Review Article: Surgery: Urological Surgery

The impact of transurethral *en bloc* resection of bladder tumour on pathological and oncological outcomes

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Abstract: Transurethral resection of bladder tumour (TURBT) is the current gold standard in managing non-muscle invasive bladder cancer (NMIBC), but it is associated with suboptimal pathological and oncological outcomes. There are two main problems with TURBT. First, it is difficult to ascertain complete tumour removal upon piecemeal resection. Second, tumour fragmentation upon resection may lead to increased risk of tumour re-implantation. En bloc resection of bladder tumour (ERBT) has been proposed to tackle these problems. First, it allows full resection of the tumour in one piece including the underlying detrusor muscle, hence providing better evaluation of the resection margins and local staging. As tumours can be completely resected with clear margins, residual disease is less likely with this technique. Second, ERBT avoids manipulation and fragmentation of the bladder tumour, hence minimizing the amount of floating cells and reducing the risk of tumour re-implantation after the surgery. By upholding oncological principles as much as possible, oncological outcomes of NMIBC may be optimised. The future of ERBT is promising in providing better pathological and oncological outcomes, but larger randomised controlled trials are crucial in establishing solid evidence in clinically important outcomes and answering some technical uncertainties regarding ERBT.

Keywords: *En bloc* resection of bladder; en bloc resection of bladder tumour (ERBT); bladder cancer; pathological outcome; oncological outcome

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Introduction

Transurethral resection of bladder tumour (TURBT) has been the gold standard in managing non-muscle invasive bladder cancer (NMIBC). However, this technique violates typical oncological principles as the implantation of scattered and exfoliated tumours cells from the "piece-meal" resection can lead to increased recurrence rate (1). Other downfalls of the traditional TURBT include unclear resection margins, inability to ensure inclusion of detrusor muscle, along with poor quality of resection which can directly affect accuracy of staging and oncological outcomes of NMIBC (2). Hence, en bloc resection of bladder tumour (ERBT) has been proposed to overcome such difficulties.

The concept of ERBT aims to remove the tumour in a "one-piece" fashion. This was first described by Kawada *et al.* in 1997 (3) and is now commonly performed by making a circular incision around the margin of the tumour, followed by removal of the tumour with underlying detrusor muscle (4). ERBT specimens can maintain the 3D architecture of the tumour, thus allowing more accurate staging of bladder cancer with proper assessment of the resection margins (5-7).

A good assessment of the depth of invasion suggested the possibility of avoiding second look TURBT even in T1 or high-grade diseases (8,9). It also opened up discussions on the role of ERBT in pathologies previously not treated by TURBT definitively, such as carcinoma-in-situ (CIS) of the bladder and MIBC.

Aims and objectives

This review aims to provide the latest information on the development of ERBT and its effect on pathological and oncological outcome of NMIBC. We also discussed the possibilities of ERBT being applied to clinical practice for other pathologies of the bladder given the benefits of ERBT.

Literature search and evidence acquisition

Literature search was performed on EMBASE and MEDLINE using combinations of keywords such as "en bloc resection", "pathological outcomes", "oncological outcomes" and "second look TURBT". Only publications in English or with an English abstract are included. No cut-off date was set for the literature search and all publications such as journal articles and conference abstracts are included.

Pathological outcomes

Detrusor muscle sampling rate and quality of specimens in ERBT

Despite being the current gold standard in managing NMIBC, conventional piecemeal resection has been associated with poor detrusor muscle sampling rate and poor staging accuracy (5,10). The absence of detrusor muscle in TURBT specimen is associated with higher risk of residual disease, early recurrence and tumour under-staging (11). ERBT has been described as a potential solution to increase the detrusor muscle sampling rate. According to a retrospective cohort of 256 patients with primary NMIBC, 85.8% of TURBT specimens had detrusor muscle as opposed to 95.6% in ERBT specimens (P=0.006) (12). Prospective and retrospective studies by both our working groups and other groups showed similar results (13-15). ERBT can avoid cautery damage and crush artefacts to the specimen. Tangential sections of the tissue and random embedding of the tumour tissue can also be avoided (2,16). In a case series of 26 patients by Dymov *et al.* the ERBT group performed significantly better in both the identification of lamina propria of the detrusor muscle and the depth of thermal damage (P<0.05) (17). Yanagiswawa *et al.* also reported that ERBT allowed better evaluation of the detrusor muscle and significantly quicker and higher correct diagnostic and staging rate of NMIBC (18). ERBT has an additional advantage of higher staging accuracy in light of recent developments in digital pathology allowing three-dimensional histopathological reconstruction of specimens (5). A randomized trial investigating the detrusor sampling rate after ERBT is currently under way (19).

