



## Transurethral Resection of Non-muscle-invasive Bladder Cancer

Marko Babjuk \*

Department of Urology, General Teaching Hospital, 1st Faculty of Medicine, Charles University, Ke Karlovu 6, 12808, Praha 2, Czech Republic

### Article info

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### Abstract

Transurethral resection of the bladder (TURB) is the initial and critical step in the management of bladder tumours. The aim of the procedure is to establish the histologic diagnosis, determine the tumour stage and grade, and achieve complete removal of papillary non-muscle-invasive tumours. Although TURB is a frequently performed procedure, its results are limited by the high recurrence rate and by the risk of tumour understaging. The major prerequisite for optimal outcomes is a systematically and meticulously performed procedure by a well-trained urologist. Smaller tumours can be resected en bloc; tumours >1 cm should be resected separately in fractions. Deep resection, including the detrusor muscle, is essential for correct staging. The biopsy should be taken from all areas suggestive of carcinoma in situ (CIS), and biopsies from normal-looking mucosa are recommended only in patients with positive cytology or non-papillary tumours. TURB should be performed with modern equipment, including new telescopes and video systems. Moreover, urologists should be aware of promising innovations, including new imaging techniques, and their possible benefits.

Re-TUR can improve recurrence-free survival (RFS) and tumour staging. It is recommended in any patient with a T1 or high-grade tumour at initial resection and when the pathologist has reported that the specimen contained no muscle. It should also be considered in cases where the urologist is not sure that the initial resection was complete, especially in extensive and multiple tumours.

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\* Tel. +420224967848; Fax: +420224967102.  
 E-mail address: [marko.babjuk@lf1.cuni.cz](mailto:marko.babjuk@lf1.cuni.cz).

### 1. Introduction

Worldwide, bladder cancer (BC) is the seventh most common malignancy in men and the seventeenth most common malignancy in women. It is estimated that, in 2002, about 357 000 new cases of BC were diagnosed [1]. Approximately 75–85% of all patients with BC have disease confined to the mucosa (stage Ta or stage carcinoma in situ [CIS]) or submucosa (stage T1). This group of tumours is referred to as *non-muscle-invasive* or *superficial* BC as opposed to muscle-invasive disease staged as T2–T4.

The success of treatment in non-muscle-invasive BC (NMIBC) depends upon the biologic characteristics of the

tumour and on the treatment strategy, which must be appropriately selected and correctly performed. Endoscopic surgery remains the dominant treatment in exophytic non-muscle-invasive tumours (Ta and T1), which can theoretically be completely removed. Its role in flat lesions (CIS) is predominantly in diagnosis, as it is accepted that CIS cannot be completely resected.

Transurethral resection of the bladder (TURB) is the initial and critical step in the management of non-muscle-invasive tumours. The aim of the procedure is to (1) establish the histologic diagnosis of the bladder tumour; (2) determine the tumour stage (the pathologist must be able to evaluate the depth of tumour invasion from the surgical

specimen); (3) determine all clinically important prognostic factors, such as the grade, number, size, and configuration of the tumour as well as the presence of CIS; (4) achieve complete removal of papillary non-muscle-invasive tumours.

Unfortunately, the efficiency of the procedure is not optimal. Although TURB is a procedure familiar to all urologists, it is not easy to perform and may not always achieve the desired goals. Moreover, its potential failures have negative impacts on patient outcomes. It was shown that many of the so-called early recurrences are in fact persistent tumours that were overlooked and left behind during resection [2]. Even more importantly, inaccurate diagnosis—particularly understaging—can adversely affect the survival of the patient. To achieve optimal results and overcome all limitations, efforts have been made to standardise all steps performed during the procedure and introduce potential technological improvements.

The goal of this article is to specify the value and correct performance of individual steps during the procedure and to discuss the potential of new innovations.

## 2. The performance of transurethral resection of the bladder step by step

### 2.1. Preoperative considerations

Surgeons should remember and consider all known details about the history of the disease (eg, size, number, location, and frequency of previous tumours; previous treatment) as well as the location of the tumour if it was detected by previous office cystoscopy.

It is advisable to be aware of the result of voided urine cytology, as urinary cytology has excellent sensitivity and specificity in high-grade lesions, including CIS [3]. In the case of positive cytology, the presence of urothelial cancer is highly probable, even if it cannot be visualised, and all necessary measures should be considered and performed (eg, random biopsy, prostatic urethra biopsy, fluorescence cystoscopy).

