En bloc transurethral resection of bladder tumors: A review of current techniques

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Abstract

Introduction: Growing interest surrounds the concept of en bloc transurethral resection of bladder tumors (ERBT). Theoretical advantages include improved adherence to oncological principles and potential yield of superior pathological specimens. Multiple ERBT methods exist. This review summarizes the current evidence regarding application of differing techniques and technologies to ERBT.
Methods: A systematic review of MEDLINE/EMBASE/Scopus databases was performed, using terms "en bloc," "ERBT," "bladder," and "urinary bladder neoplasm." Template-based data extraction included technique of ERBT, feasibility, tumor size, activation of obturator nerve reflex, operative complications, detrusor muscle sampling rate, and recurrence data.
Results: Multiple approaches to ERBT have evolved, using a variety of energy sources. The feasibility of electrocautery, laser, combined waterjet/electrocautery, and polypectomy snare techniques have been confirmed in achieving ERBT. ERBT appears safe, with a low complication rate. The use of laser energy sources reduces the risk of activating the obturator nerve reflex during lateral wall resections. Otherwise, no energy source is unequivocally superior in achieving ERBT. The rate of detrusor muscle sampling is high with use of ERBT and appears superior to that achieved with conventional TURBT (cTURBT) in multiple comparative studies. A limited number of largely non-randomized trials assess bladder tumor recurrence; current evidence suggests this is similar between ERBT and cTURBT groups.
Conclusions: ERBT using a variety of technologies is feasible and safe, with a high detrusor muscle sampling rate. Further research is required to determine whether rates of residual disease or recurrence can be reduced with ERBT vs. cTURBT.

Introduction

Bladder cancer is the 12th most common malignancy worldwide.[1] The cornerstone of accurate diagnosis and local staging is a well-performed transurethral resection of bladder tumor (TURBT), which additionally serves as the primary treatment strategy for non-muscle-invasive disease. The conventional approach to TURBT (cTURBT) involves resection of the tumor in layers, resulting in multiple tumor fragments that are evacuated for histological analysis.[2] Such a technique may promote 'tumor scatter.' This is a longstanding concern in urologic oncology, since the reimplantation theory of malignant urothelial cells was proposed by Albarran and Imbert in 1903.[3] Efforts to remove bladder tumors whole have been described as far back as 1980, with a polypectomy snare.[4] The current concept of transurethral energy-assisted resection of a bladder tumor as a single intact specimen with the inclusion of lamina propria ± muscularis propria fibres was described in 2000.[5] This technique adheres to the oncological principle of excising malignant tissue 'en bloc' with a negative resection margin.[6] In addition, en bloc TURBT (ERBT) allows accurate orientation of the extracted tumor specimen,[7] and may be associated with greater rates of detrusor muscle sampling than alternative techniques,[8] thus facilitating pathological staging.[9]

A variety of ERBT techniques have been described. The purpose of this review is to summarize the available modalities of ERBT and to report the current evidence for each technique.

Methods

Following prospective study registration (PROSPERO: CRD42020223162), a systematic review of MEDLINE/EMBASE/Scopus databases was performed by two reviewers using free-text and MESH term combinations ("en bloc"/"ERBT"/"bladder"/"urinary bladder neoplasm"). English-language, full-text papers published pre-July 2021 were eligible. Case reports, animal studies, and non-transurethral studies were excluded. Data was extracted by a template and narrative synthesis performed. Variables recorded included study design, technique, feasibility of ERBT, size of bladder tumors resected, tumor location, obturator kick reflex for lateral wall tumors, complication data, specimen quality and presence of detrusor muscle, T stage and recurrence data where available. Risk of bias was assessed using the RoB 2 tool[10] for randomized studies (outcome options: low/some concerns/high) and the ROBINS-1 tool[11] (outcome options: risk low/moderate/serious/critical/no information) for non-randomized comparative studies.

Results

Literature review

Search strategy produced a total of 2067 results, yielding 1109 unique abstracts or articles following removal of duplicates. After screening, 48 full-text papers were included for narrative synthesis (21 [19 unique cohorts] relating to electrocautery ERBT, 20 to laser ERBT, three to hydrodissection/electrocautery ERBT, three to polypectomy snare ERBT, and three to mixed cohorts). Findings are discussed below and presented in Supplementary Tables 1–3; available at *cuaj.ca*.

