11 TURBT: An Old Operation with New Insights

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Abstract

Transurethral resection of bladder tumour (TURBT) is the gold standard in diagnosing and treating non-muscle-invasive bladder cancer (NMIBC). The first resectoscope has been introduced more than a century ago, and TURBT remains as a cornerstone in the management of bladder cancer. Although it is a minimally-invasive surgery that has gained favour over the years, the recurrence rate of NMIBC is in general unsatisfactory ranging from 15% to 61% at 1 year and 31% to 78% at 5 years. Tremendous efforts have been made to improve the treatment outcomes of NMIBC, and the current treatment algorithm has been shaped over the past decades. This book chapter shall first discuss about the history of TURBT and the current standard of the initial management of NMIBC, followed by newer concepts that have been proposed including enhanced imaging during TURBT and en bloc resection of bladder tumour. We hope to provide our readers the backbone of the TURBT procedure and new insights that might be helpful in optimizing the management of NMIBC.

Keywords

Bladder cancer · TURBT · Photodynamic diagnosis Narrow-band imaging · En bloc resection

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11.1 History of Transurethral Resection of Bladder Tumour

The dedication, wisdom and creativity of our great predecessors had cultivated the standard of modern transurethral resection of bladder tumour (TURBT). Development of TURBT was nonetheless a reflection of milestones in scientific discoveries and technical advancements. The history of TURBT is indeed a story of modern industrial development and the success of various innovative inventions.

Earliest documented surgeries for removal of bladder tumours were dated back in the sixteenth and seventeenth century. Franco and Couillard removed tumours in open suprapubic approaches in 1561 and 1639 respectively. Removal of bladder tumours blindly through the urethra has also been reported. Early operations were mainly limited in women, in which bladder neck or urethral tumours were grasped and amputated (Herr 2006). Before the invention of endoscopy, diagnosis and treatment of bladder tumours were very limited.

Thanks to the inventors of endoscope, endoluminal visualization of bladder becomes possible. Philipp Bozzini (1773–1809) used candle light as an external light source, and illuminated the bladder through a metal tube. However, the design was criticised to be unpractical. It was further optimized by Antonin Jean Desormeaux (1815–1894). Alcohol lamp was used instead of candle, and concave mirror was used for reflection. His cystoscope was regarded as more usable. The improved vision allowed simple endoscopic operation such as chemical cauterization and extraction of urethral papillomas. Another breakthrough was achieved by a Hungarian urologist, Josef Grunfeld (1840–1912), who equipped a set of simple endoscopic instruments to his urethroscope. He was the first to report removal of a bladder papilloma endoscopically (Herr 2005; European Museum of Urology 2017).

A significant problem which hindered further development of endoscopic diagnosis or treatment was the small field of vision. This problem had been tackled by Maximilian

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Nitze, who revolutionised the design of cystoscope and was widely regarded as the father of modern cystoscope. He had invented multiple refinements to the existing cystoscope. He recognised that in order to improve cystoscopic vision, the light source must be brought inside the bladder. Therefore, a built-in light source was subsequently designed. The bladder interior could always be illuminated in a bright light no matter how the instrument was angled and manipulated. Initially a galvanized platinum wire was adopted as light source, later it was modified into a miniaturized light bulb after Edison's invention of electric light bulb. More importantly, the field of vision was also expanded by using optical microscopy technology (Nezhat n.d.; European Museum of Urology 2017).

Apart from the important contributions in cystoscopy, Nitze was also one of the pioneers in transurethral bladder tumour treatment. He created an operating cystoscope by equipping the cystoscope with a platinum wire loop and galvanocautery. A 150 cases of successful endoscopic treatment of bladder tumours by cutting and coagulating the bladder tumours with wire loop were reported. This result was remarkable and had inspired Edwin Beer, another brilliant inventor and urologist, to modify the surgery and bring endoscopic surgery forward. Beer was the first to utilize high frequency electric current to cauterize bladder tumours, employing similar electrocauterization technique for treatment of skin warts by Oudin (Beer 1983). He used a Nitze cystoscope with two channels, one for the insertion of an insulated copper electrode and another for irrigation. Tumour was fulgurated by applying direct current at the tumour surface. This technique was a very influential discovery, and it is still being used nowadays for effective treatment of small papillary growths (Beer 1983; Herr 2005).

The prototype of modern resectoscope was created and optimized by Maximilian Stern (1843–1946), Theodore Davis (1889–1973) and Joseph McCarthy (1874–1965) (Surgeons TBAoU Virtual Museum Resectoscopes n.d.). The first resectoscope had been introduced by Stern. Its major problem was failure of deep coagulation. It was subsequently refined by Davis, who incorporated both cutting and coagulation current in the instrument. A foot pedal was also invented which allows switching of the electrical current by the surgeon intra-operatively. McCarthy had further improved the design and encased the instrument into non-conducting Bakelite sheath. This resectoscope was also known as the Stern-McCarthy resectoscope. It had swiftly replaced Beer's fulguration and had been popularised among urologists internationally. Subsequent modifications happened but they largely followed the prototype of Stern-McCarthy design. Since then, TURBT with resectoscope has become the cornerstone for endoscopic treatment of bladder cancer (Nezhat n.d.; Surgeons TBAoU Virtual Museum Resectoscopes n.d.).

