

**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:** En bloc resection of bladder tumors 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 12<sup>th</sup> most common malignancy worldwide.<sup>1</sup> The cornerstone of accurate diagnosis and local staging is a well-performed transurethral resection of bladder tumour (TURBT), which additionally serves as the primary treatment strategy for non-muscle invasive disease. The conventional approach to TURBT (cTURBT) involves resection of the tumour in layers, resulting in multiple tumour fragments that are evacuated for histological analysis.<sup>2</sup> Such a technique may promote ‘tumour 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.<sup>3</sup> Efforts to remove bladder tumours whole have been described as far back as 1980, with a polypectomy snare.<sup>4</sup> The current concept of transurethral energy-assisted resection of a bladder tumour as a single intact specimen with the inclusion of lamina propria +/- muscularis propria fibres, was described in 2000.<sup>5</sup> This technique adheres to the oncological principle of excising malignant tissue ‘en bloc’ with a negative resection margin.<sup>6</sup> In addition, en bloc TURBT (ERBT) allows accurate orientation of the extracted tumour specimen,<sup>7</sup> and may be associated with greater rates of detrusor muscle sampling than alternative techniques,<sup>8</sup> thus facilitating pathological staging.<sup>9</sup>

A variety of en bloc bladder tumour resection (ERBT) techniques have been described. This purpose of this review is to summarise 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 tumours resected, tumour location, obturator kick reflex for lateral wall tumours, 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<sup>10</sup> for randomised studies (outcome options: low/some concerns/high) and the ROBINS-1 tool<sup>11</sup> (outcome options: risk low/ moderate/ serious /critical/no information) for non-randomised comparative studies.

## Results

### *Literature review*

Search strategy produced a total of 2,067 results, yielding 1,109 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, 3 to hydrodissection/electrocautery ERBT, 3 to polypectomy snare ERBT and 3 to mixed cohorts). Findings are discussed below and presented in Tables 1-3.

### *Principles and general techniques*

En bloc resection of a bladder tumour (EBRT) is generally described with the use of a continuous flow resectoscope, with sheath size 22 – 27Fr.<sup>12-14</sup> A laser guide probe may be used with laser.<sup>14</sup> The choice of irrigation fluid relates to the energy source in use – glycine or mannitol is used in monopolar electrocautery (including monopolar HybridKnife®)<sup>15-18</sup> and 0.9% NaCl is widely used for bipolar electrocautery<sup>19-21</sup> and laser.<sup>22-25</sup> Distilled water has also been used with laser.<sup>14</sup> Authors describe demarcation of the tumour edge with the energy source in use, generally with a 2-10mm margin of macroscopically normal bladder mucosa;<sup>13-15, 19-21, 25-31</sup> margins of up to 2cm have been described. The optimal margin has not been determined. The clinical significance of positive horizontal margins remains uncertain, whilst positive vertical margins appear associated with residual tumour on reresection of T1 disease.<sup>21</sup> Where electrocautery or combined electrocautery/waterjet is the energy source in use, the coagulation current is sometimes advocated for this step.<sup>15, 20, 28, 32, 33</sup> With the use of laser technology, some authors alter the energy settings to provide a coagulation effect for the first line of demarcation,<sup>14, 25, 34, 35</sup> whilst others describe an initial cutting incision.<sup>12, 22, 23, 31, 36</sup> The line of demarcation in the bladder mucosa is deepened to the level of detrusor muscle using the energy source of choice, vertically<sup>25</sup> or in a ‘fan’ shape.<sup>30</sup> The deepening technique may involve, for example, ‘flash-firing’ short and rapid cutting current of an electrocautery loop,<sup>28</sup> or laser ‘cutting’ or vapourisation.<sup>25</sup> Blunt dissection to the muscularis layer has also been described.<sup>21</sup> Dissection within the muscularis layer, using retrograde or combined retrograde-antegrade approaches, with energy and/or blunt dissection is performed, until the tumour is lifted free of the base en bloc.<sup>13, 15, 20, 21, 26-29, 32</sup> Blunt dissection is performed with the electrode in electrocautery series, and has been described in laser series with the tip of the laser fibre,<sup>36</sup> retracting peaks of a laser guide probe,<sup>14</sup> or the tip of the resectoscope sheath.<sup>23, 25, 37, 38</sup> The base and edges may be coagulated/fulgurated in the usual fashion where electrocautery is used,<sup>13, 15, 19</sup> or ‘coagulated’ with laser.<sup>22-24, 34, 35, 37, 38</sup> The tumour may then be extracted, using the resectoscope sheath and siphon effect, an Ellik evacuator, a tissue forceps, a laparoscopic grasping forceps or a specimen retrieval bag (Tables 1-3). Larger tumours, for example those >3cm, may be divided within the bladder before extraction in a controlled fashion (Tables 1-3). Images 1-4 illustrate en bloc resection of a bladder tumour using an electrocautery loop.

