



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

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To Cite This Article: Shahrokh F Shariat. En-Bloc Transurethral Resection of Non-Muscle-Invasive Bladder Cancer. Current Evidence and Glimpses into the Future. *Am J Biomed Sci & Res.* 2019 - 4(1). *AJBSR.MS.ID.000756*. DOI: [10.34297/AJBSR.2019.04.000756](https://doi.org/10.34297/AJBSR.2019.04.000756)

Received: July 04, 2019 | Published: July 17, 2019

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) [3-5].

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

Table 1: Prospective trials evaluating the role of en-bloc resection for non-muscle-invasive bladder including at least 30 patients.

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% pT1 17.7%	G1 69.4 G2 16.1 G3 14.5	NR	NR	Feasibility and safety
Muto et al. [16]	Prospective, single arm	55	Ta 56.4% T1 32.7% T2 10.9%	LG 56.4% HG 34.6%	100%	0% second look performed within 90 days	Perioperative outcomes
He et al. [19]	Prospective, single arm	45	Ta: 27 T1: 15 T2a: 3	N. A.	100%	NR	Feasibility and safety
Kramer et al. 2015 [18]	Prospective multicenter, multiarm, non-randomized	156 electro eTRUB 65 laser eTURB	Ta 83; T1 62; T2 11 Ta 39; T1 26; T2 0	LG 72; HG 84 LG 33; HG 32	96.2% 100%	0% 0% Evaluated by biopsies from the margins at the end of the procedure	Staging quality measured by detrusor muscle involvement, various perioperative parameters, and 12-month follow-up data

Migliari et al. [23]	Prospective single arm	58	Ta 30; T1 37; T2 5	LG 30; HG 37	100%	0% 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	Tis 1; Ta 55; T1 15 Tis 3; Ta 43; T1 25	LG 54; HG 17 LG 48; HG 23	NR	NR	18 months RFS, p = 0.38
Liu et al. [15]	RCT	56 cTURB 64 eTURB	Ta 60.7%; T1 39.4% Ta 57.8%; T1 42.2%	LG 91.1%; HG 8.9% LG 89.1%; HG 10.9%	NR	0% 0% Evaluated by biopsies from the margins	RFS
Xishuang et al [22]	Prospective, three arms, non-randomized	eTURB: 64 cTURB (monopolar or bipolar): 109	Ta 36; T1 23; Tis 5 Ta 65; T1 36; Tis 8	LG 44; HG 20 LG 75; HG 34	NR	NR	Safety and efficiency
Ukai et al. [25]	Prospective, single arm	97	Ta 30; T1 60; T2 7	G1 3; G2 46; G3 48	82%	7% Defined as positive deep margin at patho- logic evaluation	Accuracy of patho- logical staging

RCT = Randomized Controlled Trial; NR = Not Reported; RFS = Recurrence Free Survival

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].

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 Bloc 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 Bloc 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 Bloc Resection Of Bladder Tumor	cTURB	Urology and Nephrology Center in Mansoura, Egypt.	Not yet Recruiting

NCT02951078	A Study of Comparing Effects of Thulium Laser en Bloc Resection and Electrical Transurethral Resection of the Non-muscle Invasive Bladder Cancer	The residual rate of tumor in the second operation of the two surgical methods	172	Thulium Laser eTURB	cTURB	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 allowed)	cTURB	Medical University of Vienna Vienna, Austria	Recruiting
NCT03221062	"En Bloc" Resection of NMIBC: a Prospective Randomized Study	The pathological staging assessment	180	1. Laser eTURB 2. Hydroknife eTURB	cTURB	Tongji Medical College Huazhong University of Science & Technology	Not yet recruiting
eTURB = en-bloc TURB; cTURB = conventional TURB							

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 cTURB and eTURB in 476 patients. This trial is powered for the primary endpoint. However, recurrence rate will be analyzed as secondary endpoint.

Conclusion

In summary, eTURB 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.

Acknowledgements

None

Conflict of interest

David D'Andrea reports a grant from the Austrian Urological Association for the conduction of the eBLOC study.

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