Principles and general techniques

ERBT is generally described with the use of a continuous flow resectoscope, with sheath size 22–27 Fr.[12-14] A laser guide probe may be used with laser.[14] The choice of irrigation fluid relates to the energy source in use — glycine or mannitol is used in monopolar electrocautery (including monopolar HybridKnife®)[15-18] and 0.9% NaCl is widely used for bipolar electrocautery[19-21] and laser.[22-25] Distilled water has also been used with laser.[14] Authors describe demarcation of the tumor edge with the energy source in use, generally with a 2–10 mm margin of macroscopically normal bladder mucosa;[13-15,19-21,25-31] margins of up to 2 cm have been described. The optimal margin has not been determined. The clinical significance of positive horizontal margins remains uncertain, while positive vertical margins appear associated with residual tumor on reresection of T1 disease.[21] Where electrocautery or combined electrocautery/waterjet is the energy source in use, the coagulation current is sometimes advocated for this step.[15,20,28,32,33]

With the use of laser technology, some authors alter the energy settings to provide a coagulation effect for the first line of demarcation,[14,25,34,35] while others describe an initial cutting incision.[12,22,23,31,36] The line of demarcation in the bladder mucosa is deepened to the level of detrusor muscle using the energy source of choice, vertically[25] or in a 'fan' shape.[30] The deepening technique may involve, for example, 'flash-firing' short and rapid cutting current of an electrocautery loop,[28] or laser 'cutting' or vaporization.[25]

Blunt dissection to the muscularis layer has also been described.[21] Dissection within the muscularis layer, using retrograde or combined retrograde-antegrade approaches, with energy and/or blunt dissection is performed, until the tumor is lifted free of the base en bloc.[13,15,20,21,26-29,32] Blunt dissection is performed with the electrode in electrocautery series, and has been described in laser series with the tip of the laser fibre,[36] retracting peaks of a laser guide probe[14] or the tip of the resectoscope sheath.[23,25,37,38] The base and edges may be coagulated/fulgurated in the usual fashion where electrocautery is used,[13,15,19] or 'coagulated' with laser.[22-24,34,35,37,38] The tumor may then be extracted, using the resectoscope sheath and siphon effect, an Ellik evacuator, a tissue forceps, laparoscopic grasping forceps, or a specimen retrieval bag (Supplementary Tables 1–3; available at *cuaj.ca*). Larger tumors, for example those >3 cm, may be

Figure 1. Papillary bladder tumor is identified cystoscopically.

Figure 2. The edges of the tumor are demarcated with a narrow margin of macroscopically normal mucosa.

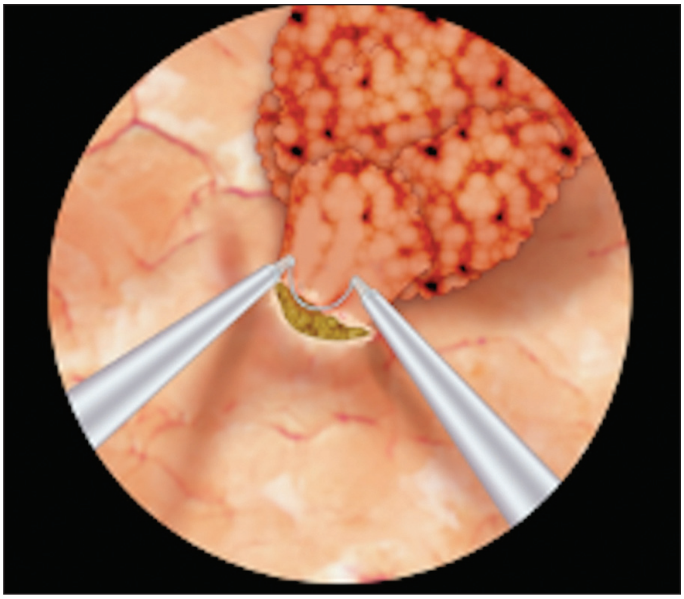

Figure 3. The mucosa and lamina propria are incised until the muscularis propria is reached.