### ***Electrocautery ERBT***

Use of electrocautery enables most surgeons to perform en bloc resection of bladder tumours (ERBT) with equipment already established in the unit for cTURBT. The findings of 19 papers evaluating electrocautery ERBT are presented in Table 1. Both monopolar and bipolar electrocautery have been used with success. The electrode of choice is most commonly a standard loop,<sup>5, 13, 19, 26, 28, 32, 39, 40</sup> which may be bent to 45 degrees to create an angled intersection with the bladder mucosa.<sup>5, 13, 26, 32</sup> Some authors have found a flat loop to be useful in ERBT,<sup>15, 41</sup> whilst others describe the use of a plasma button,<sup>19, 20</sup> Collin’s knife,<sup>27, 29</sup> or needle electrode<sup>21</sup> 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.<sup>18</sup> The upper limit of tumour size for electrocautery ERBT has been set at 2cm – 6cm,<sup>5, 13, 18, 40</sup> however ‘larger’ tumours (for example those >3cm) may require

division within the bladder prior to extraction.<sup>5, 42</sup> Analysis of ERBT feasibility confirms a decline with increasing tumour size with current technology, particularly above a threshold of 3cm.<sup>40</sup> Whether controlled intravesical tumour division negates any of the hypothesized benefits of ERBT regarding tumour scatter is unknown. The majority of electrocautery ERBT papers include tumours of diverse locations within the bladder. Some authors, however, avoid ERBT of tumours in particular locations, such as the anterior wall or dome,<sup>15, 27</sup> or overlying the ureteric orifices.<sup>18, 19</sup> 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.<sup>41</sup>

Occurrence of the obturator nerve reflex is reported in 0 – 23% of electrocautery ERBT studies, where discussed.<sup>16, 18, 19, 21, 27, 28, 42</sup> It is difficult to draw precise conclusions on this figure in the absence of detailed, comparable data surrounding lateral wall tumour location and anaesthesia. A bladder perforation rate of 0 – 5%<sup>15, 16, 18, 21, 26-29</sup> and a bleeding rate of 0-7.3%,<sup>5, 15, 18-21, 26-29, 40, 42</sup> 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 3 non-randomised comparative studies.<sup>26, 28, 41</sup> 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).<sup>8, 13, 15, 18-21, 26-29, 41, 43</sup> In comparative studies, 4 of 5 papers found electrocautery ERBT to result in higher rates of muscularis identification compared to cTURBT controls ( $p < 0.01$ ).<sup>26, 28, 29, 43</sup> One study reported equal detrusor sampling rates between ERBT and cTURBT, however 100% sampling rates were achieved in each arm.<sup>19</sup> Decreased cautery artefact in ERBT compared to controls was observed in some studies,<sup>19, 28</sup> and improved T1 substaging with ERBT has been reported also.<sup>44-46</sup> 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.<sup>28, 29, 43</sup> 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.<sup>20, 42</sup> Three relatively small studies reported decreased recurrence rates with ERBT compared to cTURBT at 3-39 month follow-up;<sup>19, 32, 43</sup> whilst three other comparative studies identified no difference in recurrence rates at 3 – 18 month follow up.<sup>28, 29, 41</sup> Evaluation of recurrence is limited by heterogenous risk stratification, reporting, intravesical treatment regimens and follow-up 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 vaporise tissue layers to dissect a bladder lesion free from its base and surrounding tissues.<sup>47</sup> 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.<sup>47</sup> 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 Table 2. Laser ERBT of tumours up to 4.5-5.5cm in diameter is reported.<sup>12, 14, 23, 48</sup> Whilst some series

do not include tumours located at the dome or anterior wall of the bladder,<sup>14, 35, 38</sup> others have confirmed feasibility of laser ERBT in virtually all locations throughout the bladder.<sup>12, 22, 24, 30, 34, 37, 48, 49</sup> Some authors describe a specific technique<sup>22</sup> or use a flexible cystoscope<sup>24</sup> 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 versus cTURBT has been described in several comparative studies.<sup>14, 30, 31, 34, 36, 37, 49, 50</sup> Rates of bladder perforation are described at 0 – 1.4 %, <sup>12, 14, 22-25, 30, 34, 35, 37, 38, 42, 48, 49, 51</sup> 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,<sup>14, 31</sup> but did not appear to differ in other comparative studies.

A bleeding rate of 0 – 5.97% is reported,<sup>12, 14, 22-24, 31, 34, 35, 37, 38, 42, 48, 49</sup> 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,<sup>12, 14, 22, 23, 25, 30, 31, 35-38, 42, 48, 52</sup> although in only 30.7% of specimen in one study.<sup>52</sup> Detrusor sampling rate demonstrate statistically significant superiority to cTURBT controls.<sup>12, 14, 31, 36, 37, 52</sup> Cautery artefact appears reduced with laser ERBT,<sup>14</sup> and improved identification of muscularis mucosa layer<sup>30</sup> and T1 substaging<sup>14</sup> with laser ERBT versus 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,<sup>23, 25, 35</sup> or advocate use for a short period of several hours only.<sup>31, 37</sup> Urethral catheter time varies from mean 1.76 – 5 days.<sup>12, 14, 22, 31, 42</sup> Several comparative studies have found a significant reduction in catheter duration following laser ERBT versus cTURBT,<sup>12, 14, 31, 34, 37, 49</sup> and one blinded comparative study found catheter duration to be similar.<sup>30</sup> Whilst one study (n=64) reports lower recurrence and progression rates with laser ERBT as compared to cTURBT at 12 month follow-up, 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 mean 12 – 41 month follow-up based on findings of nine studies, three of which risk stratified the patients in each group according to EAU guidelines.<sup>12, 14, 30, 31, 34, 37, 42, 48, 49</sup> The authors of one such study reported that it was under-powered to the question of recurrence however, and identified a reduced rate of residual disease at routine 4 week re-resection following ERBT versus cTURBT (p=0.01).<sup>14</sup> Risk reduction in recurrence of high-risk bladder cancer with maintenance Pirarubicin following laser ERBT was reported in one series,<sup>38</sup> however this was the drug of choice due to unavailability of BCG 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.<sup>25</sup> 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.<sup>53, 54</sup> Four studies identified described the use of hydrodissection to perform ERBT (Table 3).<sup>17, 33, 55, 56</sup> 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,<sup>33</sup> followed by waterjet function used to elevate the mucosa to be excised, creating a ‘cushion’ underneath it. Indigo-carmin colouration of the saline fluid can be used to assist visualisation.<sup>56</sup> The electrocautery function is used to incise the tissues allowing en bloc resection, and to coagulate the base.<sup>33</sup> HybridKnife® en bloc resection appears feasible for papillary bladder lesions ≤4cm, 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,  $p=0.034$ .<sup>17</sup> Gakis et al., in the only randomised study, did not observe a difference in complications between HybridKnife® and conventional arms.<sup>33</sup> The detrusor sampling rate with HybridKnife® EBRT is inconsistently reported and confounded by differing techniques, with some authors performing separate cold cup muscle biopsies.<sup>17, 55</sup> 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.<sup>33</sup> Mean postoperative catheter time varied 1.6 – 2.5 days in all studies, with Cheng et al. observing mean 9 hours less irrigation time and 1 day less catheter time than controls.<sup>17</sup>

