Should Bladder Biopsies be Performed Routinely after Bacillus Calmette-Guérin Treatment for High-Risk Superficial Transitional Cell Cancer of the Bladder?

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Abstract

Objective: After endoscopic resection of high-grade superficial urothelial neoplasms (Ta, T1 or Tis), adjuvant bacillus Calmette-Guérin (BCG) therapy is performed routinely to avoid recurrence and/or progression. Vesical biopsies often are performed to assess the efficacy of treatment. The aim of our study was to evaluate the usefulness of these biopsies.

Materials and methods: During this retrospective bi-centre study, 130 patients who had undergone vesical high-grade tumour resection were included. There were 40 Ta associated with Tis in three cases, 87 T1 associated with Tis in 13 cases, and three isolated Tis. After BCG treatment, the following parameters were studied: cystoscopic findings, urine cytology and the histologic results of systematised biopsies.

Results: Urine cytology was positive (high-grade) for 26 patients and negative (normal or low-grade) for 104 patients. For the 26 patients with positive cytology, vesical flexible cystoscopy findings were considered suspicious in 18 patients and normal in eight patients. As for the 104 patients who presented negative cytology, cystoscopic findings were considered negative in 76 patients and suspicious in 28 patients. In the present study, the sensitivity of cytology and cystoscopy in the detection of recurrence after BCG treatment was 56% and 87.5%, respectively; specificity was 56% and 81.6%, respectively. When the two examinations were combined, sensitivity was 100%, and specificity was 76%.

Conclusions: After BCG therapy, the association of negative flexible cystoscopy findings and normal urine cytology made it possible to avoid routine biopsies. Patients could therefore avoid the morbidity of this procedure.

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1. Introduction

Transurethral resection constitutes the first stage in the treatment of bladder tumours [1]. Once superficial transitional cell cancer with a poor prognosis has been diagnosed (high-grade, T1, multiple locations, recurrence, etc), adjuvant treatment is performed either by intravesical chemotherapy or by intravesical immunotherapy (bacillus Calmette-Guérin [BCG]) [2–4]. After BCG treatment, high-grade carcinomas are cured in the long term in one third of the cases, with recurrence in the same form in one third of the cases and, in the remaining one third, evolve into an infiltrating form [5–7]. An accurate diagnosis of recurrence of a high-grade tumour is of utmost importance, since it implies a major worsening of prognosis and leads to the decision to perform cystectomy [1].

The efficacy of treatment usually is monitored by urine cytology and cystoscopy. In addition, some urologists routinely assess that efficacy by performing biopsies during cystoscopy under general anaesthesia. This practice has been criticised owing to its reported low yield [8–10]. The aim of this study was to evaluate the possible usefulness of these biopsies for the early diagnosis of recurrence and/or tumour progression.

2. Materials and methods

The charts of all of the patients who were submitted to intravesical immunotherapy in two different urology departments between January 1, 1997, and December 31, 2002, were reviewed retrospectively. All patients with a diagnosis of high-grade superficial bladder urothelial carcinoma (Ta, T1 or Tis) who had undergone at least six BCG instillations were considered for this study (the pathologic classification used in both departments was the TNM Classification of Malignant Tumors, 1997) [11]. One month after the end of treatment, these patients were explored by voided urine cytology and cystoscopy (under anaesthesia). Owing to different department policies, these biopsies were systematic at any grade (Ta, T1 or Tis) in one department, whereas, in the other department, they were performed only on T1 tumours. Taking into account these criteria, we finally included the 130 consecutive patients who had undergone biopsies.

The same pathologist analyzed the tumours pre- and post-BCG in both urology departments. The initial histologic findings are provided in Fig. 1. The cystoscopic findings after BCG treatment were described by the operator as normal or suspicious. A suspicious cystoscopy corresponded to papillary lesions or to any lesion with an inflammatory or petechial appearance without papillary lesions. Biopsies were performed systematically on the right and left lateral sides, the trigone, the fundus and the dome, as well as on any suspicious zones. Urine cytology, performed before the procedure, was reviewed and classified as negative (normal or low-grade) or positive (high-grade) according to the Bladder Consensus Conference Committee of 1998 [12].

