En-Bloc Transurethral Resection of Non-Muscle-Invasive Bladder Cancer: Current Evidence and Glimpses into the Future

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Abstract

Background: The purpose of this review was to summarize the current evidence on en-bloc transurethral resection (eTURB) of non-muscle-invasive bladder cancer compared to conventional TURB (cTURB) with a particular emphasis on ongoing randomized trials.

Materials and methods: A PubMed/MEDLINE search of the English-language literature from its inception until June 2019 using the following terms in isolation or combination “bladder cancer”, “en bloc”, “TURB” and “resection” was performed.

Evidence synthesis: Compared to cTURB, eTURB has been shown to achieve higher rates of detrusor muscle (>95%) and better quality of the specimen for pathological evaluation. Complication rates and perioperative outcomes are comparable between the two techniques. Moreover, eTURB seems to achieve lower recurrence rates. However, the retrospective nature of the studies and underpowered prospective trials limit the interpretation of these results. There are currently two active randomized trials which are evaluating the one-year recurrence rate (EB-StaR) and difference in the rate of detrusor muscle in the specimen between cTURB and eTURB (eBLOC), respectively.

Conclusion: eTURB seems to provide a significant improvement in the surgical management of NMIBC with regards to oncology and safety outcomes.

Keywords: Bladder cancer; En-bloc; Transurethral resection

Abbreviations: NMIBC: Non-Muscle-Invasive Bladder Cancer; TURB: Transurethral Resection of the Bladder; MIBC: Muscle-Invasive Bladder Cancer; BCG: Bacillus Calmette Guérin; RFS: Recurrence-Free Survival; PFS: Progression-Free Survival; OS: Overall Survival; eTURB: En-Bloc Transurethral Resection of the Bladder; cTURB: Conventional Transurethral Resection of the Bladder
Introduction

Standard treatment of non-muscle-invasive bladder cancer (NMIBC) consists of transurethral resection of the tumor (TURB) with adjuvant intravesical instillation therapy, when needed, according to the tumor risk of recurrence and progression [1,2]. Despite adequate treatment, two thirds of patients will experience intravesical recurrence and one out of five will experience disease progression to muscle-invasive disease (MIBC) [3-a5].

The quality of the TURB determines the patients’ prognosis and resulting treatment costs [1,6-10]. In a retrospective multi-institutional cohort of 2,451 patients with T1G3/HG tumors treated with adjuvant bacillus Calmette Guérin (BCG), 935 patients received a re-TURB. The second resection improved recurrence-free survival (RFS), progression-free survival (PFS) and overall survival (OS) only in patients without muscle in the specimen from initial resection [11]. Moreover, it has been confirmed that the absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease, early recurrence and tumor under staging [12]. Therefore, the presence of detrusor muscle in the specimen is considered as criteria for resection quality. Interestingly, two recent systematic reviews showed that residual tumor at re-TURB can be found in up to 67% of patients with Ta and in up to 71% with T1 BC, even if muscle was present in the initial specimen [13,14]. In contrast, a retrospective multicenter analysis reported only 6.4% of residual cancer at re-TURB after en-bloc TURB (eTURB) for high-risk NMIBC [15].

Regardless of significant heterogeneity between studies, these data generate the hypothesis that conventional TURB (cTURB) resection technique does not guarantee a complete tumor removal resulting in residual disease while also limiting the pathologist ability to deliver an accurate pathological review due to the fragmented, charred and disoriented specimen. Indeed, cTURB of tumors larger than 1cm requires fragmentation of the tumor which breaks the principles of oncologic handling. This results in multiple chips which may contain detrusor muscle, but do not allow a pathologic evaluation regarding resection margins, completeness of resection and orientation of the specimen. Therefore, there is an unmet need for improvement of resection techniques in order to better risk stratify and stage patients, reduce unnecessary interventions with risks (i.e. reTURB), improve patients’ outcomes, and lower cost and burden of care [16-18]. In this context, eTURB is a novel method that promises to address these challenges of cTURB. Indeed, this technique has been shown to achieve higher rates of detrusor muscle (>95%) and better quality of the specimen for pathological evaluation compared to cTURB in non-controlled studies [19]. eTURB can be performed with several techniques. Most commonly used are laser fibers (thulium or holmium), hydro dissection (Hybrid knife) and electric slings [20,21]. The aim of this review was to summarize the current evidence on eTURB.