***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 (Table 4). All identified papers used this technique in combination with another, for example cold cup biopsy of the tumour base,<sup>57</sup> conventional TURBT of the tumour base,<sup>58</sup> or en bloc resection of the tumour base.<sup>59</sup> Muscularis sampling rates of up to 75% are reported from the very small case series;<sup>58</sup> however authors advocate the technique as a debulking strategy prior to formal sampling of the tumour bed. Polypectomy snare TURBT has been proposed to allow relatively removal of tumours that may be too large for conventional ERBT, with lesions >5cm excised,<sup>57, 59</sup> and to potentially pose a more time efficient strategy to removal of large bladder tumours, although the latter is unproven in the literature.<sup>59</sup>

***ERBT techniques compared***

A small number of studies compare different modalities of ERBT. In 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.<sup>42</sup> The electrocautery ERBT group was associated with a higher conversion rate to conventional TURBT and with a greater decrease in haemoglobin compared to laser ERBT; however the absolute change in haemoglobin was low (<0.5g/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 versus laser ERBT.<sup>60</sup>

Kramer et al. (n=221, prospective multicentre trial) found no difference in recurrence rates at 12 month follow-up with electrocautery versus laser ERBT.<sup>42</sup> Conversely, Li et al. in a retrospective study (n=115) 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 conventional TURBT, preserved at multivariate analysis (p=0.023);<sup>61</sup> complication rates were not discussed. A histopathological study of ERBT specimen found no statistically significant difference in rates of muscularis muscle sampling or in confirmation of tumour architecture to be associated with the energy source used during resection (electrocautery, thulium laser or HybridKnife®), although sample size was small (n=34).<sup>62</sup>

### ***Maximum tumor size***

The upper limit of tumour size is set at 3cm or 4cm in many series, as outlined in the data tables. This historically appears to have been an arbitrary measurement, however a marked decline in technical success rates (29.6% vs 84.3% for tumours >3cm vs those ≤3cm) has recently been confirmed.<sup>40</sup> Nonetheless, ERBT of tumours up to 6cm in size is reported, with factors such as tumour location and morphology perhaps exerting an influence.<sup>40</sup> Pertinently, larger tumours may require modified extraction techniques, or intra-vesical division prior to extraction.<sup>5, 42</sup> The oncological impact of this is uncertain. There is currently inadequate stratification of outcome data according to tumour size in the literature to assess any influence that tumour 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.<sup>63</sup> Re-resection of the visualised scar with a J electrode (Collins loop) was feasible in all cases and safe, with no instances of bladder perforation or uncontrollable bleeding. Tumours 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,<sup>64</sup> perhaps suggesting a superior initial resection with ERBT, but further analysis of such a hypothesis would be required.

### ***Enhanced visualisation techniques for ERBT***

The utility of enhanced visualisation techniques during ERBT has been poorly explored. Photodynamic diagnosis,<sup>33, 41, 56, 65</sup> narrowband imaging<sup>17, 21</sup> and near-infrared molecular imaging<sup>16</sup> techniques have been described in a small number of studies using electrocautery and hydrodissection. Presumably enhanced visualisation 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 randomised or other comparative studies is presented within the data tables. RoB 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-randomised 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

En bloc resection of bladder tumours is feasible using a variety of techniques and energy sources, which are synthesised 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, randomised studies, although these may be anticipated.<sup>66</sup> The use of laser energy sources may eliminate obturator nerve reflex 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 follow-up 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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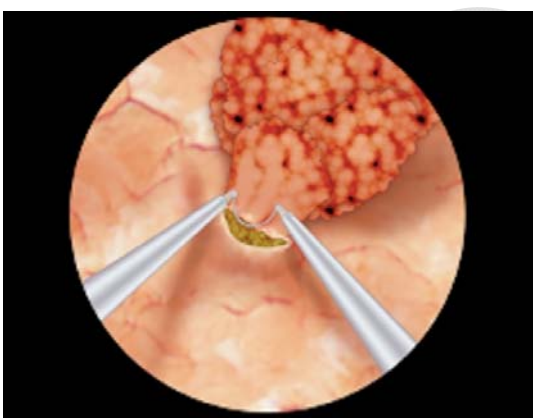
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## Figures and Tables

*Fig. 1.* Papillary bladder tumor is identified cystoscopically.