3. Results

Urine cytology was positive in 26 patients and negative in 104 patients. In the 26 patients with positive cytology, the cystoscopy findings were considered suspicious in 18 patients and normal in eight patients (Table 1).

- Of the 18 patients who presented positive cytology and cystoscopy, histologic recurrence was confirmed in 14 cases and invalidated in four cases (Table 2). In 13 cases, recurrence corresponded to high-grade Ta or T1 carcinoma and in one case, to an infiltrating form. (As for the four patients with no tumour revealed on biopsy, two had recurrence [T2 and T4] within 2 years).
- Of the 8 patients with positive cytology and normal cystoscopic findings, histologic recurrence was confirmed on biopsy in four cases (two CIS and two T1G3) and invalidated in the other four cases. (Three of these last four patients had recurrence within 2 years [2 patients with T1G3 and one patient with T2G3]).

In the 104 patients with negative cytology, cystoscopic findings were considered negative in 76 patients and suspicious in 28 patients.

- Of the 28 patients with positive cytology and suspicious cystoscopy, 14 had no tumour lesions on biopsy. The other 14 patients presented the following: five with low-grade tumours and nine with high-grade tumours. Ta made up nine of the 14 cases.

In the present study, the sensitivity of cytology and cystoscopy for the detection of recurrence after...
BCG treatment was 56% and 87.5%, respectively; the specificity of these examinations was 92% and 81.6%, respectively. When we combined both examinations, sensitivity was 100%, and specificity was 76% (Table 3).

4. Discussion

Superficial bladder tumours have a high potential for recurrence and/or progression, depending on their stage and histologic grade [5]. Treatment guidelines for these lesions have been well defined in the literature [13,14]. After a macroscopically complete resection (a second resection currently is recommended in high-risk tumours), intravesical immunotherapy by BCG has proven its efficacy in reducing the recurrence of superficial bladder tumours [3]. It also is the only treatment that has proven its ability to reduce progression of this carcinoma [3,15–17].

In addition to official guidelines, bladder biopsies can be performed under anaesthesia after BCG instillations. These biopsies are part of the SWOG protocols (Southwest Oncology Group) whose aim was to evaluate the efficacy of BCG [18–20]. Although the thorough investigations performed in such randomised trials are not taken in clinical practice, bladder biopsies have become a standard for verification of therapeutic efficacy for many urologic teams. Some teams perform these biopsies in patients after BCG therapy, while others do biopsies in only patients with T1 tumours. The timing for these biopsies also is variable in the literature: 1 month after the end of BCG or 3–6 months after BCG, as stipulated in the SWOG trials and in most protocols. To choose the best waiting time, one has to take into account the risk of progression of a high-grade tumour, if this tumour is not responding to BCG, and the fact that BCG activity could produce endoscopic and histologic changes that last up to 6 months.

The role of these biopsies can be discussed only within the framework of a general strategy to detect post-BCG recurrence.

In 1999, Highshaw [10], who did not perform cytology examinations, recommended limiting biopsies to patients with suspicious cystoscopy findings. In the present series, this tactic would have resulted in four false negatives in the 84 patients with a negative cystoscopy. That would appear to be minor, but the four false-negative patients presented high-grade tumours on histology. Contrary to the author, we believe that such a strategy is inappropriate.

On the other hand, should the urologist be satisfied with cytology alone? In the present series, the sensitivity of cytology was 56%, and its specificity was 92%. In the literature, the sensitivity of urine cytology for the recurrence of high-risk tumours is a parameter that varies from 44% to 97% [21,22]. However, it is important to note that in the literature, the sensitivity of this examination is reduced by its inability to detect low-grade tumours whose risk of progression is very low and therefore do not require early diagnosis. Otherwise, the interpretation of urine cytology findings after BCG treatment is difficult and requires an experienced

