



Indication and prognostic value of second transurethral resection in bladder cancer patients

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Abstract: Second look transurethral resection of the bladder (re-TURB) is nowadays mandatory for high-grade (HG) non-muscle invasive bladder cancer (NMIBC); being recommended by all available guidelines. Nonetheless, its staging value as well as the ability to improve oncological outcomes of patients is debatable. Therefore, our aim is to evaluate current indications and prognostic value of re-TURB, trying to elucidate its current role in managing HG NMIBC. A Medline non-systematic review was performed including articles published in the last two decades, article selection was based on clinical significance only. At present, TURB appears frequently inadequate in removing all the cancerous tissue and in retrieving a correct diagnosis. Re-TURB maximizes staging accuracy, residual cancer removal and possibly improves prognosis. It seems also to provide therapeutic benefit by improving recurrence- and progression-free survivals. Nonetheless, few recent large studies evidenced that in case of presence of the detrusor muscle in the specimen of the first TURB those benefits are limited. The advent of new resection technologies such as *en bloc* resection and new endoscopic technology seem to improve the quality of first TURB making re-TURB sometimes useless. In lights of this, the development of methods or algorithms able to select patients for re-TURB may be the preferable way to reduce this procedure that remains, at present the common rule.

Keywords: Second look transurethral resection of the bladder (re-TURB); high-grade non-muscle invasive bladder cancer (HG NMIBC); trans urethral resection of the bladder (TURB)

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Introduction

Bladder cancer is currently the ninth most common oncologic disease, in the urothelial or transitional cell carcinoma (TCC) form. The incidence rate is 10.1 per 100,000 for men and 2.5 per 100,000 for women (1).

The non-muscle-invasive form (stages Ta and T1) account for the majority (60–80%) of bladder cancer cases (1,2). Those tumors generally show a high recurrence but low progression rate. Non-muscle invasive bladder cancer (NMIBC) is therefore usually curable but prone to recurrence, and patients with multifocal stage Ta–T1 high-

grade urothelial carcinoma have a higher risk of recurrence ($\geq 40\%$ after 12 months) and progression (5% after 12 months) (2).

Gold standard treatment for NMIBC is still trans urethral resection of the bladder (TURB) followed by intravesical instillation of immunotherapy/chemotherapy agents (2).

Moreover, quality series concerning initial TURB, potentially linked to the experience of the surgeon, suggest that staging may be inadequate in a high percentage of patients with high-risk NMIBC (3). Important differences on staging accuracy and oncological outcomes of the

procedure have been so far reported in several series (4,5). As a consequence, residual tumor at re-TURB is found in up to 50% of cases (6).

Even when detrusor muscle is present in the first TURB specimen, 58% of patients had residual disease 11% experienced upstaging after re-TURB according to a recent meta-analysis (7), those data remained stable among studies in different decades.

Re-TURB plays a role in diagnosis, prognosis and treatment (2). For these reasons, both the American Urological Association (AUA) and the European Association of Urology (EAU) guidelines consider it mandatory in high-risk NMIBC (2,8). The timing to perform re-TURB has been fixed performed within 4 to 6 weeks from the first resection when lamina propria involvement (9,10) or HG disease (9) is documented at the initial TURB.

Despite official recommendations, several recent evidences make systematic re-TURB debatable (11,12). The introduction of new surgical approaches as *en bloc* resection technique (EBRT) (13) and the development of new endoscopic technologies narrow band imaging (NBI) (14) and photodynamic diagnosis (PDD) (15) question the role of re-TURB to enhance the accuracy of tumor staging. Finally, new imaging techniques (16) promise a more accurate preoperative staging possibly making re-TURB obsolete.

Objective of this work is to provide an overview on current indications, possible contra indications and prognostic value of second-look resection.