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



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



**Fig. 4.** Gradual tumor resection within the muscularis layer is continued until the tumor specimen is separated from its base ‘en bloc.’



DRAFT



**Table 1. Electrocautery**

Table 1. Electrocautery																		
Author	Yr	ERB T^ (n)	Mod-ality	Design	cTURBT control group?	Age (Avg)	Male %	Feas-ibility	Max. tumor size	Extraction	Anes-thesia	Obtur-ator reflex	Bladder perforation	Signifi-cant bleeding *	Muscularis propria identified in specimen?	pTa	pT1	≥pT2
Lodde <sup>15</sup>	2003	37	Monopolar (flat loop)	Prosp.	No	64.7	86.5% (32/37)	All	2.5cm	Syringe	Mixed	NR	2.7% (1/37)	None	100% (37/37)	82.25% (51/62)*	17.8% (11/62)	0
Ukai <sup>5</sup>	2010	97	Energy NR (bent loop)	Prosp.	No	71.2	85.5% (83/97)	Unclear (some mixed technique)	5.5cm^	NR	Spinal	NR	None (0/97)	None	82.5% (80/97)	30.9% (30/97)	60.8% (59/97)	7.21% (7/97)
Upadhyay <sup>26</sup>	2012	21	Monopolar (bent loop)	Prosp. Non-Ran	Yes	NR	NR	All	<3cm	NR	General for lateral wall; otherwise spinal	NR	None (0/21)	0	95.2% (20/21)	57.15% (12/21)	28.6% (6/21)	14.3% (3/21)
Upadhyay control n=25						-	-	-	-	-	“	-	4% (1/25)	0	60% (15/25)	48% (12/25)	32% (8/25)	20% (5/25)
RoB: in general = Moderate; Re recurrence = N/A																		
Statistical significance						-	-	-	-	-	-	-	NS	-	<0.001	NS	NS	NS
Sureka <sup>32</sup>	2014	21	Monopolar (bent loop)	Prosp. Non-Ran	Yes	52.6	NR	All	4cm^	Grasping forceps via nephroscope for large	NR	NR	NR	NR	All, but excluded if muscle not present	57.14% (12/21)	42.8% (9/21)	0
Sureka control n = 24						55	NR	-	-	-	NR	NR	NR	NR	All, but excluded if muscle not present	54.16% (13/24)	45.8% (11/24)	0
RoB: in general = Moderate; Re recurrence = Serious																		

Statistical significance						-	-	-	-	-	-	-	-	-	-	-	-	-
Kramer <sup>42</sup> (Monopolar Arm)	2015	91	Monopolar	Prosp.	No	69	78% (71/91)	26.3% of electrocauterly switched to cTURBT	<5cm^	Forceps (occasionally specimen bag)	NR	1.09% (1/91)	NR	3.9% (6/156)	96.2% (150/156)	54.9% (50/91)	36.3% (33/91)	8.8% (8/91)
Kramer <sup>42</sup> (Bipolar Arm)	2015	65	Bipolar	Prosp.	No	65.5	83% (54/65)		<5cm^		NR	None 0/65	NR			50.7% (33/65)	44.62% (29/65)	4.61% (3/65)
Hurle <sup>27</sup>	2016	74	Energy NR (Collins loop)	Prosp.	No	71	78.4% (58/74)	0.97% (1/103 tumors) converted	3cm	Ellik (laparoscopic graspers via nephroscope for large)	NR	1.35% (1/74)	1.35% (1/74)	0	100% (74/74)	72.3% (47/65)	41.5% (27/65)	X
Zhang KY <sup>28</sup>	2017	40	Monopolar (Loop)	Retro.	Yes	60.65	87.5% (35/40)	Combination technique for large	>3cm	Ellik	GA	22.5% (9/40)	5% (2/40)	0	100% (40/40)	37.5% (15/40)	62.5% (25/40)	None
Zhang control n= 50						60.8	76% (38/50)	-	-	-	GA	4% (2/50)	8% (4/50)	0	54% (27/50) in specimen (base cold cup biopsies separately)	54% (27/50)	46% (23/50)	None
RoB: in general = Moderate; Re recurrence = Serious																		
Statistical Significance						-	-	-	-	-	-	p=0.867	p=0.689	0	p<0.01	-	-	None

