



Technique of TUR of Bladder Tumours: Value of Repeat TUR and Random Biopsies

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Abstract

In this review we will indicate the evidence and indications for a repeat TUR-B and for the random bladder biopsies.

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1. Introduction

Of all the patients who present with bladder cancer, approximately 75–85% present with disease confined to the mucosa (stage Tis carcinoma in situ [CIS] or stage Ta) or submucosa (stage T1). These groups of bladder cancer are referred to as non-muscle-invasive or superficial bladder cancer, in contrast with muscle-invasive bladder cancer (stage T2, or advanced stage T3–T4). These anatomic classifications are based on the tumour-node-metastases (TNM) classification of 2002, which was approved by the Union International Contre le Cancer (UICC) [1]. At the start of the new millennium, the histologic grading of non-muscle-invasive bladder cancer is still based on a World Health Organization (WHO) classification system from 1973. Although a new classification of noninvasive urothelial tumours was proposed by the WHO and the International Society of Urological Pathology (ISUP) in 1998 and published in 2004, this new classification system is yet to be validated in more clinical trials [2,3]. In contrast with the 1973 WHO classification, in the 2004 WHO classification the disputed intermediate (moderately differentiated) group is eliminated [4].

The subgrouping of Tis, Ta, and T1 as non-muscle-invasive bladder cancer is based on therapeutic options and, therefore, controversial. Although the treatment of choice for a Ta and T1 lesion is transurethral resection of the bladder tumour (TURB), it is widely accepted that it is not possible to completely resect Tis. Also the potential aggressive behaviour of high-grade CIS and invasive potential of high-grade T1 makes the rather benign terminology “superficial” bladder cancer a suboptimal choice.

For this review article, we would like to highlight two standing controversies in the large group of non-muscle-invasive bladder cancer: the value and indications for a second-look TURB and the value and indications for random or selected bladder biopsies. We will focus on the guidelines of the European Association of Urology (EAU) [5], combined with references of recent publications on the subject. At the end we will state our conclusions and recommendations.

The EAU guidelines concerning a re-TURB state that a re-TURB or a second-look TUR-B should be performed when the initial resection has been incomplete, for example, when multiple or large

tumours are present or when the pathologist has reported that the specimen contains no muscle tissue. Furthermore, a re-TURB should also be performed when a high-grade Ta or T1 tumour has been detected at the initial TURB [5].

With regard to bladder biopsies, the EAU guidelines state that it is not advised to routinely perform random biopsies in normal-appearing bladder mucosa. However, when cytology is positive or when abnormal areas of urothelium are seen, it is advised to take "cold cup" biopsies, or biopsies with a resection loop, the so-called selected biopsies [5]. We will critically review these recommendations with regard to recent publications concerning these subjects.

2. TURB and re-TURB

Although most of the patients with a Ta or T1 non-muscle-invasive bladder tumour present with haematuria, the diagnosis of Ta or T1 non-muscle-invasive bladder tumours ultimately depends on the findings on cystoscopy, urine cytology, and definitive histology of the resected tumour. The cornerstone of this diagnostic pathway is a textbook TURB. The procedure of a textbook TURB is assessment of the bladder wall by endoscopy, bimanual palpation, and TURB. The goal of a well-performed, textbook TURB is 3-fold: (1) diagnostic as well as therapeutic removal of the bladder tumour; (2) endoscopic assessment of size, aspect, multiplicity, and location of the bladder tumour; and (3) acquisition of an adequate histologic specimen for definitive diagnosis (type, grade, and extent) of the bladder tumour. The EAU guidelines on the subject of a TURB are quite clear. A small tumour may be resected in one chip, where the chip contains the complete tumours with part of the underlying bladder wall. For large tumours the strategy is somewhat different. First, a resection of the exophytic part and second a separate resection of the underlying bladder wall with adequate amount of detrusor muscle are done. Separate resection of the margins is advocated because CIS may be present in these margins [5]. Without an adequate part of underlying detrusor muscle, the pathologist will not be able to fully differentiate between Ta, T1, and T2 bladder tumour. If a TURB is performed following the mentioned guidelines, about 90% of all Ta tumours are correctly assessed [6]. However, for T1 bladder tumours this is not the case. Although exact figures are not present at the moment, several studies have investigated the staging errors in cystectomy series: both under-staging and over-staging [7,8].

