REVIEW ARTICLE

Is ‘second-look’ (re-staging) transurethral resection of bladder tumours a new standard of care?

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Introduction

Transurethral resection (TUR) is the essential surgical procedure used to diagnose, stage and treat nonmuscle-invasive (NMIBC) bladder tumours. TUR of bladder tumours is a diagnostic, prognostic and therapeutic operation. TUR aims to provide adequate specimen material to determine the histological type and grade of bladder tumours, to determine the presence and depth of tumour invasion, and to remove visible and microscopic superficial and invasive tumours. The findings are used to direct further therapy, dictate follow-up schedules, and indicate prognosis [1].

Although TUR is a common operation familiar to most urologists, it is a stochastic procedure subject to unquantifiable variables related to the surgeon, tumour and pathology; as a result, its diagnostic and therapeutic purposes are not always achieved. To overcome these limitations, a second-look, or re-resection 2–6 weeks after an initial TUR has been incorporated more frequently into clinical practice, especially for high-risk tumours. The European Association of Urology guidelines recommend a repeat TUR in all patients with stage T1 or high-grade tumours [2]. We believe a second-look TUR should be considered the new standard of care for high-risk NMIBC.

Rationale for second-look TUR of bladder tumours

The successful management of NMIBC is driven by two overarching principles, one dependent on the other. First, all visible papillary tumours, especially invasive T1 lesions, should be completely resected. Second, intravesical therapy is most effective when used against minimal residual disease. For example, intravesical BCG is used to eradicate carcinoma in situ, not to treat T1 tumours. Despite these caveats, the residual tumour is frequently found on a contemporary second TUR, and persistent tumours are commonly found at the 3-month cystoscopy after diagnosis, often at the same sites of disease. A third variable that affects the outcome of NMIBC is the pathological evaluation of tumour specimens. Although pathologists might differ in their interpretation, they can only assess what they are given by the urologist. As an example, one study found that muscularis propria was missing in up to 51% of TUR specimens [3]. Furthermore, tumours are most often submitted in multiple pieces, from which pathologists are asked to reconstruct the whole tumour type, configuration and extent. It seems reasonable that the more specimens that are submitted, the greater the likelihood that a pathologist will correctly define a tumour(s). These facts argue that a second-look TUR might better stage NMIBC, as well as provide better local control, rather than relying on the initial TUR alone.

Detection of residual tumour and reducing staging errors

The rate of the residual tumour detected by second TUR is 27–78% [4]. Disease persists in 27–72% of Ta and 33–78% of T1
tumours. The residual tumour is detected in 3.4–21% of single
tumours and in 7.4–46% of multiple tumours. An incomplete
resection is responsible for most early recurrences. In patients
undergoing cystectomy for NMIBC, up to 40% are upstaged
to muscle invasion, especially if no muscle was included in a
first TUR. Table 1 shows our updated results in 1312 patients
with NMIBC, referred by outside urologists, in whom we did a
second contemporary TUR [1]. A significant proportion (74%)
was found on second TUR to have residual tumour, and
only 26% of patients had no tumour found in the bladder.
Re-staging TUR was not helpful for low-grade papillary
tumours. However, for patients with high-grade lesions, half
the Ta tumours had residual disease, and 15% were upstaged;
for T1 tumours, 48% had persistent NMIBC, and 30% were
upstaged to muscle invasion. The second TUR staged papillary
tumours more accurately while at the same time providing
better local treatment of multiple primary lesions.

Re-staging TUR helps to select patients for cystectomy vs.
intralesional therapy

Despite judicious management, NMIBC progresses to muscle-
invasion in 20–30% cases, usually within 5 years. Once that
occurs, survival is worse than if a cystectomy had been done
before muscle-invasion [5]. Fig. 1 shows the progression-free
survival rate of 710 patients with NMIBC who received
BCG therapy after an initial (left) or re-staged (right) TUR,
stratified by stage and grade. After a first TUR, all tumour cat-
egories appear to be appropriate candidates for intravesical
treatments, but most patients with residual T1 disease on sec-
ond TUR eventually progressed (regardless of their original
pathology), including many who responded initially to BCG
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egories appear to be appropriate candidates for intravesical
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ond TUR eventually progressed (regardless of their original
pathology), including many who responded initially to BCG
therapy [6]. We advise patients who have large-volume or mul-
tiple T1 tumours on a second TUR to undergo an immediate
cystectomy [7]. Patients with no tumour or non-T1 disease
on re-staging TUR are candidates for bladder-sparing treat-
ments. This has been confirmed in a recent study in which pa-
tients having no tumour on repeat resection had fewer
recurrences, longer times to tumour recurrence, and less pro-
gression than patients who had a single TUR [8].

Re-staging TUR improves outcomes of NMIBC

A 5-year observational study in 124 patients showed that 63%
undergoing a second TUR had tumour-free bladders,
compared to 40% of patients after one TUR [9]. Progression
to muscle-invasion occurred in only two (3%) patients after
re-staging TUR. A second therapeutic TUR also appears to
improve the short-term response to BCG therapy [10]. In a
prospective, nonrandomized, phase II study of 340 cases,
59% of the patients after one TUR had recurred by 12 months,
compared to 16% after two TURs; after 5 years of follow-up,
32% of patients had progressed after one TUR vs. 7% after
two TURs. Fig. 2 shows that the overall recurrence-free and
progression-free survival rate was significantly better with
BCG therapy after two vs. one TUR.