Evidence acquisition

We performed a PubMed/MEDLINE search of the English-language literature from its inception until June 2019 using the following terms in isolation or combination “bladder cancer”, “en bloc”, “TURB” and “resection”. Reference lists in pertinent articles were reviewed to augment source material. Only prospective trials including ≥30 patients were included.

In total, 10 articles were included in our analysis.

Evidence synthesis

| Author          | Design                  | No of pts | T stage     | Grade     | Presence of detrusor muscle | Residual tumor | Endpoints                          |
|-----------------|-------------------------|-----------|-------------|-----------|-----------------------------|----------------|------------------------------------|
| Lodde et al. [17] | Prospective, single arm | 37        | pTa 82.3%   | G1 69.4   | NR                          | NR             | Feasibility and safety             |
|                 |                         |           | pT1 17.7%   | G2 16.1   |                             |                |                                    |
|                 |                         |           |             | G3 14.5   |                             |                |                                    |
| Muto et al. [16]  | Prospective, single arm | 55        | Ta 56.4%    | LG 5.6%   | 100%                        | 0%             | second look performed within 90 days |
|                 |                         |           | T1 32.7%    | HG 34.6%  |                             |                |                                    |
|                 |                         |           | T2 10.9%    |           |                             |                |                                    |
| He et al. [19]   | Prospective, single arm | 45        | Ta: 27      | N.A.      | 100%                        | NR             | Feasibility and safety             |
|                 |                         |           | T1: 15      |           |                             |                |                                    |
|                 |                         |           | T2a: 3      |           |                             |                |                                    |
| Kramer et al. 2015 [18] | Prospective multicenter, multiarm, non-randomized | 156 electro eTURB | Ta 83; T1 62; T2 11 | LG 72; HG 84 | 96.2%                   | 0%             | Staging quality measured by detrusor muscle involvement, various perioperative parameters, and 12-month follow-up data |
|                 |                         |           | Ta 39; T1 26; T2 0 | LG 33; HG 32 | 100%                   | 0%             | Evaluated by biopsies from the margins at the end of the procedure |

Table 1: Prospective trials evaluating the role of en-bloc resection for non-muscle-invasive bladder including at least 30 patients.
Oncologic efficacy of en-bloc resection: While promising, the current body of evidence relies mainly on retrospective or prospective, nonrandomized studies (Table 1). Two prospective randomized trials compared RFS in eTURB performed with thulium laser resection with cTURB. No difference in RFS could be observed at 18 and 36 months (p = 0.38 and p = 0.89, respectively) [22,23]. In the study by Liu et al., completeness of resection was evaluated by biopsies of the resection margins but in both studies the second look TURB data was omitted. Limitations of the procedure are inherent to tumor size, specimen retrieval and location of the tumor. Indeed, specimens beyond 3cm in size cannot be removed in their entirety because of the limited urethral sheath diameter.

A retrospective multicenter series compared operative outcomes and RFS rates in 226 patients treated with laser eTURB (holmium or thulium) or electro eTURB (monopolar or bipolar). Both techniques were comparable with the main advantage of harvesting high quality specimens for pathological analysis with the detrusor muscle present in 97% of the cases [24]. This is consistent with most eTURB studies which reported high rates of detrusor muscle in the specimen [21,24-26]. In addition, a meta-analysis of seven retrospective studies with 886 patients, reported a significant difference in 24-months RFS in favor of eTURB (odds ratio 0.66, 95% confidence interval 0.47-0.92, p=0.02) [27].