Evidence acquisition

We performed a non-systematic literature search in Medline/PubMed using different combinations of the following terms: “bladder cancer”, “second look transurethral resection of the bladder”, “second look TURB”, “re-TURB”, “upstaging”, “T1HG bladder cancer”, “outcomes” and “residual tumor”. No time period filter was applied, but special regards was given to researches published in the last decade. Only articles written in English were included in the analysis. One single article in Spanish has been considered for final analysis due to its important value. Due to the narrative nature of this review, clinical relevance was the unique judgment criteria for article inclusion. PRISMA guidelines were, therefore not employed.

Globally 22 original articles and 20 between reviews; systematic reviews and meta-analysis were analyzed.

Evidence synthesis

Why to perform re-TURB

To achieve a correct staging of NMIBC, the quality of TURB is crucial, as this is one of the most important factors affecting disease recurrence rate (17). The removal of all visible lesions including a sufficient amount of DM is mandatory but, not always achieved, even in experienced hands (18-20). It has been calculated that DM is present in TURB specimens only in 50% to 80% of the cases according to different series (21). This translates into 30% to 60% of T1HG tumors at first resection showing to be muscle invasive at re-TURB. Moreover, presence/absence of DM was reported to have an impact on residual tumor, early recurrence and tumor upstaging at final pathological examination after cystectomy (4,22-24).

Investigating historic cohorts of pT1 patients, in the absence of DM in first TURB specimen, residual tumor was found in about 83% of cases at re-TURB (22). Early NMIBC recurrence was also found to be associated with the absence of DM at the first TURB by two different studies conducted by Mariappian *et al.* (4,23). Tumor upstaging at final pathology, after cystectomy, happened in up to 49% of patients receiving incomplete first TURB, while only in 14% of patient in presence of DM (23,24).

Thus, TURB is far from being an accurate staging procedure, especially in case of carcinoma in situ (CIS). The chances those non-papillary lesions are very high when TURB is performed using conventional with light. CIS, although a non-invasive and rare stand-alone entity (accounting for 1% to 10% NMIBC) (25,26), may be associated to Ta or T1 disease in 10% to 40% of the cases. When this happens, CIS represents an independent factor increasing twice the risk of recurrence and 3 times the risk of progression (27).

A therapeutic benefit has also been claimed for re-TURB. In patients with T1HG tumors who are treated with BCG, those with no residual tumor (or Ta tumor) at re-TURB have better recurrence free survival (RFS), Cancer specific survival (CSS) and progression free survival (PFS) than those presenting T1 tumor (28,29). In other words, re-TURB may complete a previously incomplete resection conferring possible better response to BCG.

What emerges from current published data can be resumed by the fact that, at present, the indication of re-TURB lies on three pillars (21):

- (I) Re-TURB is able to maximize the diagnostic accuracy and clears residual cancer;

- (II) The identification of possibly missed MIBC and of NMIBC at high risk of BCG failure (those patients may benefit from early cystectomy);
- (III) A therapeutic benefit is provided by re-TURB.

Why and when not to perform re-TURB

Despite the aforementioned benefits of re-TURB, this procedure is not devoid of complications. Furthermore, it requires, spinal or general anesthesia few weeks after the first intervention, and this may have a negative impact especially in aged or fragile patients. Several authors have investigated clinic-pathological features of first resection that may help to identify those patients in which re-TURB could be avoidable (30). Those studies found selected subgroup of patients in which re-TURB wasn't worthwhile not for staging nor for prognostic purposes (11,12,20).

Presence of DM in the first TURB specimen

Gontero *et al.* (11) in a recent multicentric retrospective study found that improvements provided by re-TURB on cancer specific survival (CSS), recurrence free survival (RFS) and overall survival (OS) occurred only in patients where DM was not present in the specimen of the first TURB. Likewise, the single-center experience reported by Gaya (12) found DM absence as the only risk factor for tumor under staging. Those evidences let the authors of these two studies suggest that systematic re-TURB may be unnecessary when DM is present in the first resection specimen.