### 2.2. Anaesthesia

Safe resection and biopsy require appropriate anaesthesia, which ensures relaxation of the bladder and abdominal wall. The procedure can be performed under general or spinal anaesthesia according to the preference of the surgeon and anaesthesiologist [4–6].

### 2.3. Bimanual palpation

Bimanual palpation of the bladder under anaesthesia before and after TURB may provide additional information about a tumour's extent. Palpable tumours are usually invasive; any mass present after resection indicates deep muscle or even extravesical invasion.

### 2.4. Urethrocystoscopy

The procedure begins with a careful endoscopic examination of the entire urethra during insertion of the cystoscope.

Subsequently, all areas of the bladder are inspected using a 70° telescope. The urologist should register the size (by comparison with the diameter of the resection loop), number, and location of tumours as well as regions of erythema and mucosal abnormalities suggestive of CIS. All these findings must be documented in the diagram immediately after the procedure.

### 2.5. Tumour resection

The strategy of tumour resection depends on the size of the tumour. Smaller tumours—those <1 cm—can be resected en bloc, where the specimen contains the complete tumour with part of the underlying bladder wall. Larger tumours should be resected separately in fractions that include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area (differential resection) [7,8]. The specimens from different fractions must be referred to the pathologist in separate containers.

The strongest argument for careful management and wide resection of the visible lesion is the risk of tumour persistence at its original site. In one study, by evaluation of repeat resection, positivity was found in 33% of 124 cases; in 81% of those cases, the tumour was present at the original TURB site [9]. In another study, deep resection of the underlying bladder wall and surrounding area—at least 2 cm lateral to the visible lesion—could detect residual tumours in 13% of Ta and in 35% of T1 tumours [10].

Deep resection, including the appropriate part of the detrusor muscle, is essential for correct staging. It was shown that the risk of understaging in T1 tumours was strongly dependent on whether the muscle was resected during initial TURB [8,11]. Tumours were upstaged by second resection in 15% of 421 patients with muscle, compared to 45% of 280 patients without muscle, in the specimen from initial resection [8].

In spite of some bleeding, cauterisation has to be avoided as much as possible during the resection. Excessive cautery artefact may make interpretation of tissue by pathologist examination difficult.

### 2.6. Mucosal biopsies

A typical feature of urothelial carcinoma (UC) of the bladder is its multifocality. The exophytic lesions can be accompanied by mucosal abnormalities, such as CIS. There is no doubt that areas of erythema or velvet-like mucosa, which are suggestive of the presence of CIS, should be sampled for histologic examination.

In contrast, the value of biopsies from normal-looking mucosa in patients with exophytic non-muscle-invasive tumours—so called *random biopsies* (R-biopsies)—is controversial. To be able to clarify this issue, we must discuss the importance and impact of the information obtained.

The large retrospective analysis of 995 patients enrolled in two European Organization for Research and Treatment of Cancer (EORTC) trials found no abnormality detected by R-biopsies in 95.6% of low-risk and in 88.4% of high-risk

tumours. The authors conclude that the biopsies contribute neither to the staging nor to the choice of adjuvant therapy after TURB [12]. In another study, May found mucosal abnormalities detected by R-biopsies in 12.4% of 1033 consecutive patients with NMIBC. Moreover, information obtained altered the treatment recommendation after TURB in 7% of cases. Based on these data, the authors recommended R-biopsies as part of the routine management of NMIBC. We should remember, however, that the group did not perform biopsies in patients with small, primary, and solitary lesions and did not consider the result of pre-TURB urinary cytology [13].

The incorporation of R-biopsies as a routine part of TURB in patients with NMIBC was investigated in a population-based study published as early as 1994. The authors compared two hypothetical management policies: without and with random biopsies during TURB. In the “no-biopsy policy,” all patients were treated with TURB alone, except for patients with T1G3 tumours, who were treated with adjuvant intravesical therapy. In the “biopsy policy,” the choice of treatment was influenced by the findings in biopsy specimens, except for patients with T1G3 tumours, who always received adjuvant treatment. The evaluation showed, in both groups, nearly the same 3-yr recurrence rate and progression rate: 54% and 11% in no-biopsy and 52% and 11% in the biopsy groups, respectively. This means that the result of biopsies from normal-looking mucosa had no impact on patients’ outcome [14].

The recommendations of European Association of Urology (EAU) guidelines reflect these data. The biopsy should be taken from all areas suggestive of CIS, and R-biopsies are recommended only in patients with positive cytology or non-papillary tumours [7]. To prevent cautery artefact, biopsies are preferentially performed using cold-cup biopsy forceps.