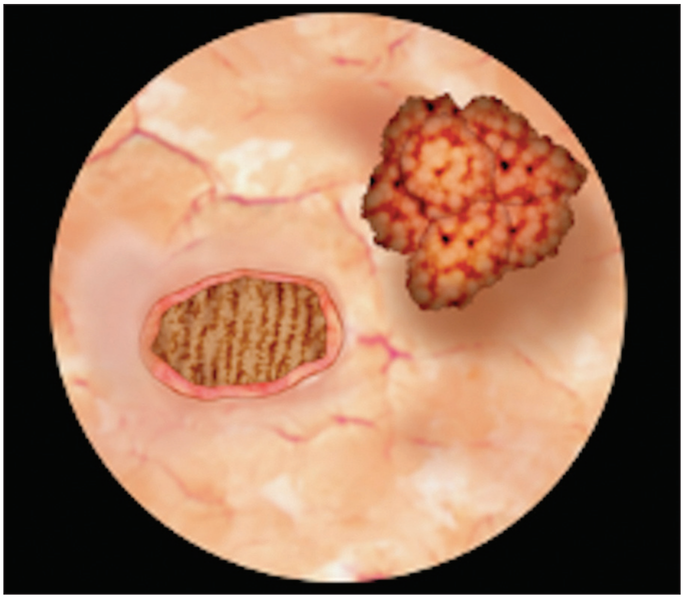

Figure 4. Gradual tumor resection within the muscularis layer is continued until the tumor specimen is separated from its base 'en bloc.'

divided within the bladder before extraction in a controlled fashion (Supplementary Tables 1–3; available at *cuaj.ca*). Figures 1–4 illustrate ERBT using an electrocautery loop.

Electrocautery ERBT

Use of electrocautery enables most surgeons to perform ERBT with equipment already established in the unit for cTURBT. The findings of 19 papers evaluating electrocautery ERBT are presented in Supplementary Table 1 (available at *cuaj.ca*). Both monopolar and bipolar electrocautery have been used with success. The electrode of choice is most commonly a standard loop,[5,13,19,26,28,32,39,40] which may be bent to 45 degrees to create an angled intersection with the bladder mucosa.[5,13,26,32] Some authors have found a flat loop to be useful in ERBT,[15,41] while others describe the use of a plasma button,[19,20] Collin's knife,[27,29] or needle electrode[21] either alone or in conjunction with a loop electrode. A novel approach of primarily cold excision with Zedd excision scissors and minimal electrocautery has recently been described.[18] The upper limit of tumor size for electrocautery ERBT has been set at 2–6cm,[5,13,18,40] however, larger tumors (for example, those >3 cm) may require division within the bladder prior to extraction.[5,42]

Analysis of ERBT feasibility confirms a decline with increasing tumor size with current technology, particularly above a threshold of 3 cm.[40] Whether controlled intravesical tumor division negates any of the hypothesized benefits of ERBT regarding tumor scatter is unknown.

The majority of electrocautery ERBT papers include tumors of diverse locations within the bladder. Some authors, however, avoid ERBT of tumors in particular locations, such as the anterior wall or dome,[15,27] or overlying the ureteric orifices.[18,19] Conversely, one paper proposes that use of ERBT may, in fact, be superior to cTURBT around the ureteric orifices due to purported greater control of coagulation, having confirmed post-ERBT ureteric patency with indigo carmine.[41]

Occurrence of the obturator nerve reflex is reported in 0–23% of electrocautery ERBT studies, where discussed.[16,18,19,21,27,28,42] It is difficult to draw precise conclusions on this figure in the absence of detailed, comparable data surrounding lateral wall tumor location and anesthesia.