Balan <sup>19</sup>	2018	45	Bipolar (plasma button + loop)	RCT	Yes	64.7	NR	All	<3cm	NR	NR	11.1% (5/45)	NR	NR; mean Hb drop 0.28g/dL	100%	53.3% (24/45)	46.7% (21/45)	None
Balan control n = 45 (monopolar cTURBT)						66.1		-	-	-	-	4.4% (2/45)	NR	NR; mean Hb drop 0.76g/dL	100%	51.1% (23/45)	48.9% (22/45)	None
RoB: in general = Some concerns; Re recurrence = Some concerns																		
Statistical significance						-	-	-	-	-	-	p<0.05 ~	-	p<0.05	No difference	-	-	-
Zhang J <sup>20</sup>	2018	82	Bipolar (plasma button)	Observ. Unclear	No	58.4	74.4% (61/82)	NR	<4cm	Ellik	NR	None	None	None	100%	26	51	5
Huang <sup>39</sup>	2020	12	Monopolar (loop)	Prosp. Non-Ran	Yes	NR	75% (9/12)	All	<3cm	NR	NR	NR	NR	NR	NR	6/12	6/12	None
Huang control n= 9						NR	77.8% (7/9)	-	-	-	-	-	-	-	-	6/9	3/9	None
RoB: in general = Moderate; Re recurrence = Serious																		
Statistical significance						-	-	-	-	-	-	-	-	-	-	-	-	-
Yang Y <sup>16</sup>	2020	26	Monopolar	Retro.	No	62.39	80.7% (21/26)	All	<3cm	Ellik, occasionally forceps	Spinal +Epidural	23% (6/26)	3.8% (1/26)	NR	88.5% (23/26)	42.3% (11/26)	57.7% (15/26)	X
Bangash <sup>29</sup>	2020	41	Monopolar (Collins knife)	Prosp. Non-Ran	Yes	58.46	82.9% (34/41)	NR	<3cm	NR	NR	NR	None (0/41)	7.3% (3/41) haematuria	100%	48.8% (20/41)	51.2% (21/41)	46.3% (19/41)
Bangash control n = 41						58.59	-	-	-	-	-	-	NR	9.75% (4/41)	56.1% (23/41)	46.3% (19/41)	53.7% (22/41)	None
RoB: in general = Moderate; Re recurrence = Moderate																		
Statistical significance						-	-	-	-	-	-	-	-	0.68	<0.001	NS	NS	None

## CUAJ – Review

Croghan et al  
En bloc TURBT

Miyake <sup>41</sup>	2020	12	Bipolar (flat loop)	Prosp. Non-Ran	Yes	76.5	91.67% (11/12)	All	<2.5cm	Grasping forceps	General or spinal	NR	8.34% (1/12)	NR	100% (12/12)	83.34% (10/12)	16.7% (2/12)	None
Miyake control n=28						74.6	89.3% (25/28)	-	-	-	-	NR	0	NR	NR	21/28	7/28	None
RoB: in general = Moderate; Re recurrence = Moderate-Serious																		
Statistical Significance						-	-	-	-	-	-	-	NS		-	-	-	-
Eissa <sup>13</sup>	2020	50	Monopolar (bent loop)	Retro.	No	72.26	80% (40/50)	All but this was ERBT cohort	2cm	Forceps or Ellik	General	NR	4% (2/50)	None	90% (45/50)	28% (14/50)	72% (36/50)	X
Hameed <sup>18</sup>	2021	23	Zeddis Scissors	Prosp.	No	64	69.6 (16/23)	NR	2.6cm	3 pronged grasper or Ellik	NR	0	0	0	91% (21/23)	35% (8/23)	57% (13/23)	9% (2/23)
Yanagisawa <sup>21^^</sup>	2021	140	Bipolar (needle electrode)	Prosp. Non-Ran	No	72	75% (105/140)	All, but en bloc cohort studied	<3cm	Biopsy forceps	NR	0 (n=67 lateral)	0.71% (1/140)	1.42% (2/140)	90%	66% (93/140)	34% (47/140)	X
Teoh <sup>40</sup>	2021	135	Mixed mono/bipolar (loop)	Prosp. Non-Ran	Not intention-to-treat (cases converted to cTURBT included)	71.3	71.1% (96/135)	94.3% <1cm	6cm (80% ≤ 3 cm)	NR	NR	NR	0	5.1% (5/99)	80.8%	65%**	17.2%**	X
								82.2% 1.01–2 cm										
								75% 2.01–3 cm										
								29.6% > 3cm										

<b>Yasui<sup>46</sup></b>	2021	61	Bipolar	Retro.	No	76	83.6% (51/61)	NR (ERBT cohort)	<3cm majority. >3cm cTURBT of exophytic and ERBT of base.	NR	NR	NR	NR	NR	NR	X	100% (61) – selected. Stratified pT1a,b,c	X
<b>Poletajew<sup>43</sup></b>	2021	153	Mixed (predominantly monopolar) Collins knife or resection loop	Prosp. Non-Ran	Yes	68	76.5% (117/153)	“very scarce,” excluded from analysis	≤ 4cm	NR	NR	NR	NR	NR	91.3% (126/138) (propensity score matched)	61.4% (94/153)**	24.8% (38/153) **	3.9% (6/153) **
Poletajew control n=274						69.5	73.4% (201/274)	-	-	-	-	-	-	-	68.8% (95/138)	46% (126/274)	21.1% (58/274)	11.7% (32/274)
RoB: in general = Moderate; Re recurrence = Serious						NS	NS	-	-	-	-	-	-	-	P<0.001	-	-	-
Statistical significance						NS	NS	-	-	-	-	-	-	-	P<0.001	-	-	-

^Larger tumors were divided prior to extraction however (3cm cut off for Kramer). \*Each individual lesion analysed rather than each patient hence bigger denominator. ~Lower rates of obturator reflex activation, however breakdown of lateral wall location unclear. \*\*Remainder T0. ^^Additional papers by same author referenced but not tabulated as patient cohorts overlapping. non-ran: non-randomized; NR: not reported; observ: observational; prosp: prospective; RCT: randomized controlled trial; RoB: risk of bias; X: excluded.