### 2.7. Prostatic urethra biopsies

NMIBC can be accompanied by the involvement of mucosa in prostatic urethra or ducts. Recently, CIS in prostatic urethra was reported in 10.3% of men with T1G3 bladder carcinoma [15]. It was shown that the risk is higher in tumours located on the trigone or bladder neck when CIS is present in the bladder and in multiple lesions [16,17]. The EAU guidelines recommend biopsies of the prostatic urethra in these cases and when abnormalities in the prostatic urethra are visible. Biopsy should also be performed when urinary cytology is positive but there is no evidence of tumour in the bladder [7]. As cold-cup biopsy is usually insufficient in prostatic urethra because the CIS in the ducts can be missed in small piece of tissue, using resection loops and resecting the floor of the prostatic urethra is recommended. The precollicular area is selected because of the preferential location of ducts in this region [4].

### 2.8. Completion of transurethral resection of the bladder

Careful haemostasis is obtained by fulguration of resected and biopsied areas using a rollerball electrode; the

completeness of resection is controlled using a 70° telescope [2]. The procedure is finished by the insertion of a catheter and bimanual examination. As mentioned before, all findings and the location of resected areas and biopsies should be immediately documented in the bladder diagram by the operating urologist.

### 2.9. Pathologic report

The pathologic report must contain all necessary information for correct decisions relating to further treatment steps. The pathologist should specify the histologic tumour type, its stage, and its grade and provide information as to whether muscle was present in the specimen. The operating urologist and pathologist should cooperate and regularly review and discuss the specimens.

## 3. Quality assessment of transurethral resection of the bladder

Although TURB is a routine urologic procedure, the principles of which have not been changed for decades, the criteria of its quality have never been clearly defined. The definition of benchmarks is extremely important, because it could help us to improve the results.

There is general acceptance that TURB is successful if there are no missed non-muscle-invasive lesions (ie, the early recurrence rate is low), if the staging of the disease was assessed correctly (ie, there is no tumour understaging), and if the procedure was performed without complications.

### 3.1. Early recurrences after transurethral resection of the bladder

Recurrences after TURB are observed in about 50–80% of patients with non-muscle-invasive disease, most of which occur during the first year [18]. The source can be found in incomplete TURB, in tumour cell implantation, or in aggressive tumour biology.

The analysis of 2410 patients from seven phase 3 trials by the EORTC showed substantial variations in early recurrence rates among different institutions. The frequency of 3-mo recurrence ranged from 0% to 46%. These differences are not the result of the clinical features of the tumour but probably of the quality of TURB performed by individual surgeons [2].

### 3.2. Tumour understaging

The risk of tumour understaging by initial TURB was discovered by investigation of cystectomy specimens. It is known that as much as 40% of clinically T1 tumours are upstaged to pathologic muscle-invasive disease [19]. The most important risk factor of T1 tumour understaging is absence of muscle in the tissue obtained by TURB [7,10,18]. Unfortunately, the muscularis propria is missing in 30–50% of submitted specimens [20–22]. The presence of detrusor muscle in resected tissue is today considered the most

important surrogate marker indicating a complete TURB [8,22].

### 3.3. Complications of transurethral resection of the bladder

The complications after TURB are reported in about 5–6% of patients [8,23,24]. The frequency of complications is higher with large tumours, multiple tumours, and in tumours located in the bladder dome and depends on the experience of the surgeon [8,25]. The most common complication is bleeding, occurring in 2.3–2.8% of cases [23,24]. Haemorrhage can be avoided by meticulous haemostasis during TURB and by prevention of bladder overdistension post-operatively.

A more serious complication is bladder perforation, which was reported in 1.3–3.5% of patients [23,24]. We expect, however, that clinically silent extraperitoneal extravasation of urine can appear much more frequently [26]. Most perforations are extraperitoneal, which can be managed by a few days of catheter drainage. Intraperitoneal perforations are less common, but some of them require open surgical exploration with suture closure of the defect [6,8].

The perforation can appear as a consequence of obturator nerve stimulation with muscle contraction and rapid movement of the lower extremity. The stimulation can be prevented by local anaesthesia or by utilization of bipolar electrocautery. The surgeon should avoid resection on an overdistended bladder.

## 4. Improving the quality and results of transurethral resection of the bladder

The major prerequisite for optimal outcomes achieved by TURB is a systematically and meticulously performed procedure by a well-trained urologist. It is important to use modern equipment, including new telescopes and video systems. Moreover, the urologist is faced today with many technical innovations that are not routinely used but offer promise for the future.