A bladder perforation rate of 0–5%[15,16,18,21,26-29] and a bleeding rate of 0–7.3%,[5,15,18-21,26-29,40,42] allowing for heterogeneity in definition of significant bleeding, are associated with electrocautery ERBT. Bladder perforation rates show no statistically significant difference to cTURBT controls in three non-randomized comparative studies.[26,28,41]

Detrusor muscle sampling rates of >80% are associated with electrocautery ERBT in all studies where this is reported; rates of ≥90% are reported in 13 of 16 studies (on propensity score matching in one).[8,13,15,18-21,26-29,41,43] In comparative studies, 4/5 papers found electrocautery ERBT to result in higher rates of muscularis identification compared to cTURBT controls ($p<0.01$).[26,28,29,43] One study reported equal detrusor sampling rates between ERBT and cTURBT, however, 100% sampling rates were achieved in each arm.[19]

Decreased cautery artefact in ERBT compared to controls was observed in some studies,[19,28] and improved T1 substaging with ERBT has also been reported.[44-46] Duration of irrigation and catheter time vary between studies and are likely influenced by local practice; no clear difference is apparent between ERBT and cTURBT.[28,29,43]

Where risk stratified, recurrence rates in the range of 0–11.5% for low-risk and 25.5–29.86% for high-risk bladder cancer at 12–18 months were reported.[20,42] Three relatively small studies reported decreased recurrence rates with ERBT compared to cTURBT at 3–39-month followup,[19,32,43] while three other comparative studies identified no difference in recurrence rates at 3–18-month followup.[28,29,41] Evaluation of recurrence is limited by heterogenous risk stratification, reporting, intravesical treatment regimens, and followup protocols.

Laser ERBT

The principles of laser ERBT involve the use of laser beams, of which a variety of wavelengths and penetration depths may be obtained, to separate, incise, or vaporize tissue layers to dissect a bladder lesion free from its base and surrounding tissues.[47] Multiple laser subtypes have been used to perform ERBT and none has proven clear superiority.

Endoscopic laser resection is often considered a safe technique without cessation of anti-platelet or anti-coagulant drugs, potentially a great advantage to its use.[47] The numbers of patients taking such medications is, however, poorly reported in laser ERBT series throughout the literature. Twenty papers presenting findings of ERBT are outlined in Supplementary Table 2 (available at *cuaj.ca*).

Laser ERBT of tumors up to 4.5–5.5 cm in diameter is reported.[12,14,23,48] While some series do not include tumors located at the dome or anterior wall of the bladder,[14,35,38] others have confirmed feasibility of laser ERBT in virtually all locations throughout the bladder.[12,22,24,30,34,37,48,49] Some authors describe a specific technique[22] or use a flexible cystoscope[24] to approach lesions located at the dome.

No occurrences of an obturator nerve reflex (ONR) were identified from the literature, and a statistically significant reduction in ONR with laser vs. cTURBT has been described in several comparative studies.[14,30,31,34,36,37,49,50]

Rates of bladder perforation are described at 0–1.4 %,[12,14,22-25,30,34,35,37,38,42,48,49,51] although this was not specifically reported in five studies. It is noteworthy that the majority of published studies evaluate outcomes of single or limited-number experienced operators. Bladder perforation rates were lower with laser ERBT than cTURBT in two studies,[14,31] but did not appear to differ in other comparative studies.

A bleeding rate of 0–5.97% is reported,[12,14,22-24,31,34,35,37,38,42,48,49] although complicated by non-uniform definitions and unclear use of anti-platelets/coagulants.

Histological identification of muscularis propria fibres was confirmed in 80–100% of laser ERBT specimens in 14 studies,[12,14,22,23,25,30,31,35-38,42,48,52] although in only 30.7% of specimens in one study.[52]

Detrusor sampling rates demonstrate statistically significant superiority to cTURBT controls.[12,14,31,36,37,52] Cautery artefact appears reduced with laser ERBT,[14] and improved identification of muscularis mucosa layer[30] and T1 substaging[14] with laser ERBT vs. cTURBT has also been described, although remaining limited.