Earlier Dutta *et al.* (20) found no improvements in RFS, progression-free survival, CSS and OS, when DM was present in the first resection specimen. Staging inaccuracy at TURB in cT1 tumors resulted critically dependent from DM presence in the specimen. Final pathological exam after cystectomy resulted in tumor upstage in 62% *vs.* 30% of the cases according to absence or presence of DM at TURB. In the same way, Palou *et al.* (28) documented persistent tumor in 85.9% of patients where no DM was present at first resection *vs.* 65.1% in presence of DM ($P < 0.001$), in a recent retrospective single-center study. The rate of persistent T1 disease was similarly higher when no DM was present (40.2% *vs.* 26.6%, $P < 0.001$).

The selection of patients who may and may not benefit from re-TURB may be led by the presence of DM in TURB specimen, even if DM alone is probably not enough to drive decisions alone. Indeed, DM is still not detected in up to 30% of resections, even in the most recent series and in experienced surgeons' hands (31).

En bloc tumor resection

To surmount the limitations of conventional TURB, en bloc resection technique (EBRT), using different sources of energy (monopolar, bipolar, laser, waterjet) has been recently proposed (32,33). This approach allows the surgeon to resect neoplasm with approximately 1 cm margin from the tumor base and precisely separate detrusor muscle as well as connective tissue. EBRT, may yield the merit of shorter operative time, as it avoids piece by piece removal alongside the necessity to perform repeated hemostasis so as to improve visibility (13,32).

A retrospective multicentric study led by Kramer *et al.* (34) evidenced the presence of DM in 97% of patients treated with EBRT, and similar results have also been reported by Hurler *et al.* (35). (100% of DM detection using EBRT on 90 patients in a single center). When compared to standard resection, EBRT showed a DM presence rate of 95% *vs.* 60% in an Indian prospective single center nonrandomized study (36). Re-TURB or biopsy performed after EBRT, showed a tumor recurrence rate close to 0% in different series (37,38). Moreover, Zhang *et al.* (32) analyzed 19 original papers in a recent meta-analysis comparing conventional TURB *vs.* EBRT (2,561 patients, 1,369 of those treated with EBRT). The authors found no difference in DM retrieval rate among the two techniques. Nonetheless, patients treated with EBRT had significantly lower intraoperative and postoperative complications, and 24-month recurrence rate than those treated with conventional TURB. An earlier systematic-review (38) reported a 96% incidence of DM incidence in the specimens of patients treated with EBRT. At present, the learning curve of this technique is unclear, due to the different sources of energy and surgical approaches employed to perform EBRT (33). Nonetheless, a prospective Indian study considered EBRT to be a rather more controlled technique of resection than TURB, so with a flatter learning curve in experienced hands (39).

Enhanced vision during TURB (PDD and NBI technology)

TURB using PDD, resulted in better residual tumor rate compared to conventional resection according to a recent systematic review of the literature (15). Residual tumor rate in patients treated PDD was 4.5% to 32.7% while it was 25.2% to 53.1% in those treated with conventional white light (WL) resection, according to the different studies analyzed [odds ratio (OR) 0.28, relative risk 2.77-fold higher with WL].

Current available trials showed that NBI-TURB reduced the recurrence risk of NMIBC compared with conventional WL (14,40). Naselli *et al.* (41) reported a 1-year recurrence-risk of 32.9% in the NBI group 51.4% in the WL group (OR 0.62; P=0.0141). Similar impact on recurrence rate has been seen by different authors (42,43). PDD resection was reported to improve DM rate and residual tumor when compared to WL (78% *vs.* 62% for tumor detection and 26% *vs.* 40.5% for residual tumor at re-TURB) (23).