### 4.1. Dedicated teaching programs

Brausi recently introduced the dedicated teaching program on surgical treatment of TURB and evaluated its impact on patient outcome. The program included the routine use of video-transurethral resection (TUR) and bipolar resection, the presence of a senior urologist in theatre during the procedure, and regular teaching session meetings on bladder tumours. Its application reduced the 3-mo recurrence rate in patients operated on by resident urologists from 28% to 16%, increased the presence of the muscle from 50% to 88%, and decreased the complication rate [27].

### 4.2. Technical innovations

An innovative working element for the resectoscope was described in which the standard linear direction of the handgrip is replaced by a side-to-side lateral rotating

motion. It allows better control of the depth of resection, which improves pathologic assessment of tumour invasion and reduces the risk of bladder perforation [28].

The application of bipolar electrocautery already used for TUR of the prostate has also been considered for TURB. Its advantage is the absence of obturator nerve stimulation and the ability to resect in saline. It can help to avoid bladder perforation and transurethral resection syndrome [6].

### 4.3. New imaging technologies

The major limitation of conventional white-light cystoscopy is its low accuracy in the detection of flat lesions such as CIS or dysplasias. It can, however, also miss papillary tumours, particularly if they are small and multiple. As a consequence, we can observe tumour persistence after presumably complete TURB. Recently, new endoscopic imaging techniques were presented that improve the sensitivity of BC detection [29]. These methods can be utilized during TURB for guidance in resection or biopsies and can theoretically improve outcomes of the procedure.

#### 4.3.1. Fluorescence cystoscopy

The principle of fluorescence cystoscopy (FC) is based on selective accumulation of protoporphyrin IX in tumour tissue after intravesical instillation of 5-aminolevulinic acid (5-ALA) or its ester hexaminolevulinic acid (HAL). Protoporphyrin IX emits intensive red fluorescence after illumination with blue light. By inducing this photodynamic process, FC enhances the visual contrast between benign and malignant tissue in the bladder [30].

It was confirmed that with FC we can detect significantly more tumour lesions compared to standard white-light investigation. In a large multicentre study with 311 patients, there was a detection rate in Ta and T1 tumours of 95% and 95%, respectively, in HAL FC and 83% and 86%, respectively, in white-light cystoscopy [31]. The benefit is even more evident in flat lesions such as CIS or dysplasias. In the same study population, 92% of CIS lesions were detected by FC but only 68% by conventional cystoscopy [32]. These results confirm those from a previously published European trial in which lesions in 80 of 83 patients with CIS were detected by HAL FC compared with only 64 by white-light cystoscopy [33].

It was shown that a better detection rate results in a reduction of the recurrence rate. Three smaller prospective, randomised trials confirmed improved recurrence-free survival (RFS) in patients where 5-ALA FC-guided TURB was performed [34–36]. In the study with the longest follow-up, Denzinger reported an 8-yr RFS of 71% in the FC arm compared to only 45% in the white-light arm [36]. The reduced recurrence rate was recently confirmed by the first analysis of a prospective, multicenter, randomised trial using HAL in the FC arm [37].

#### 4.3.2. Narrow-band imaging

Narrow-band imaging (NBI) technology enhances the contrast between mucosal surfaces and microvascular structures by filtration of white light into two narrow

**Table 1 – Results of re-transurethral resection in patients with Ta and T1 tumours**

Author	Initial stage, No.	Stage in persistent tumours on re-TUR				Total, %
		CIS, %	Ta, %	T1, %	≥T2, %	
Grimm [9]	Ta 61					27
	T1 17				4	53
Klän [41]	T1 46		15	26	2	44
Brauers [43]	T1 42	19	17	24	5	64
Schips [44]	Ta 31		32	6		39
	T1 76		11	14	8	33
Herr [8]	Ta high grade 396	50		10	5	65
	T1 701	23		25	30	78
Schweibold [45]	T1 136	11		8	24	10
Divrik [46]	T1 74					52
Zurkirchen [47]	Ta 99					34
	T1 115					27

TUR = transurethral resection; CIS = carcinoma in situ

bands (415 nm and 540 nm). Because these wavelengths are strongly absorbed by haemoglobin, the vascular structures appear dark brown or green against a pink mucosa. First reports showed better detection rates compared to white-light cystoscopy, particularly in small, recurrent tumours [38].

#### 4.3.3. Other imaging technologies under investigation

We are faced today with rapid advances in new optical technologies like optical-coherence tomography (OCT), laser scanning confocal microscopy, or Raman spectroscopy. These promising methods could improve BC detection by allowing surgeons to take real-time in vivo optical biopsies during endoscopy [29]. For their routine application, however, more research has to be conducted.