In a prospective, randomized trial involving 210 patients,
Divrik et al. [11] showed that 40% recurred after two TURs
compared to 71% after one TUR. Fig. 3 shows longer recur-
rence-free (47 months) and progression-free (73 months) sur-
vival times after second TUR rather than no second TUR
(12 and 53 months, respectively). Overall survival in both
groups was similar, but only 2% of patients died from urothe-
lial cancer after undergoing two TURs, compared with 11%
after one TUR. Divrik et al. [12] also reported similar results
in patients randomized to intravesical mitomycin C with or
without a second-look TUR; the recurrence-free survival rate
at 3 years was 69% in patients who were treated after two
TURs vs. 37% in patients who receive mitomycin C after a sin-
gle TUR.

Quality of TUR

An analysis of seven randomized trials showed substantial var-
ation in early recurrence rates among different institutions.
The frequency of 3-month recurrences was 0–46%, because of
the quality of the TUR performed by different surgeons
[13]. Even patients treated by experienced urologists have a
high percentage of persistent carcinoma after the initial
TUR. Of 214 patients undergoing re-staging TUR for TaT1
tumours, carcinoma was present in 37% of those treated by se-
nior urologists and 26% treated by urologists in training [14].
In an earlier study, deep resection of the bladder wall underly-
ing the tumour and surrounding areas detected more cancer in
13% of Ta and 35% of T1 tumours [15]. Likewise, we under-
took a first and second TUR in 71 patients with T1 disease and
found that 25% had residual lamina propria invasion [16].

So the question is why there is a high rate of persistent tu-
mour after the first TUR for NMIBC, or put another way,
why cannot even experienced urologists ‘do it right the first
time’? The answer lies in the technical difficulties of the proce-
dure itself and in the nature of bladder tumours. Visibly com-
plete TUR of multiple papillary lesions, especially T1 tumours
associated with carcinoma in situ, is often difficult the first
time. Tumours might be overlooked if extensive or involve
sometimes difficult-to-reach regions of the bladder, such as
the dome, anterior wall, bladder neck or urethra. Tumour
spread at the margins or invading lamina propria is not always

| Table 1  | Re-staging pTa and pT1 bladder tumours. |
|----------|----------------------------------------|
| Tumour type | No. of patients | % Pathology on re-staging TUR |
|           |              | pT0 | pTa LG | pTa HG/CIS | pT1 | pT2 |
| pTa LG    | 215          | 49  | 46     | 5         | 0   | 0   |
| pTa HG    | 396          | 35  | 0      | 50        | 10  | 5   |
| pT1       | 701          | 22  | 0      | 23        | 25  | 30  |
| Muscle    | 421          | 25  | 0      | 31        | 29  | 15  |
| No muscle | 280          | 20  | 0      | 15        | 20  | 45  |

LG, low-grade; HG, high-grade papillary tumours; CIS, carcinoma in situ.
visible at cystoscopy and is often more extensive than the surface appearance of the tumour suggests. As the resection proceeds, vision can become obscured, because of mucosal oedema, bladder spasms, and bleeding, making it increasingly difficult to differentiate benign from tumour-bearing mucosa, and to obtain clear negative surgical margins. TUR is a random, partially blind and technically difficult procedure that, combined with uncertainty of tumour growth, conspires to limit the urologist’s ability to always perform a reliably complete TUR! We can teach ourselves and others to perform high-quality TURs [17] but that alone will not completely negate the value or need for a contemporary second TUR for most NMIBC [1]. Perhaps new optical-enhancement methods under investigation, such as fluorescence cystoscopy and narrow-band imaging, will help to improve the performance of the initial TUR, but they will not solve the problem of understaging.

Who should have a second TUR?

A second TUR is recommended for any high-grade NMIBC detected at the initial TUR [2]. A second TUR achieves better local control, improves the response to intravesical therapy, reduces understaging, and often leads to changes in treatment resulting in better outcomes, defining it as a diagnostic, therapeutic, prognostic and predictive procedure. Most authors recommend resection 2–6 weeks after the initial TUR, which should include a thorough TUR of the primary tumour site, any overlooked tumours and TUR or fulguration of all overt or suspected areas of carcinoma in situ. In most cases the results are better when all tumours have been eradicated before subsequent intravesical treatments.

On the other hand, NMIBC represents a heterogeneous spectrum of diseases, and not all patients need or benefit from a second TUR. For example, another TUR is not helpful nor does it change the management for low-grade papillary tumours. In addition, we found that low-grade T1 tumours, albeit rare, are easily controlled by the first TUR [18]. Others have questioned whether re-TUR is necessary after a well-performed resection of high-grade T1 that shows limited lamina propria invasion (T1a) and when BCG treatment is planned [19]. These latter exceptions are reasonable, but only if the urologist is confident in his/her ability to completely resect all tumours (seen and unseen), and knows the capability

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**Figure 1** Progression-free survival of 710 patients with NMIBC, according to stage and grade, after first (left) or second-look (right) TUR.

**Figure 2** Recurrence-free (left) and progression-free (right) survival in 340 patients with NMIBC treated with BCG after one vs. two TURs.
of the pathologist. Re-staging, or second-look, TUR is required for multiple tumours, high-grade tumours, most T1 tumours, incompletely resected tumours, and if no muscle is identified in submitted tumour specimens.

Conclusions

Second-look, or re-staging, TUR of NMIBC achieves optimal local control by removing residual tumours, improves staging accuracy, provides additional histological material favouring a more accurate diagnosis, leads to changes in treatment with improved outcomes, facilitates the response to intravesical therapy, and provides important prognostic information. A second-look TUR is a diagnostic, therapeutic, prognostic and predictive procedure, essential to the successful management of high-risk NMIBC.

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