11.2 Standard TURBT

TURBT remains as the standard in the initial management of bladder tumours. In terms of diagnosis, it can ascertain the pathological diagnosis, local staging and tumour grading. Therapeutically, it may cure non-muscle-invasive bladder cancers (NMIBC) (Herr 1987), palliate symptoms for bleeding tumours and play an important role in multi-modal bladder sparing treatment for muscle-invasive bladder cancer (Ploussard et al. 2014). Upon TURBT, we aim to remove all endoscopically visible tumours and sample detrusor muscle for assessment of any muscle invasion. Presence of detrusor muscle in the pathological specimen serves as a surrogate marker for the quality of resection (Mariappan et al. 2010). TURBT is a very common urological procedure, which is in general easy to learn but difficult to master (Herr and Donat 2008). It is indeed important to perform the procedure properly, and it has a strong influence on the tumour recurrence rate (Brausi et al. 2002).

11.2.1 Preoperative Preparations

The general condition of the patient should be assessed. Patients with poor mobility should be carefully examined for lower limb contracture. Presence of severe lower limb contracture and hip joints diseases would render lithotomy position difficult.

Comprehensive anaesthetist assessment is essential. Blood tests should be taken to assess the serum haemoglobin, platelet count, serum creatinine, electrolyte and clotting profile. Urine culture should be saved prior to operation. Presence of bacteriuria should be treated to reduce chance of postoperative infections (Badenoch et al. 1990). Upper tract imaging with computer tomography urogram should be considered to detect synchronous upper tract urothelial cancers (UTUC). The incidence of concomitant UTUC is general low at 1.8%, however, the risk increases in patients with multiple or trigonal tumours (Palou et al. 2005).

Locations of bladder tumours should be reviewed. Liaison should be sought with anaesthetists to arrange either general anaesthesia with muscle relaxant or spinal anaesthesia with obturator block for lateral wall tumours to reduce occurrence of obturator jerk. Sudden adductor contraction may potentially lead to inadvertent bladder perforation (Augspurger and Donohue 1980).

11.2.2 Operating Procedures

Prophylactic antibiotics should be given upon induction of anaesthesia (Alsaywid and Smith 2013). A dorsal lithotomy position is adopted. Ensure pressure points are well padded and avoid excessive hip flexion or rotation to prevent femoral or peroneal nerve palsy.

Bimanual examination of the pelvis has a vital role in assessing the clinical stage. It should be performed before and after surgery, and the surgeon should assess for any extra-vesicle disease and tumour fixation, which corresponds to T3 and T4 diseases respectively (Rozanskia et al. 2015).

A thorough cystoscopic examination is necessary. Use 30° and 70° lens to examine the urethra, prostate, bladder and ureteric orifice completely. Number, locations, morphology, size of bladder tumours and any involvement of the ureteric orifice should be documented. Either monopolar or bipolar resectoscopes can be used for resection with 1.5% glycine or 0.9% saline as irrigant respectively. Conventionally, the exophytic portion of the bladder tumours are first resected in a piecemeal manner (Babjuk et al. 2017). The resection width and depth have practical implications for tumour staging and treatment. Appreciation of the ideal resection extent requires considerable judgement, experience and skill (Herr and Donat 2008).The underlying bladder wall and the edges of the resection area should also be resected and sent separately to provide information about the vertical and horizontal extent of the tumour (Richterstetter et al. 2012).

Extra caution should be paid when resecting large tumours and tumours which are located at the bladder dome region, as the risks of extraperitoneal and intraperitoneal perforation are higher, and may necessitate laparotomy for bladder repair (Balbay et al. 2005). Overdistention of bladder should be avoided, as it may cause thinning of bladder wall and increase chance of inadvertent perforation (Wein et al. 2012). Some anterior wall or dome tumours may require simultaneous suprapubic compression to position tumours within your range of resection. This requires one hand manipulation of the resectoscope and beginners may find it difficult. In any difficult circumstances, assistance from scrub nurses could always be sought to perform the suprapubic compression.

Occurrence of obturator jerk during resection of lateral wall tumours could result in bladder perforation (Augspurger and Donohue 1980). Meticulous technique and rigorous attention are required to avoid excitation of obturator nerves. As mentioned previously, for bladder tumours which are located at the lateral wall, anaesthetist should be liased for spinal anaesthesia with obturator nerve block or general anaesthesia with muscle relaxant. Resection can be performed at lower energy with an intermittent burst technique to reduce chance of obturator jerk (Wein et al. 2012; Blandy and Reynard 2005). The use of bipolar energy may reduce obturator jerk by localized current, however, one should be aware that obturator jerk may still occur despite use of this energy source (Gupta et al. 2011; Ozer et al. 2015).