One of the most compelling problems with the diagnosis of non-muscle-invasive bladder cancer is the problem of early recurrence and progression to aggressive invasive bladder cancer. Of all Ta and T1 non-muscle-invasive bladder cancer, most will recur and about 15–30% will progress to muscle-invasive disease, usually within 5 yr. Especially Ta grade 3 and T1 grade 3 have the aggressive potential of early progression. Other risk factors for early progression are multiple tumours, size (>3.0 cm), concomitant CIS, and presence of tumour at the first follow-up cystoscopy after treatment [9–11]. Sylvester also found the same risk factors in a large review of European Organization for Research and Treatment of Cancer (EORTC) data, addressing the issue of the prediction of recurrence and progression [12]. Concerning the prognosis of muscle-invasive bladder cancer, Schrier et al evaluated the difference in prognosis between primary muscle-invasive bladder cancer and secondary muscle-invasive bladder cancer as a progressive stage from primary non-muscle-invasive bladder cancer. A group of 74 patients with progressive muscle-invasive bladder cancer were matched against 89 patients with primary muscle-invasive bladder cancer. The 3-yr survival rate in the progression group was 37% and in the primary group 67%. The authors concluded the patients with muscle-invasive bladder cancer and a history of non-muscle-invasive bladder cancer had a worse prognosis than patients with primary muscle-invasive bladder cancer [13]. This highlights the importance of a sound and adequate diagnosis by TURB for patients who present with a first episode of non-muscle-invasive bladder cancer.

As mentioned earlier, the EAU guidelines advocate a re-TURB in these high-risk patients. In 2006, Schwaibold et al investigated the value of a second TURB 4–6 wk after initial resection for patients with a T1 bladder cancer. Of an initial group of 134 patients, 71 patients (52%) had residual tumour at re-TURB. In 21% of the patients histopathologic changes that worsened the prognosis (>T1 or concomitant Tis) were found at second resection. Residual tumour tissue was mostly found on the location of the initial resection (86%). As a conclusion the authors give the recommendation for a re-TURB in all patients with T1 transitional cell carcinoma (TCC) to achieve a more complete tumour resection and to identify patients who should have a prompt cystectomy [14].

Herr et al investigated the value of re-TURB in a group of 710 patients presenting with multiple non-muscle-invasive bladder tumours. The re-TURB was scheduled 2–4 wk after the initial operation. Of the

710 patients, 490 patients (69%) had recurrence of disease and 149 (21%) had progression of disease over 5 yr. Eighty patients had T1 grade 3 on re-TURB, of whom 61 (76%) progressed to muscle-invasive disease, compared to 88 (14%) of 630 patients with T0 or Ta after restaging re-TURB. Of all 710 patients, only 278 patients (39%) had no evidence of disease after the re-TURB. As a conclusion they state that a re-TURB can identify patients who are at risk for early tumour progression [15]. This conclusion is supported by Divirik et al who described in two separate manuscripts that also the chance for recurrence of an initial T1 bladder tumour will decrease after a re-TURB and also for the high-grade tumours [16,17].

In an excellent manuscript concerning the subject of a second-look TURB in T1 non-muscle-invasive bladder cancer, Jakse et al reviewed the current literature on the subject. They found that, because of the potential lethal character of medium- and high-grade tumours, the necessity of accurate assessment of the tumour is of eminent importance. The quality of the TURB is crucial for the pathologist to adequately diagnose the malignancy. A second-look TURB within 2–4 wk after the initial surgery is the most appropriate treatment in T1 non-muscle-invasive bladder cancer because of the prognostic and therapeutic implications. An incomplete resected T1 tumour will be “discovered” at 3-mo follow-up as a rapid recurrence of a T1 bladder tumour, a very important negative prognostic factor. These patients may be incorrectly diagnosed with an rapid recurrence and thus aggressive bladder tumour, and be unnecessarily scheduled for cystectomy [18]. The finding that the quality of the initial TURB is of eminent importance is also confirmed by Brausi et al who investigated the recurrence rate of bladder cancer at first follow-up in a large cohort of 2410 patients included in several EORTC trials. In this large cohort the recurrence rate of bladder cancer varied considerably, for instance, for a single tumour 3.4–20.6% and for multiple tumours 7.4–45.8%. The recurrence rates varied among institutions and could not be explained by the factors they had assessed. They suggest that the quality of the TURB performed by the individual surgeons may be responsible [19]. One can only conclude at this point that a textbook TURB is one of the more challenging operations in the urologic armamentarium.