Resection margins

Quality of TURBT has long been recognised as an important factor for optimizing disease control (20-22). However, the top-down resection approach in conventional TURBT may cause cauterisation in the resection bed, rendering complete resection a difficult task to judge and achieve. Moreover, TURBT specimens are fragmented and resection margins cannot be assessed. Our working group established a 97.2% rate of clear circumferential and deep resection margins in a prospective cohort in 2017 (14) with Kawauchi *et al.* achieving a similar result of 94% in 2012 (23). In a retrospective cohort of 193 patients with NMIBC, 98.9% of specimens achieved clear resection margins upon ERBT (24). The use of enhanced imaging including narrow band imaging and photodynamic diagnosis may also facilitate the intended resection margins during ERBT (25). A retrospective study showed that negative tumour margin was associated with significantly longer recurrence free survival (RFS) and lower recurrence rate (26). This is likely to represent a lower proportion of residual disease following ERBT and this may have significant impact in terms of oncological outcomes.

Second-look TURBT

Over 50% of patients who underwent conventional TURBT had residual cancer upon second look TURBT (8,9,27). A prospective, randomised control trial by Divrik *et al.* in 2010 compared recurrence rate, progression rate, and disease specific survival in T1 NMIBC patients who underwent second-look TURBT and those who did not. Of the 105 patients who underwent second-look TURBT, residual cancer was found in 33.3% of patients of which 7.6% upstaged to pT2. Upon comparison of RFS, those who underwent second-look TURBT had a significantly

higher RFS of 59% compared to 32% at the end of 5 years (P=0.0001). Similar result was found upon comparing progression free survival (PFS). Progression-free survival was 93% in those who underwent second-look TURBT but 79% in those who did not at 5 years' time (P=0.0001). Cancer-specific mortality was also in favour of the second-look TURBT group (16.7% *vs.* 31.4%, P=0.038) (28). The latest EAU guidelines suggests performing a second-look TURBT after 2–6 weeks of initial resection in cases of inadequate specimen resection, absence of detrusor muscle (other than Ta low grade and CIS tumours) and T1 tumours (11). However, whether second-look TURBT is still necessary after ERBT is unknown. A prospective study by Hurle *et al.* of 78 patients explored *en bloc* re-resection of high risk NMIBCs after initial ERBT. Results showed that only five patients had residual cancer with no upstaging of any tumours (29). The group raised doubts about the efficacy of *en bloc* re-resection after initial ERBT. The benefit of a second-look TURBT largely relies on poor quality of resection upon conventional TURBT. As ERBT dramatically improves the quality of specimen in terms of the presence of detrusor muscle and clear resection margins, the necessity, efficacy and cost effectiveness of a second-look TURBT following ERBT is in question. Two randomized trials investigating the proportion of residual tumour upon second TURBT following initial ERBT are currently under way (30,31).

T1 substaging

The prognostic value of T1 substaging in NMIBC has been recognised in the literature (7,32). However, the poor TURBT specimen quality renders such assessment difficult and even impossible (6,7). To the contrary, ERBT may improve the assessment of T1 substage and possibly provide more prognostic information (7). There are two systems assessing T1 substage. First, the T1a/b/c system assess depth of tumour invasion with reference to the muscularis mucosae layer (6). Second, the T1e/T1m system measures the number or size of microinvasive tumour invading the muscularis mucosae layer, with T1e suggesting extensive-invasion and T1m suggesting microinvasion (33,34). Although the T1a/b/c system is recommended by the 2016 World Health Organisation, consensus has yet to be reached on the optimal system for T1 substaging (7,11,34). The introduction of ERBT will greatly improve the diagnostic accuracy of T1 substage, and we may learn more about its prognostic value in terms of disease recurrence and progression in the future (20-26).

Oncological outcomes

Recurrence

Whether ERBT can reduce recurrence rate of NMIBC is controversial. There were two randomized trials showing no significant difference in recurrence rate (35,36). To the contrary, two conference presentations on randomized trials showed superiority of ERBT in reducing recurrence rate. In a cohort of 75 patients, 5.3% of patients in the ERBT had local recurrence, compared to a 21.6% in the TURBT group (37). A cohort of 90 patients reported similar results by Geavlete *et al.* (38). A prospective study by Sureka *et al.* reported a significantly longer RFS in patients who have undergone ERBT, with a mean RFS of 45.1 months compared to 28.5 months in the TURBT group (39). The benefit of ERBT was also reported in other studies (15,24,39). Overall, although the results of ERBT seem to be promising, there is limited high-quality prospective trial data on the recurrence rate following ERBT. The EB-StaR study is a multi-centre randomized trial comparing between bipolar EBRT and TURBT in patients with bladder tumours of ≤3 cm with a primary outcome 1-year recurrence rate (40). The results are eagerly awaited.