Safety and complications of en-bloc resection: It is assumed that eTURB has a complication profile comparable to cTURB. Nevertheless, current literature does not deliver sufficient evidence because of study heterogeneity and differences in complication assessments [27]. In general, eTURB seems to have less perforation and obturator nerve reflex rates compared to cTURB, is assumed to result from the higher cutting precision of this technique and the use of laser [15,23,28-31].

| Study | Design | Patients | Ta | T1 | Tis | LG | HG | RFS | Margin | TURB | p | Reference |
|-------|--------|----------|----|----|-----|----|----|-----|--------|-------|----|-----------|
| Migliari et al. [23] | Prospective single arm | 58 | Ta30; T1 37; T2 5 | LG 30; HG 37 | 100% | second look performed within 90 days | Feasibility and comparison to a historical cohort of 61 patients |
| Chen et al. [14] | RCT | 71 cTURB, 71 eTURB | Ta 30; T1 37 | LG 30; HG 37 | 0% | Not Reported | 18 months RFS, p = 0.38 |
| Liu et al. [15] | RCT | 56 cTURB, 64 eTURB | Ta 60.7%; T1 39.4% | LG 91.1%; HG 8.9% | 0% | Evaluated by biopsies from the margins |
| Xishuang et al. [22] | Prospective, three arms, non-randomized | eTURB: 64 cTURB (monopolar or bipolar): 109 | Ta 36; T1 33; Tis 5 | LG 44; HG 20 | NR | Safety and efficiency |
| Ukai et al. [25] | Prospective, single arm | 97 | Ta30; T1 60; T2 7 | G1 3; G2 46; G3 48 | 7% | Defined as positive deep margin at pathological evaluation |

**Table 2:** Ongoing clinical trials registered on ClinicalTrials.gov

| ClinicalTrials.gov Identifier | Title | Primary outcome | No planned | Experimental arm | Active Comparator | Leading center | Status |
|------------------------------|-------|-----------------|------------|------------------|------------------|----------------|--------|
| NCT02993211 | Transurethral En BOC Versus Standard Resection of Bladder Tumour: A Multi-centre Randomised Controlled Trial (EB-StaR Study) | One-year recurrence rate | 350 | Bipolar eTURB | Bipolar cTURB | Caritas Medical Centre, Hong Kong, Hong Kong | Recruiting |
| NCT02555163 | Laser En BOC Resection Of Bladder Tumor (HoLERBT) VS. Conventional Transurethral Resection Of Bladder Tumors (cTURBT) (HoLERBT) | residual disease at re-staging transurethral bladder biopsy | 100 | Holmium (Ho: YAG) Laser En BOC Resection Of Bladder Tumor | cTURB | Urology and Nephrology Center in Mansoura, Egypt. | Not yet Recruiting |
Ongoing randomized trials: We identified five RCTs registered on ClinicalTrials.gov with two being active and recruiting patients (Table 2). The EB-STAR (NCT02993211) has as primary endpoint the one-year recurrence rate. A total 350 patients are planned to be recruited. It should be considered that the time frame of one year for recurrence rates is probably too short to demonstrate a statistically significant difference between the two groups. Therefore, this trial is likely to result in an underpowered analysis for this endpoint. The eBLOC (NCT03718754) aims to assess a difference in the rate of detrusor muscle in the specimen between eTURB and iTURB in 476 patients. This trial is powered for the primary endpoint. However, recurrence rate will be analyzed as secondary endpoint.

Conclusion

In summary, iTURB seems to provide a significant improvement in the surgical management of NMIBC with regards to oncology and safety outcomes. Nevertheless, the results of ongoing RCTs are required to assess its true value in tumor control and its potential to help reduce unnecessary re-TURB, eventually.

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None

Conflict of interest

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NCT02951078 A Study of Comparing Effects of Thulium Laser en bloc Resection and Electrical Transurethral Resection of the Non-muscle Invasive Bladder Cancer 172 Thulium Laser eTURB iTURB Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine Unknown

NCT03718754 En-bloc vs Conventional Resection of Primary Bladder Tumor (eBLOC) Detrusor muscle in the specimen 476 eTURB (all techniques allied) iTURB Medical University of Vienna Vienna, Austria Recruiting

NCT03221062 “En Bloc” Resection of NMIBC: a Prospective Single Centre Randomized Study The pathological staging assessment 180 1. Laser eTURB 2. Hydroknife eTURB iTURB Tongji Medical College Huazhong University of Science & Technology Not yet recruiting
eTURB = en-bloc TURB; iTURB = conventional TURB
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