Table 2 – Laser ERBT

Table 2 – Laser ERBT																			
Author	Laser	Yr	ER BT ^ n	Study Desig n	cTURB T Control Group?	Age (Av g)	Male %	Laser para- meter s	Feasibilit y	Max tumor size	Extractio n	Anesthes ia	Obturato r reflex	Bladder perforati on	Signific ant bleedin g*	Muscul aris propria identifi ed in specim en?	pTa	pT1	≥pT2
Holmium laser																			
Kramer <sup>42</sup>	Holmi um arm	201 5	50	Prosp.	No	62.2	72% (36/50)	1-2J 15- 30Hz	98% (49/50)*	<4cm	Specimen retrieval bags in some	NR	0	NR	2% (1/50)*	50/50 (100%)	58% (29/5 0)	42% (21/50)	0
Mahesh -wari <sup>22</sup>	Holmi um	202 0	67	Retro.	No	57.8	77.6% (52/67)	550u 1-2J 40- 50Hz	All	4cm^	Ellik	General or regional	0	0	5.97% (4/67)	57/67 (85%)	82% (55/6 7)	17.9% (12/67)	X
Hashe m <sup>14</sup>	Holmi um	202 0	50	RCT	Yes	60.4	74% (37/50)	1-2J 10- 15Hz 10- 30W	All	<5cm	Cold- crown loop	NR	0	0	0	98% (49/50)	4.5% (2/50)	95.5% (42/50)	4% (2/50)
Hashem control n = 50						61.1	78% (39/50)	-	-	-	-	-	24% (12/50)	12% (6/50)	6% (3/50)	62% (31/50)	6.1% (3/50)	93.9% (46/50)	0
RoB: in general = Low; Re recurrence = Some concerns																			
Statistical significance						-	-	-	-	-	-	-	<0.001	-	NS	<0.001	NS	NS	NS
Green light laser																			
He <sup>35</sup>	Green Light (KTP) front- firing	201 4	45	Retro.	No	57.8	NR	0.6J 50Hz (30W )	All, but wire loop coagulati on required in 1	3cm	Ellik	Continuo us epidural	0	0	Irrigatio n n=1 Hb mean 1.1g/dL decreas e	100% (45/45)	60% (27/4 5)	33.4% (15/45)	6.67% (3/45)
Chen <sup>34</sup>	Green Light 6F	201 6	83	Prosp.	Yes	63.4 3	72.3% (60/83)	120- 160W (cut)	NR	3cm	Ellik	Continuo us epidural	0	0	NR (less Hb drop)	NR	84.3% (70/8 3)	15.6% (13/83)	0

	side-firing							30-50W (coag)							with LASER 0.87 vs 1g/dL)				
Chen control n = 75						65.31	68% (51/75)	-	-	-	-	-	12% (9/75)	2.67% (2/75)		NR	85.3% (64/75)	14.7% (11/75)	0
RoB: in general = Low-moderate; Re recurrence = Moderate																			
Statistical significance						-	-	-	-	-	-	-	0.001	NS	-	-	-	-	-
Cheng <sup>36</sup>	Green Light front-firing	2017	34	Retro.	Yes	59.41	82.4% (28/34)	120W	NR	3cm	Ellik	Spinal / Epidural	0	NR	NR	97% (33/34)	41.2% (14/34)	16 (47.06%)	4 (11.76%)
Cheng control n=30						63.13	90% (27/30)	-	-	-	-	-	10	NR	NR	80% (24/30)	43.33% (13/30)	50% (15/30)	6.7% (2/30)
RoB: in general = Moderate; Re recurrence = NA																			
Statistical significance						-	-	-	-	-	-	-	p<0.001	-	-	p=0.04	NS	NS	NS
Liang <sup>52</sup>	Green Light (KTP) front-firing	2019	88	Retro.	Yes	58	88.6% (78/88)	0.6J 50Hz (30W)	NR	NR	NR	NR	NR	NR	NR	30.7% (27/88)	33% (29/88)	67% (59/88)	0
Liang control n= 70						-	-	-	-	-	-	-	-	-	-	11.4% (8/70)	47.1% (33/70)	52.9% (37/70)	0
RoB: in general = Low; Re recurrence = N/A																			
Statistical significance						-	-	-	-	-	-	-	-	-	-	Significant	NS	NS	-
Fan <sup>30</sup>	Green-light Front firing	2021	116	RCT	Yes	60	83.2% (96/116)	532nm 0.6J x 50Hz (30W)	Appears all	<3cm	Via sheath /resection loop/End obag	NR	0	0	NR (less EBL with Laser)	89.7% (104/116)	78.5% (91/116)	21.5% (25/116)	X
Fan control n = 117						57	74% (87/117)	-	-	-	-	-	7.7% (9/117)	0.9% (1/117)	-	71.8% (84/117)	88.9% (104/117)	11.1% (13/117)	-
RoB: in general = Some concerns; Re recurrence = Some concerns																			
Statistical significance						NS	-	-	-	-	-	-	0.002	NS	-	<0.005	0.031		-
Thulium laser																			