Progression

Since most NMIBC were detected early, and most patients undergo stringent surveillance cystoscopy protocol, the progression rate is generally low. Moreover, ERBT is usually technically feasible for smaller tumours, hence this pre-selection may further lower the progression rate following ERBT. The only comparative study assessing progression rate and PFS to date by Sureka *et al.* (39) did not show any significant benefit of ERBT. However, as we gain more experiences in ERBT, we realise that the biggest advantage of ERBT appears to be ensuring a correct depth of resection (hence complete resection) rather than the theoretical benefit of preventing tumour re-implantation. Modified approaches of ERBT, e.g., resecting the exophytic part of the tumour and resecting the tumour base *en bloc*, may ensure complete resection even for bigger NMIBC and therefore prevent disease progression. An exploratory study on modified ERBT in large bladder tumours is currently under way (41).

Does energy modality matter in ERBT?

Common energy modalities used in ERBT included

Table 1 On-going clinical trials investigating the role of ERBT

Principal investigator	Comparison	Primary outcome	Aimed sample size
Teoh (41)	Bipolar ERBT *vs.* bipolar TURBT	1-year recurrence rate	350
Elshal (48)	Laser ERBT *vs.* electrical ERBT	Number of failed ERBT	100
Shariat (19)	ERBT *vs.* TURBT	Detrusor muscle sampling rate	476
Elshal (31)	Holmium ERBT *vs.* electrical TURBT	Residual tumour upon 2nd TURBT	100
Hu (49)	Laser ERBT *vs.* hydrodissection ERBT *vs.* conventional TURBT	Pathological staging	180
Liu (30)	Thulium laser ERBT *vs.* electrical TURBT	Residual tumour upon 2nd TURBT	172

ERBT, en bloc resection of bladder tumour; TURBT, transurethral resection of bladder tumour.

electrocautery (monopolar and bipolar), laser (holmium and thulium) and hydrodissection. Electrical ERBT allows blunt dissection and instant conversion to conventional TURBT in case technical difficulty arises. Laser ERBT can avoid obturator reflex in lateral wall bladder tumours. Hydrodissection aims to achieve a safer surgery by submucosal elevation, however, its impact on the yield of detrusor muscle and the success of achieving complete resection was unknown. There is currently no consensus on the best energy source for ERBT (21). A European multicentre study by Kramer *et al.* did not show any significant difference in recurrence rate between electrical and laser ERBT (4). With relevant experiences, ERBT should be able to achieve similar outcomes regardless energy modality. In principle, surgical technique is primary and energy modality is secondary.

The role of ERBT in managing MIBC

As radical cystectomy is associated with significant morbidity (42), it is perhaps reasonable to consider ERBT as a bladder-preserving treatment option for early MIBC. Yang *et al.* described a transurethral partial cystectomy technique using 2 μm laser for partial cystectomy in T1 and T2a patients (43). The ability to assess deep resection margin may provide persuasive information on whether complete local resection has been achieved. The use of MRI scan and the VI-RADS scoring system may provide valuable information on which patients to subject to ERBT (44,45). By ensuring maximal resection, ERBT may also serve as a major step in trimodal therapy (42,45). The major limitation, however, is the inability to assess the nodal status even if completely resection of early MIBC has been achieved. Further studies will be needed in this area.

The role of ERBT in managing bladder CIS

CIS of the bladder is often managed with intravesical BCG instillation and/or radical cystectomy (11). EAU guidelines suggested CIS cannot be managed endoscopically alone as CIS is often multifocal and easily missed on imaging (11,46). However, data on the biology of CIS is very limited and whether 'focal' CIS exists is unknown. Given that just under 50% of patients undergoing BCG instillations responds completely to the treatment (46), and radical cystectomy as a second line treatment is often associated with significant morbidity, a good transurethral resection may potentially optimize the oncological outcome in BCG-unresponsive patients who refuse or who are unfit for radical cystectomy (47). Further studies on enhanced imaging-assisted ERBT for patients with bladder CIS will be needed in the future.

Summary: how can ERBT change current clinical practice?

Although there is a lack of randomised controlled trials confirming the superiority of ERBT, it is no doubt a promising technique in treating bladder cancer. As ERBT can be performed essentially using the same equipment for TURBT, it can be generalised globally without much resources problem once its superiority has been confirmed. Benefits on the pathological aspects are appealing, but we need more clinically important benefits in order to justify the use of ERBT. Whether ERBT can avoid the need of second-look TURBT, and reduce the recurrence rate of NMIBC are important questions to be answered. Results from on-going clinical trials are to be awaited (*Table 1*).

On the other hand, tumour size appears to be the major

limitation of ERBT. Whether a modified ERBT approach is considered an acceptable compromise for larger bladder tumours remains to be explored. From the authors' perspective, we should always try to uphold the oncological principles as much as we can regardless of tumour size. Only with such mentality can we optimize the oncological outcomes of NMIBC.

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