Variable durations of bladder irrigation and catheter time post-laser ERBT are reported, likely reflecting surgeon practice. Some authors report irrigation to rarely be necessary following ERBT,[23,25,35] or advocate use of a short period of several hours only.[31,37]

Urethral catheter time varies from mean 1.76–5 days.[12,14,22,31,42] Several comparative studies have found a significant reduction in catheter duration following laser ERBT vs. cTURBT,[12,14,31,34,37,49] and one blinded, comparative study found catheter duration to be similar.[30]

While one study (n=64) reports lower recurrence and progression rates with laser ERBT as compared to cTURBT at 12-month followup, these results are not reiterated in other literature. Laser ERBT does not appear to alter the recurrence rate of non-muscle-invasive bladder cancer compared to cTURBT controls at a mean 12–41-month followup based on findings of nine studies, three of which risk stratified the patients in each group according to European Association of Urology guidelines.[12,14,30,31,34,37,42,48,49] The authors of one such study reported that it was underpowered to the question of recurrence, but identified a reduced rate of residual disease at routine four-week re-resection following laser ERBT vs. cTURBT (p=0.01).[14] Risk reduction in recurrence of high-risk bladder cancer with maintenance Pirarubicin following laser ERBT was reported in one series;[38] this was the drug of choice due to unavailability of bacillus Calmette-Guérin in the region in question. No additional oncological benefit was demonstrated with use of overnight saline irrigation following thulium ERBT and intravesical Pirarubicin in one study.[25] Further studies of intravesical regimens post-ERBT are awaited.

Waterjet hydrodissection

Waterjet technology employs a high-pressure jet of fluid to divide tissues with hydroabrasive energy, with a unique level of tissue selectivity reported.[53,54] Four studies identified described the use of hydrodissection to perform ERBT (Supplementary Table 3; available at *cuaj.ca*).[17,33,55,56] Hydrodissection was combined with electrosurgery via a HybridKnife® (ERBE, Tübingen, Germany) in all of these studies. HybridKnife technique may begin with demarcation of the perimeter of the lesion to be resected with the electrocautery function,[33] followed by use of waterjet function to elevate the mucosa to be excised, creating a 'cushion' underneath it. Indigo-carmine coloration of the saline fluid can be used to assist visualization.[56] The electrocautery function is used to incise the tissues allowing en bloc resection, and to coagulate the base.[33]

HybridKnife en bloc resection appears feasible for papillary bladder lesions ≤4 cm, with a low complication rate.

Compared to cTURBT controls, Cheng et al found the occurrence of ONR and pooled complications to be lower in the HybridKnife en bloc group, p=0.034.[17] Gakis et al, in the only randomized study, did not observe a difference in complications between HybridKnife and conventional arms.[33]

The detrusor sampling rate with HybridKnife ERBT is inconsistently reported and confounded by differing techniques, with some authors performing separate cold cup muscle biopsies.[17,55] High rates of muscularis sampling appear achievable based on the 77% reported by Gakis et al, although statistical superiority to cTURBT in muscle sampling is unproven.[33] Mean postoperative catheter time varied from 1.6–2.5 days in all studies, with Cheng et al observing a mean nine hours less irrigation time and one day less catheter time than controls.[17]

Polypectomy snare

A limited amount of literature pertains to the use of electrosurgical polypectomy snares, such as those used in gastrointestinal endomucosal resection, for ERBT (Supplementary Table 4; available at *cuaj.ca*). All identified papers used this technique in combination with another, for example cold cup biopsy of the tumor base,[57] conventional TURBT of the tumor base,[58] or en bloc resection of the tumor base.[59] Muscularis sampling rates of up to 75% are reported from the very small case series;[58] however, authors advocate the technique as a debulking strategy prior to formal sampling of the tumor bed. Polypectomy snare TURBT has been proposed to allow relatively removal of tumors that may be too large for conventional ERBT, with lesions >5 cm excised,[57,59] and to potentially pose a more time-efficient strategy to remove large bladder tumors, although the latter is unproven in the literature.[59]

ERBT techniques compared

A small number of studies compare different modalities of ERBT. In a comparison of electrocautery (monopolar or bipolar) and laser (holmium or thulium) ERBT, Kramer et al found no difference in clinically relevant complications, detrusor muscle sampling, irrigation or catheter time.[42] The electrocautery ERBT group was associated with a higher conversion rate to cTURBT and with a greater decrease in hemoglobin compared to laser ERBT; however, the absolute change in hemoglobin was low (<0.5 g/dL). Similarly, Yang et al (n=162) found no difference in complication rates between bipolar and holmium laser ERBT groups, although noted increased ONR with bipolar ERBT vs. laser ERBT.[60] Kramer et al (n=221, prospective, multicenter trial) found no difference in recurrence rates at 12-month followup with electrocautery vs. laser ERBT.[42] Conversely, in a retrospective study (n=115), Li et al reported a lower recurrence rate at 24 months with the use of electrocautery ERBT via a pin-shaped electrode as compared to holmium laser ERBT and to cTURBT, preserved at multivariate analysis (p=0.023);[61] complication rates were not discussed.