Muto <sup>23</sup>	Thulium-YAG	2014	55	Prosp.	No	68	89% (49/55)	800nm 30W continuous wave (20W pulse d-wave for coag)	All	4.5cm^	Grasper	Epidural	0	0	0	100% (55/55)	56.4% (31/55)	32.7% (18/55)	10.9% (6/55)
Kramer <sup>42</sup>	Thulium arm	2015	15	Prosp.	No	69.4	80% (12/15)	550u 5-15 W	*	<4cm^	Specimen retrieval bags in some	NR	0	NR	*	100% (15/15)	66.7% (10/15)	33.3% (5/15)	0
Migliari <sup>48</sup>	Thulium	2015	58	Prosp. Non-Ran (retro control)	Yes	71	70.7% (41/58)	Continuous wave 30W. 1470nm Diode for coagulation at 20W	NR	4.5cm	Via sheath with loop	Spinal	0	0	0	100% (58/58)	56.4% (30/58)	32.7% (23/58)	10.9% (5/58)
Migliari control n =61						72.5	73.8% (45/61)	-	-	-	-	-	8	NR	3.27% (2/61)	91.8% (56/61) (3 not valuable due thermal artifact)	-	-	-
RoB: in general = Low-moderate; Re recurrence = N/A																			
Statistical significance																			
Zhang <sup>24</sup>	Thulium Vela	2016	38	Prosps.	No	62	81.6% (31/38)	1.94um	All	3cm	Sheath or grasper	General	NR	0	0	100% (38/38)	39.5% (15/38)	57.9% (22/38)	2.63% (1/38)



								600u m fibre 50W											
Xu H <sup>12</sup>	Thuli um Vela	201 8	26	Retro.	Yes	55.9	92.3% (24/26)	1.9um 30W	NR	4.5cm	Sheath or with loop	General	0	0	0	100% (30/30) on initial analysis	33.34 % (10/3 0)	40% (12/30)	X
Xu control n = 44						59.7	79.5% (35/44)	-	-	-	-	-	16% (7/44)	6.8% (3/44)	0	69.8% (44/63) On initial analysis (exclud ed w/o muscle)	56.8% (25/4 4)	36.36% (16/44)	X
RoB: in general = Moderate; Re recurrence = Serious																			
Statistical significance						-	-	-	-	-	-	-	-	-	-	P=0.04	-	-	-
Li <sup>37</sup>	Thuli um	201 8	136	Retro.	Yes (plasma - kinetic)	NR	80.9% (110/13 6)	550u m 1.5J 20Hz 30W	-	<3.5cm	Ellik	Spinal	0	0	0	95.6% (130/13 6)	NR	NR	NR
Li control n = 120						NR	81.7% (98/120 )	-	-	-	-	-	4	1	1.67% (2/120)	85.8% (103/12 0)	NR	NR	NR
RoB: in general = Moderate; Re recurrence = Serious																			
Statistical significance						-	-	-	-	-	-	-	0.032	NS	NS	P=0.00 6	-	-	-
Xu S <sup>38</sup> 2um	Thuli um	202 0	141	Retro.	No	67	81.6% (115/14 1)	1.5J 20Hz 30W	NR	4cm	Ellik^	NR	NR	1.4% (2/141)	NR	100% (141/14 1)	70.2% (99/1 41)	29.7% (42/141 )	X
Liu <sup>31</sup>	Thuli um	202 1	134	Retro.	Yes	61.5	75.4% (101/13 4)	30W	NR	<3cm	Via sheath	GA	0	0	0	97.4% (4 exclud ed due quality)	53.7% (72/1 34)	36.6% (49/134 )	X
Liu control n = 152 (cTURBT electrocautery. Small lesions resected en bloc with loop).						60.3	73% (111/12 5)	-	-	-	-	GA	15.8% (24/152)	5.9% (9/152)	2% (3/152)	87.6% (23 exclude)	57.2% (87/1 52)	31.6% (48/152 )	X

RoB: in general = Moderate; Re recurrence = Moderate-Serious																	d due quality)			
Statistical significance						NS	NS	-	-	-	-	-	<0.001	0.012	0.267**	0.001	NS	NS	-	
Yang <sup>25</sup>	Thulium	2021	235	Retro.	No cTURBT control	65.7	79.1% (186/235)	NR	98% (249/254 original population)	3cm	Ellik or laparoscopic forceps	Spinal/epidural	0	0	NR	Muscle = Inclusion criterion, but appears none of 254 excluded on this basis.	81.7% (192/235)	18.3% (43/235)	X	
Other lasers																				
Chen <sup>49</sup>	2 Micron	2015	71	RCT	Yes	63	76% (54/71)	30 – 50W	All	4cm	Extractor	Sacral block	0	0	0	NR	60.5% (43/71)	35.2% (25/71)	-	
Chen control n=71						62	71.8% (51/71)	-	-	-	-	-	25.4% (18/71)	0	0	NR	77.5% (55/71)	21.1% (15/71)	-	
RoB: in general = Some concerns; Re recurrence = Some concerns																				
Statistical significance						NS	NS						<0.001	NS	NS	-	-	p=0.047	-	
Severigna <sup>67</sup>	2 Wave-length	2018	34	Prosp.	No	NR	82.35% (28/34)	1.94um Th 1.56um Erb 1.0 J 10Hz 1.94um wave-length	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	X	
Tao <sup>51</sup>	980nm wave	2020	36	NR	Yes	UK	UK	UK	UK	UK	UK	UK	None (0/36)	None (0/36)	UK	UK	UK	UK	UK	

Tao control n= 48														
RoB: in general = Moderate; Re recurrence = Serious	-	-	-	-	-	-	-	12.5% (6/48)	6.25% (3/48)	-	-	-	-	-
Statistical significance	-	-	-	-	-	-	-	Apparent (NR)	Apparent (NR)	-	-	-	-	-