New imaging techniques

Del Giudice *et al.* (44) evaluated the impact of the previously described magnetic resonance (MRI) Vesical Imaging-Reporting and Data System (VI-RADS) (16). Multiparametric MRI (mpMRI) of the bladder was performed in 236 consecutive patients to discriminate MIBC from NMIBC tumors. The exam provided a sensitivity of 91.9% (95% CI: 82.2–97.3) and a specificity of 91.1% (95% CI: 85.8–94.9). VI-RADS score was also analyzed as a predictor for pathological outcome at re-TURB. The exam was able to identify patients with MIBC, before re-TURB with a sensitivity of 85% (95% CI: 62.1–96.8) and a specificity of 93.6% (95% CI: 86.6–97.6) (44).

Although at its beginnings, VI-RADS classification seems to have the potential to become widely adopted, in a near future, to select patients with high-risk NMIBC for re-TURB, 'early' cystectomy or direct intravesical therapy and follow-up. Further data are needed to evaluate the clinical value of this exam just after diagnostic cystoscopy.

Prognostic value of re-TURB

Ferro *et al.* (29) retrospectively analyzed data on 1,046 patients in a 10-year multicentric study. They reported residual T1 HG/G3 tumor at re-TURB to confer worse prognosis in patients with primary T1 HG/G3 treated with maintenance BCG. Those patients were also at higher risk of BCG failure if primary T1 HG/G3 and residual T1 HG/G3 at re-TURB.

A recent systematic review (45) strongly suggested early re-TURB in high risk patients as it reduces progression and recurrence, and improves response to BCG. Those findings were not confirmed in low risk disease. Despite this, all the four studies (46-49) analyzed by this review reported a significant lower recurrence risk for patients undergoing re-TURB compared to simple follow-up.

Recently, Soria *et al.* (30) in a multicenter retrospective study investigated possible prognostic factors for pT0 re-TURB. The authors included patients with pT1HG non-

muscle invasive bladder cancer from 4 different centers who underwent a complete first TURB and re-TURB. DM presence, absence of concomitant CIS and EBRT were able to predict a negative histology at re-TURB. Those findings may help avoid re-TURB in an extremely well-selected cohort of patients.

Investigating the BCG response of T1 HG patients, Palou *et al.* (28) found that, those presenting Ta or T0 disease at re-TURB have better progression free survival and CSM rates compared to T1. Nonetheless, progression rate was reported to be of 25.3% in case of T1 at re-TURB (far lower than previously reported). According to the authors T1 at re-TURB should not a priori exclude these patients from conservative management of BCa.

Impact of variant histology at first TURB

The number of patients with variant histology seems small because 45–50% of variant histology cases are missed by community pathologists, and variant histology is only seen after cystectomy in about half of the cases (50,51). Assessing the presence of histological variants after TURB currently remains challenging due to the limited tissue sample sizes, although the presence of these variants often indicates poor prognosis and increased risk for recurrence and progression (52). Any patient with T1HG associated with select variant urothelial histologies (i.e., micropapillary, nested, plasmacytoid, or sarcomatoid) are at a significantly increased risk of disease recurrence, progression, and mortality (53). Among those patients only squamous or glandular differentiations and deceptively benign or lymphoepithelioma-like carcinomas may be considered for conservative treatment, the remaining should be offered early cystectomy especially if young (52). In any case, variant histology remains a major indication for re-TURB, even in the presence of DM in first resection specimen

Role of biomarkers on re-TURB indications

Currently, six urinary biomarkers have been approved by the Food and Drug Administration to be used in the follow-up of NMIBC patients. Indeed, most of those tests lack specificity and no robust evidence exists for their use in current clinical practice for screening, follow-up or staging purposes (54). Despite this, it remains an evolving field that may in a recent future help to predict patients' prognosis (55).

Conclusions

In case of missing DM at first resection re-TURB, it is

mandatory to correctly stratify the patient's risk to plan subsequent treatments. Current evidences particularly highlighted the prognostic role of this procedure, even when DM is correctly resected during first TURB. Accurate patients' selection, technological development of resection and imaging techniques may sensibly reduce the need for re-TURB in the future, but this procedure remains the gold standard for T1/HG NMIC to date.

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