#### 4.4. Single postoperative intravesical instillation of chemotherapy

According to a meta-analysis of patients with stage Ta T1 tumours, one postoperative instillation of chemotherapy immediately after TURB decreased the risk of recurrence by 39%. The benefit was confirmed in both single and multiple tumours [39]. The effect can be explained by the destruction of cells circulating in the bladder after resection. Based on these arguments, EAU guidelines recommend a single instillation of mitomycin, epirubicin, or doxorubicin in all patients with presumably NMIBC. It should be given on the same day as TURB, preferentially within 6 hr [7]. Because of the risk of complications from drug absorption, it should be omitted in patients with hematuria, with overt or possible bladder perforation, and after extensive resection [7,40].

#### 4.5. Second transurethral resection

As mentioned previously, initial TURB is associated with the risk of a residual tumour that was missed during resection [2]. Moreover, the depth of tumour invasion can be underestimated by the initial procedure. To overcome these limitations, achieve the desired complete resection, and correct staging error, a second endoscopic procedure

(second TUR, or *re-TUR*) performed after 2–6 wk is recommended.

#### 4.5.1. Detecting persistent tumours and correcting staging error

The rate of residual tumour detected by re-TUR varies between 33% and 76% (Table 1) [9,11,41,42–46]. The risk is higher in multiple tumours [41,43] and in high-grade lesions [8,41,45] and increases with the stage of the original tumour. In four studies that evaluated both Ta and T1 tumours, tumour persistence was detected in 39%, 72%, 33%, and 27% in Ta and in 33%, 78%, 53%, and 37% in T1 tumours, respectively (Table 1) [9,11,43,46]. More than 80% of residual tumours were found in the location of the original lesion [9,44].

Underestimation of the depth of tumour invasion is dangerous, especially in cases where the muscle-invasive disease is missed. In tumours staged as T1 by initial TURB, the rate of understaging varied between 4% and 10% in most series, except in the case of Herr, who reported the risk at 29% [9,11,41–44]. The most important risk factor and source of error was the absence of muscle in the initial resection specimen [11].

Herr recently updated the results with re-TUR in 1312 patients with papillary tumours. The risk of tumour upstaging in muscle-invasive disease by re-TUR was 0% in Ta low-grade tumours, 5% in Ta high-grade tumours, and 30% in T1 tumours [8].

#### 4.5.2. Prognostic implications

In a prospective study with 142 patients with newly detected T1 tumours, randomised in groups with and without the re-TUR, Divrik evaluated recurrence and progression rates. Recurrence and progression were observed in 26% and 4% of patients with re-TUR, respectively, compared to 63% and 12% of patients without re-TUR, respectively. The difference in recurrence rate was significant between both arms of the trial [45].

In a recently published study, Herr presented the outcome of 352 patients with initial T1 tumours treated with re-TUR. Of the 92 patients with residual T1 cancer, 82% progressed to muscle invasion within 5 yr compared to 19%

of 260 patients without tumour or with Ta tumour detected on re-TUR [47].

#### 4.5.3. Indication of re-transurethral resection

In agreement with published data, EAU guidelines strongly recommend re-TUR in patients with high-grade and T1 tumours and always when the pathologist has reported that the specimen contained no muscle tissue. It should also be considered in cases where the urologist is not sure that the initial resection was complete, especially in extensive and multiple tumours [7].

#### 4.5.4. Technique of re-transurethral resection

There is no consensus concerning the timing and technique of re-TUR. Most authors perform the procedure between 2 and 6 wk after initial TURB [48,49]. Because of the frequent detection of persistent disease at the location of the original tumour, the deep resection of this site is advocated. The biopsies should be taken from suspect areas but not routinely from normal-looking urothelium [48].

## 5. Conclusions

The results of TURB are limited by the high recurrence rate and by the risk of tumour understaging. The major prerequisite for optimal outcomes is a systematically and meticulously performed procedure by a well-trained urologist. It is important to use modern equipment, including new telescopes and video systems. Urologists should be aware of promising innovations, including new imaging techniques, and their possible benefits.

Results can be improved by re-TUR, which should be considered according to the information obtained from the initial resection. Re-TUR is recommended in any patient with a T1 or high-grade tumour and always when the pathologist has reported that the specimen contained no muscle tissue. It should also be considered in cases where the urologist is not sure that the initial resection was complete, especially in extensive and multiple tumours.

## Conflicts of interest

M. Babjuk has received honoraria from GE Healthcare for lectures on meetings on bladder cancer.

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