\*Bleeding and conversion in Kramer paper expressed as LASER cohort – unclear if holmium or thulium arm. ^Some large tumours divided within the bladder prior to extraction. \*\*Less ‘gross haematuria’ with laser ERBT vs, cTURBT (38.1% vs 96.7%,  $p < 0.0001$ ) in this study. ‘Significant bleeding’ in table refers to return to theatre. NR: not reported; Non-Ran: non-randomized; observ: observational; prosp: prospective; RCT: randomized controlled trial; RoB: risk of bias; X: excluded

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Table 3. Hydrodissection

Author	Yr	ERB T^ (n)	Study design	Control group?	Age (Avg)	Male %	Feasibility	Max tumor Size	Extraction	Anesthesia	Obturator reflex	Bladder perforation	Significant bleeding*	Muscularis propria identified in specimen?	pTa	pT1	≥pT2
Nagele <sup>55</sup>	2011	5	Prosp.	No	77	80% (4/5)	100% (5/5)	2cm	Endoscopic bag	NR	NR	None (0/5)	None (0/5)	NR (separate cold cup muscle biopsies taken)	100% (5/5)	0	0
Fritsche <sup>56</sup>	2011	17	Prosp.	No	NR	NR	17/17 (100%)	1.6cm~	Endoscopic bag	NR	NR	None (0/17)	None (0/17)	All	41.2% (7/17)	29.4% (5/17)	5.9% (1/17)
Cheng <sup>17</sup>	2018	95	Retro.	cTURBT	62.4	70.5% (67/95)	95/95 (100%)	4cm	Nylon bag	Epidural	2.1% (2/95)	None (0/95)	None (0/95)	NR (separate cold cup muscle biopsies taken)	54.7% (52/95)	45.3% (43/95)	0
Cheng Control n=98					64.4	71.4% (70/98)	-	-	-	-	7.14% (7/98)	2% (2/98)	None (0/98)	NR	55.1% (54/98)	44.9% (44/98)	0
RoB: in general = Moderate; Re recurrence = NA						-	-	-	-	-	P=0.034 for complications overall			-	0.95		
Statistical significance				-	-	-	-	-	-	-	P=0.034 for complications overall			-	0.95		
Gakis <sup>33</sup>	2020	56	RCT	cTURBT	66.8	80.4% (45/56)	All - exclude d if not	≥ 3cm	Mixed	NR	NR	1.8% (1/56)	None (0/56)	77.4% (41/56)	89.3% (50/56)	10.7% (6/56)	0
Gakis Control n=59					70.2	79.7% (47/59)	-	-	Mixed	NR	NR	1.8% (1/56)	1.7% (1/59)	66.7% (36/59)	71.2% (42/59)	28.8% (17/59)	0
RoB: in general = Low; Re recurrence = Some concerns						-	-	-	NR	NR	p=1.0	p=0.49	p=0.28	P=0.02		-	
Statistical significance				-	-	-	-	-	-	NR	NR	p=1.0	p=0.49	p=0.28	P=0.02		-

<sup>^</sup>ERBT n = overall patient number. Multiple tumors were excised in some patients. \*Significant bleeding as reported by authors or defined as need for transfusion or manual washout postoperatively. ~ 7.5 cm tumor resected but largest extracted en bloc was 1.6 cm. cTURBT: conventional TURBT (using electrocautery in piecemeal fashion)  
NR: not reported; Non-Ran: non-randomized; observ: observational; prosp: prospective; RCT: randomized controlled trial; RoB: risk of bias; X: excluded

Author	Yr	ERBT^ (n)	Study design	cTURB T control group?	Age (Avg)	Male %	Feasibil ity	Max tumor size	Extractio n	Anesthes ia	Obtura tor reflex	Bladder perforati on	Significa nt bleeding *	Muscularis propria identified in specimen?	pTa	pT1	≥pT2
Maurice <sup>57</sup>	2012	9	Retro.	No	NR	NR	All (pedunc- ulated selected )	>5cm	Snare or endoscopi c mesh net	NR	None (0/9)	None (0/9)	0	50% polypectomy specimen Cold cup biopsy in addition -> 100%	NR	NR	NR
Adam <sup>58</sup>	2018	4 (18 lesions)	Prosp.	No	64.2	75% (3/4)	All selected lesions	2.6cm	Stone basket	General	NR	None (0/4)	0	75% polypectomy specimen (3/4)	25% (1/4)	75% (3/4)	-
Hayashida <sup>59</sup>	2019	39	Prosp.	Yes	NR	61.5% (24/39)	All selected lesions	6cm	NR	NR	NR	2.56% (1/39)	None (0/39)	All with en bloc base; not specified for polypectomy specimen	48.7% (19/39)	46.2% (18/39)	5.1% (2/39)
Hayashida control n=31					-	67.7% (21/31)	-	-	-	-	-	None (0/21)	None (0/21)	All; some cautery artefact	51.6% (16/21)	45.2% (14/21)	3.2% (1/21)
RoB: in general = Moderate; Re recurrence = Serious						-	-	-	-	-	-	NR	-	-	-	-	
Statistical significance				-	-	NS	-	-	-	-	-	NR	-	-	-	-	-

Adam: Electrosurgical polypectomy snare plus standard TURBT of base. Maurice: Electrosurgical polypectomy snare plus cold cup biopsy base. Hayashida: Electrosurgical polypectomy snare plus en bloc TURBT of base. NR: not reported; RoB: risk of bias