<table>
<thead>
<tr>
<th>Positive biopsies</th>
<th>Negative biopsies</th>
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<tbody>
<tr>
<td>Positive cytology/positive flexible cystoscopy</td>
<td>14</td>
</tr>
<tr>
<td>Positive cytology/negative flexible cystoscopy</td>
<td>4</td>
</tr>
<tr>
<td>Negative cytology/positive flexible cystoscopy</td>
<td>14</td>
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<tr>
<td>Negative cytology/negative flexible cystoscopy</td>
<td>0</td>
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<tr>
<td>32</td>
<td>98</td>
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Table 3 – Results of the series for cytology and fiberscope findings combined

<table>
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<th>Positive biopsies</th>
<th>Negative biopsies</th>
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<tr>
<td>Positive cytology or flexible cystoscopy</td>
<td>32</td>
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<tr>
<td>Negative cytology and flexible cystoscopy</td>
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pathologist [23–25]. However, even under these conditions, it should be noted that among our 14 false negatives (urine cytology), there were three high-grade tumours.

In practice, urine cytology alone therefore does not provide the absolute sensitivity required for the diagnosis of high-grade tumours.

In our series, cystoscopy and urine cytology combined had a sensitivity of 100% for the detection of bladder recurrence after BCG treatment. The negativity of these two examinations therefore makes it possible to avoid systematic biopsies and, consequently, we agree with those who contest the usefulness of cystoscopy as an additional procedure [8,9].

Once again, when urine cytology is positive, it is essential that bladder biopsies be performed, even if there is nothing suspicious on cystoscopy. Of a total of 26 patients with high-grade cytology, eight had negative cystoscopy findings, and four of them had a positive biopsy.

In light of the above findings, we propose to perform urine cytology 1 to 3 months after the end of BCG instillations:

- If cytology is normal or low grade, flexible cystoscopy examination under local anaesthesia is performed. (1) If this examination is negative, long-term monitoring is scheduled. (2) If a lesion is detected, the patient undergoes cystoscopy with biopsies under general/regional anaesthesia.
- If cytology is high grade, cystoscopy with biopsy under general/local-regional anaesthesia is performed.

This strategy would have required 28 additional cystoscopic examinations under local anaesthesia (before biopsy under general anaesthesia) but would have made it possible to avoid 76 cystoscopic examinations plus bladder biopsies under general anaesthesia. The net result in terms of both potential morbidity and cost easily favour our proposed strategy.

In a similar approach, Oosterlinck [26], analyzing the need for biopsies after intravesical chemotherapy for lower-risk superficial bladder tumour, came to the conclusion that biopsies are useless if there is no visible lesion.

5. Conclusion

According to this study of 130 consecutive patients who had all undergone urine cytology, cystoscopy and bladder biopsies after intravesical BCG treatment, the performance of biopsies is not necessary when the cytology and cystoscopy findings are negative.

While flexible cystoscopy and cytology are combined in the same office visit in most European countries, we suggest performing these two examinations in a separate setting. We therefore recommend first obtaining urinary cytology:

- If cytology is negative (normal or low-grade), a flexible cystoscopy is performed (under local anaesthesia).
- Endoscopy under general/local-regional anaesthesia and biopsies are performed only (1) in all cases of positive cytology and (2) in case of positive findings on flexible cystoscopy, when cytology is negative.

This strategy had a sensitivity of 100% in our cohort and optimised costs by reducing the number of unnecessary biopsies.

References

Performing bladder biopsies in patients who present with TaT1 bladder tumours remains a controversial issue. At-random biopsies of normal-looking urothelium in low-stage, low-grade tumours do not reveal, in most cases, significant abnormalities leading to a different approach. However, abnormal-looking urothelium should be biopsied (selected biopsies). When cytology is grade 2 or 3, biopsies should be performed as well.

In most cases, patients who have been treated adjuvantly with BCG belong to the high-risk group. Here bladder biopsies may be more significant, as tumour or cis may be found. The BCG instillations as such provoke inflammatory changes in the bladder, which makes the visual interpretation—whether tumour, cis or inflammation is present—more difficult. Also, the interpretation of urine cytology is hampered by the use of BCG.

All these factors make it difficult for the urologist to decide whether or not post-BCG biopsies should be performed. In their retrospective series of 130 patients, the authors show when to perform and when to avoid biopsies. In an algorithm, they show what to do, taking into account the results of both cytology and cystoscopic findings.