An international consensus panel on the management of T1 tumours of the bladder also tackled the problem of recurrence and the importance of a second-look TURB. The panel suggested that the risk of residual tumour after a textbook initial TURB has

been reported to be as high as 60% [20]. They also state that the result of a second-look TURB changed the treatment in 33% of the patients, mostly due to the fact of inability of accurate diagnosis of T1 tumours without muscle in the specimen [21]. Further, as they described, the risk of residual tumour at second-look TURB is also significant. For solitary, papillary-appearing tumours a risk of 24–27% is reported [22–24]. As an example, the panel investigators mentioned the experienced surgeons who were convinced and believed that the resection was complete, only to find a recurrence, possibly of higher stage, in exactly the same site a short time later. Because of these findings and significant rates, the panel recommended that a second-look TURB should be considered a standard of universal repeat resection for all patients with a high-grade Ta or T1 urothelial cancer in an attempt to prevent understaging and possible progression to metastatic disease. It is also recommended, although with lack of scientific support, to time this at 1–4 wk after initial resection [20]. This recommendation is, as we saw earlier, in concordance with the EAU guidelines [5].

As a conclusion one can suggest that you need a very good argument not to perform a second-look TURB in cases of high-grade Ta or T1, and that a second-look TURB should be part of the standard, routine work-up for these potentially aggressive tumours. After considering this extensive evidence for the value of the second-look TURB, the scientific community should wonder how to deliver this broadly supported message in such a way that a second-look TURB is not a point of repeated discussion, but of common practice. In 2006, in an attempt to define the current practice in The Netherlands and Belgian Flanders concerning the management of non-muscle-invasive bladder cancer, a survey was performed. A total of 516 urologists received a questionnaire, and the results were compared to the EAU guidelines. The results showed a wide variation in current practice for non-muscle-invasive bladder cancer, although the current practice roughly matches these guidelines. The authors concluded that there is a need for clear guidelines in the management of non-muscle-invasive bladder cancer and more important an effective implementation of such guidelines into everyday practice [26].

3. Random biopsies of the bladder

For quite some time, bladder biopsies were taken on a routinely basis for evaluation of the bladder

mucosa, even if the bladder mucosa appeared normal, following the initial TURB. Possible biopsy indicators were random bladder biopsies in normal-appearing bladder mucosa, or directed biopsies to an area of visible abnormality such as areas with erythematous, velvety or oedematous abnormalities suspicious for dysplasia or CIS. However, the indication for taking bladder biopsies has changed over recent years. As we stated earlier, with regard to bladder biopsies, the EAU guidelines state that it is not advised to routinely perform random biopsies in normal-appearing bladder mucosa. When cytology is positive or when abnormal areas of urothelium are seen, it is advised to take "cold cup" biopsies, or biopsies with a resection loop, the so-called selected biopsies [5].

As early as 1994, an epidemiologic study investigated the fact if it was worthwhile to implement routine random bladder biopsies from the normal-appearing bladder mucosa in the management of patients with primary non-muscle-invasive bladder cancer. In a hypothetical model two management policies were compared: one with and one without routine bladder biopsies. The patients in the "no-biopsy" protocol were treated with a TURB, except for the T1 grade 3 tumours, who were treated with adjuvant intravesical therapy. For the patients in the "biopsy" protocol, the choice of treatment was influenced by the presence or absence of dysplastic urothelium, except for the T1 grade 3 patients who received adjuvant intravesical therapy anyway. The results showed that the recurrence rate and progression rate over a 3-yr period was similar for the "biopsy" as well as the "no-biopsy" protocol: 52% and 11% versus 54% and 11%, respectively. The authors concluded that random biopsies of normal-appearing bladder mucosa at the time of the initial TURB had no practical value [27].

This finding was supported by van der Meijden et al in a large retrospective analysis of two large EORTC studies. A total of 995 patients underwent bladder biopsies of normal-appearing bladder mucosa, both in a low-risk group as in an intermediate/high-risk group. They described that biopsies of normal-appearing urothelium in Ta and T1 bladder cancer did not show any abnormality in about 90% of the patients. Additionally, they concluded that performing such biopsies does not contribute to the staging or to the choice of adjuvant therapy after transurethral resection [28].

