up with a combination of urine cytology and cystoscopy is mandated [1]. Although several studies support that cystoscopy and urine cytology combination may be sufficient to identify suspicion of disease recurrence, routine transurethral bladder biopsies after BCG induction scheme have been the standard of care in many urological departments, worldwide [3]. The latter is due to the fact that historical protocols of randomized trials evaluating the efficacy of BCG therapy was evaluated by cystoscopy, urinary cytology and TUR [4].

Due to the low level of evidence surrounding this daily practice question, international guidelines do neither recommend nor discourage systematic bladder biopsies [1]. Thus, it is up to the individual practice pattern whether to perform or not transurethral biopsy after an induction course of BCG. Moreover, recent improvements in initial TURB may impact the interest of such procedure [5,6]. Since we regularly perform this procedure in our institution, we reviewed our recent experience in order to evaluate the added value of post-BCG transurethral biopsy in the era of modern TURB.

Patients and Methods

Patients

After receiving institutional review board approval, we conducted a retrospective study within the urology department of Bichat-Claude-Bernard Hospital from January 2016 to December 2019 at (i.e. 4 years). We included all patients who underwent white and blue light TURB (and/or second look for T1), subsequent adjuvant induction scheme of BCG, followed by post-instillation biopsies. We excluded patients in whom a prior BCG induction course failed those with synchronous upper tract urothelial carcinoma, and those who did not receive the full 6-week course. A total of 62 patients met inclusion criteria and their records were analyzed.

Procedures

Second-look white and blue light TURB was done 4 to 6 weeks after primary resection in pT1 tumors. Patients with only pTis and/or pTa diseases did not undergo second-look TURB. Four weeks after second-look TURB, a 6-week course of intravesical BCG (Medac strain) was administrated.

Transurethral biopsy was performed using general anesthesia 4 to 6 weeks after the last instillation under rigid white light cystoscopy. Random cold cup mucosal biopsies were done, and visible tumors were removed by TURB. There was no standardized biopsy protocol and prostatic urethra biopsies were not taken routinely. Complications were graded according to the modified Clavien classification.

Clinical and Pathological Evaluation

Pathological slides were evaluated by an expert uropathologist according to the 2017 TNM classification and the International Society of Urological Pathology grading system. Cytological examinations were performed using Papanicolaou staining. Positive urinary cytology was defined as unequivocally positive or suspicious for urothelial carcinoma. Cystoscopy was classified as normal, erythema or tumor. The presence of erythema and tumor was regarded as positive.

Statistical Analyses

The categorical and continuous data were compared with the chi-square and Student t tests. Sensitivity, specificity, positive predictive value, negative predictive value, positive and negative likelihood ratios and diagnostic accuracy were calculated for cystoscopy and cytology separately and in combination. One and more variable logistic regression models assessed the factors associated with the occurrence of a positive biopsy. The analyzes were carried out with SPSS (v24) and R, version 2.10.1.

Results

A total of 62 patients were included, including 47 men (76%) and 15 women (24%). The median age was 71 years (IQR 64-78). Urothelial carcinoma was the only histological type noted with a predominance of pT1 (67%) and a concomitant CIS was detected in 32 patients (52%). All patients had high-grade disease.

After BCG, a total of 342 bladder biopsy were taken with a median of 5 (IQR 2) per case. The biopsy was positive in 13 patients (21%). The median number of positive biopsies was 2 (IQR 1) and the total number of positive biopsies was 27 (8%). The biopsy was positive at the initial tumor site in 8 patients (61.5%). Figure 1 displays the pathological stages of the biopsies.

No complications of Clavien III to V were reported. Out of 62 patients who underwent systematic transurethral biopsy, only 3 (5%) presented complications from grade I to II. Two

patients (3%) had prolonged hematuria requiring bladder irrigation, one patient (2%) presented with acute urinary retention requiring the replacement of a bladder catheter. No perforation of the bladder was recorded.

We found a significant association of positive biopsy with positive urinary cytology (p <0.001) and the presence of erythematous lesions (p <0.02) or visible tumors (p <0.001) at cystoscopy. The pre-BCG stage T (p = 0.32), the presence of CIS (p = 0.71), the multifocal tumor (p = 0.41) and the size (p = 0.52) were not associated with a positive biopsy occurrence. For normal bladder mucosa the predictive value of negative biopsy in cases with negative vs positive cytology was 98% vs 79% (p 0.001) (Table 1).

	Pathological result of the post BCG biopsy n=62
Negative (n, %)	49 (79%)
Positive (n, %)	13 (21%)
pTa (n, %)	7 (11%)
pTis (n, %)	3 (5%)
pT1 (n, %)	3 (5%)

Table 1: Distribution of patients according to histological analysis.

Discussion

The natural history of urothelial cancer is the formation of tumors in multiple foci throughout the urinary tract, either synchronous or metachronous. In fact, intravesical recurrence after TURBT has been reported in 30 to 80% of patients with NMIBC, which could be explained in part by the presence of malignant lesions of normal appearance at the time of cystoscopy. In order to decrease the risk of disease recurrence, several tools have been developed including detection improvement (photodynamic diagnosis, narrow-band imaging), perioperative treatments (second-look, single postoperative instillation of chemotherapy), adjuvant treatments (BCG maintenance). Moreover, after BCG induction, random biopsies targeting normal-looking urothelial mucosa have been proposed. However, there have been few large series studies assessing the importance of random bladder biopsies, and they have presented conflicting conclusions [7-10].

Several authors have reported that in case of negative combination of cystoscopy and cytology, biopsies are not mandatory [8,10]. Similarly to our findings Swietek, et al. showed that pre-BCG stage pathologies and the presence of Tis were not associated with a positive biopsy in a historical series (2000-2011) of 180 patients treated with BCG induction [10]. Only cystoscopy and urinary cytology which have been identified as significant variables. Our findings which interested only patients in the modern era of TURB confirm that the combination of urine cytology and cystoscopy is the cornerstone of post-BCG evaluation.

We found a significant association of positive biopsy with positive urinary cytology (p <0.001) and the presence of erythematous lesions (p <0.02) or visible tumors (p <0.001) at cystoscopy, which is in line with several other publications [8,10]. These findings highlight the improvement of in office cystoscopies due to technical improvements such as high-definition cystoscopes, narrow-band imaging [11] or use of photodynamic diagnosis (Cysview) [12].

Finally, we found that bladder biopsy performance harbored a risk of complications of 5%, which is lower than previous series. However, despite the low morbidity of the procedure, the lack of diagnostic benefit and the added cost of the procedure will make us abandon this technique.

Finally, we have to acknowledge several limitations to our study inherent to its retrospective nature with a small sample size. There was no standardized biopsy protocol, but all cystoscopies and biopsies were performed by experienced urologists. Despite dedicated uropathologists being in charge of urinary cytology and TURB specimens, we did not account for inter-observer variability by performing a re-review.

Conclusion

We found that routine transurethral bladder biopsies did not add a significant benefit over the combination of urinary cytology and cystoscopy after induction BCG treatment, in the modern era of NMIBC management.

Declaration of Interest Statement

The authors declare no conflict of interest.

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