A histopathological study of ERBT specimens found no statistically significant difference in rates of muscularis muscle sampling or in confirmation of tumor architecture to be associated with the energy source used during resection (electrocautery, thulium laser or HybridKnife), although sample size was small (n=34).[62]

Maximum tumor size

The upper limit of tumor size is set at 3 cm or 4 cm in many series. This historically appears to have been an arbitrary measurement, however, a marked decline in technical success rates (29.6% vs. 84.3% for tumors >3 cm vs. those ≤3 cm) has recently been confirmed.[40] Nonetheless, ERBT of tumors up to 6 cm in size is reported, with factors such as tumor location and morphology perhaps exerting an influence.[40] Pertinently, larger tumors may require modified extraction techniques or intravesical division prior to extraction.[5,42] The oncological impact of this is uncertain. There is currently inadequate stratification of outcome data according to tumor size in the literature to assess any influence that tumor size may bear on surgical complications.

En bloc techniques for re-resection

One paper (n=78) evaluated the use of ERBT in re-resection of high-risk bladder cancer within 40 days of initial diagnostic ERBT.[63] Re-resection of the visualized scar with a laser or electrocautery device of the surgeon's choice was feasible and safe in all cases, with no instances of bladder perforation or uncontrollable bleeding. Tumors of the anterior or posterior wall and those covering ureteric orifices were excluded. Detrusor muscle was obtained in all samples. A low rate of residual disease (pTa high-grade in 1/78, carcinoma in situ in 4/78) and no cases of muscle-invasive disease were identified at re-resection. These figures are lower than previous literature assessing re-resection of high-risk disease would estimate,[64] perhaps suggesting a superior initial resection with ERBT; however, further analysis of such a hypothesis would be required.

Enhanced visualization techniques for ERBT

The utility of enhanced visualisation techniques during ERBT has been poorly explored. Photodynamic diagnosis,[33,41,56,65] narrowband imaging[17,21] and near-infrared molecular imaging[16] techniques have been described in a small number of studies using electrocautery and hydrodissection. Presumably enhanced visualization techniques would offer similar advantage for ERBT as for cTURBT, however, further ERBT-specific exploration is required.

Risk of bias

Estimated risk of bias (RoB) for randomized or other comparative studies was assessed 'in general' (including feasibility/safety/pathological results/other non-recurrence-related primary endpoint) and 'regarding recurrence.' The majority of studies were deemed to contain moderate RoB 'in general' due to selection and/or operator bias (non-randomized studies) and due to the subjectivity of clinical outcomes, such as bleeding, irrigation time, and catheter duration, which were generally not assessed/reported as assessed by a blinded researcher. Many studies were deemed at 'serious' RoB regarding recurrence, predominantly due to lack of clarity regarding risk stratification, intravesical treatment regimens, or other potential confounders.

Conclusions

ERBT is feasible using a variety of techniques and energy sources, which are synthesized in this review. ERBT is safe, with a consistently low complication rate, and a rate of detrusor muscle sampling that appears to exceed that of cTURBT. Comparative evidence is limited by a lack of large, prospective, randomized studies, although these may be anticipated.[66] The use of laser energy sources may eliminate ONR activation, potentially providing a safer approach to resections of lesions on the lateral wall. Otherwise, no definitive superiority of any energy source has been confirmed in ERBT. Doubtlessly, surgeon experience with a particular technology is of relevance. Current evidence suggests that recurrence rates of non-muscle-invasive bladder cancer at short- to medium-term followup are similar between risk-stratified ERBT and cTURBT groups, but further research into the potential impact of ERBT on residual disease, recurrence, and progression is merited.

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