Also other studies, both prospective and retrospective, concluded that routinely taken bladder biopsies of normal-appearing bladder mucosa in patients with initial non-muscle-invasive bladder

cancer only contributed in about 8–8.3% of abnormalities including about 5% of CIS. These abnormalities, however, were found in T1 patients, in patients with multiple papillary broad-based lesions, and with positive urine cytology, where the additional value of such a biopsy result is limited [29,30].

Conversely, however, other groups did find a significant benefit for the use of random biopsies. Taguchi et al found a 24.1% positive biopsy rate (14.5% CIS and 9.6% dysplasia) for random bladder biopsies in 83 patients with non-muscle-invasive bladder cancer and normal-appearing bladder mucosa. The incidence of positive biopsies was significantly higher in the high-grade, multiple Ta, or the T1 group. They concluded that routinely taken random biopsies are useful in detecting concomitant CIS, although the series is small [31]. May et al also found that random bladder biopsies were abnormal in 12.4% of 1033 consecutive patients who presented with non-muscle-invasive bladder cancer. The random bladder biopsies altered the therapy in 7% of the patients. In 14 cases, the biopsies were found to be the only malignancy, since the TURB showed no abnormality. This group recommended random biopsies as part of the routine management of non-muscle-invasive bladder cancer. Important, however, is the fact that these authors excluded patients for random bladder biopsies who presented with small, primary, and solitary lesion and they did not incorporate the results of the pre-TURB urinary cytology in their study [32]. These findings led the international consensus panel on the management of stage T1 tumours of the bladder to recommend that patients with low-risk-appearing bladder tumours and negative cytology results not to undergo random bladder biopsies of normal-appearing bladder mucosa. In high-risk patients, patients with abnormal cytology, multiple or T1-appearing tumours, or abnormalities, visible directed bladder biopsies or random biopsies should be considered [25]. These recommendations are in concordance with the EAU guidelines [5].

4. Conclusion

Although a re-TURB, or second-look TURB, is still a matter of fierce scientific discussion, this review showed that the evidence presented strongly recommends that a second-look TURB should be performed in any patient with a high-grade Ta, or any T1 bladder tumour, even if the surgeon is convinced of a radical resection. Only in selected

cases could a second-look TURB be omitted, for instance, in the very elderly patients or in patients in whom the outcome of the second-look TURB would not alter the treatment.

For random bladder biopsies the recommendations of both the EAU guidelines, as well as the international consensus panel on the management of stage T1 tumours of the bladder, are that no biopsies should be performed in low-risk tumours with negative cytology and normal-appearing urothelium.

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CME questions

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1. Following the EAU guidelines, a second-look TURB should be performed
 - A. When the initial resection was incomplete.
 - B. When extensive tumour is present.
 - C. When a high-grade pTa or pT1 has been found.
 - D. All of the above.
2. When are random biopsies indicated?
 - A. When high-grade urinary cytology is found.
 - B. Recurrence of pTa grade 1 is found.
 - C. When a tumour >3 cm (maximum diameter) is found.
 - D. All of the above.
3. Concerning prognosis: which patients do better?
 - A. Patients with invasive bladder cancer at first diagnosis (>pT2).
 - B. Patients with progression from any initial stage to invasive bladder cancer.
 - C. Patients with initial high-grade pTa, progressed to muscle-invasive bladder cancer.
 - D. Patients with initial high-grade pT1, progressed to muscle-invasive bladder cancer.
4. Concerning timing, when should a second-look TURB be performed
 - A. 1-2 wk
 - B. 2-4 wk
 - C. 6 wk
 - D. 3 mo
5. Bladder biopsies should not be performed
 - A. When a pTa papillary lesion is found.
 - B. In patients with positive high-grade cytology.
 - C. When multiple tumours are found.
 - D. If the patient has a history of carcinoma in situ.
6. The goal of a textbook TURB is
 - A. Therapeutic removal of the bladder tumour.
 - B. Assessment of size, multiplicity, and location of the tumour.
 - C. Obtain adequate histologic specimen for diagnosis.
 - D. All of the above.