Perform biopsy on any suspicious erythematous velvety mucosa which may represent carcinoma in situ (CIS). Routine random biopsy is not recommended as the yield of detecting CIS is low. Consider random biopsy if there is a positive urine cytology but negative cystoscopy, or if endoscopic features of the bladder tumours are suggestive of high risk disease (Wein et al. 2012). Prostatic urethral involvement is an important prognostic factor for disease recurrence and progression (Palou et al. 2012), and urethrectomy may be indicated in patients with muscle-invasive bladder cancer contemplating cystectomy. Urethral biopsy should be taken at the prostatic urethra and the precollicular area in high risk cases such as trigone tumour or bladder neck tumour, multiple tumours or presence of CIS (Mungan et al. 2005).

Hemostasis should be ascertained before concluding the surgery. Distention and decompression of the bladder may reveal any occult bleeders. Complete the operation with a bimanual examination of pelvis. Any persistence of pelvic mass may indicate a T3 or above disease. Urethral catheter should be inserted and adjuvant chemotherapy instillation should be given if complete tumour resection can be achieved endoscopically without any evidence of bladder perforation.

11.3 Post-operative Adjuvant Treatment

Single instillation of intravesical chemotherapy in the immediate postoperative period has been shown to eliminate circulating tumour cells and have a chemoresection effect on any residual cancer cells in the previous resection sites (Oosterlinck et al. 1993; Brocks et al. 2005). Numerous agents including epirubicin, pirarubicin, thiotepa, gemcitabine and mitomycin C are all effective as adjuvant treatment (Oosterlinck et al. 1993; Brocks et al. 2005; Pan et al. 1989; Sylvester et al. 2016).

Extensive research has been conducted to study the efficacies of these agents. Several large meta-analyses have proven that TURBT with single instillation of chemotherapy could disease recurrence as compared to TURBT alone (Abern et al. 2013; Sylvester et al. 2016; Perlis et al. 2013). Timing of instillation is also crucial. Ideally, it should be instilled within the first few hours after the operation, as floating tumour cells may reimplant to the bladder wall and could be covered with extracellular matrix afterwards (Pode et al. 1986; Bohle et al. 2002). Immediate instillation after urethral catheterization inside the operating theatre can be considered, however, this has to be balanced with concerns of occupational hazard, logistics of drug administration and drug disposal. Contraindications of intravesical instillation of chemotherapy include allergy, extensive resection, bladder perforation, pregnancy, lactating women and macroscopic residual diseases (AUA policy statements. Intravesical Administration of Therapeutic Medication 2015. Available from: http://www.auanet.org/guidelines/intravesical-administration-of-therapeutic-medication; Wein et al. 2012).

Table 11.1 EAU risk group stratification

Risk group stratification	Characteristics
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG), <3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low- and high risk)
High-risk tumours	Any of the following: • T1 tumour • G3 (HG) tumour • Carcinoma in situ (CIS) • Multiple, recurrent and large (>3 cm) TaG1/G2/LG tumours (all features must be present)
	Subgroup of highest risk tumours:
	T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, lymphovascular invasion

A recently published meta-analysis showed that patients with a European Organisation for Research and Treatment of Cancer (EORTC) recurrence score ≥5 and/or patients with a prior recurrence rate of >1 recurrence per year, single instillation was not effective and should not be used (Sylvester et al. 2016).

Intravesical chemotherapy has also been utilized as a maintenance treatment. The exact treatment regimen, duration of chemotherapy depends on the risk stratification of bladder cancer. European Association of Urology (EAU) risk group is adopted for reference (Table 11.1). For low-risk diseases, only single dose of immediate post-operative instillation of chemotherapy is needed and further instillations are not beneficial (Sylvester et al. 2016). For intermediate-risk cases, maintenance chemotherapy up to 1 year has been shown to improve recurrence-free survival (Tolley et al. 1996) and can be considered. The ideal duration and schedule of chemotherapy, however, remains unknown because of conflicting data (Sylvester et al. 2008). For high-risk cases, maintenance chemotherapy is not preferred and intravesical bacillus Calmette-Guérin (BCG) immunotherapy is recommended (Babjuk et al. 2017).

Several methods have been proposed to improve the efficacy of chemotherapy. The drug concentration can be increased by pharmacokinetic modifications to decrease urine volume and to alkalinize urine. This has been reported to result in a longer time to recurrence, and an improved 5-year recurrence-free survival (Au et al. 2001). Few data are available for using microwave-induced hyperthermia and electromotive drug administration as adjunct (Di Stasi et al. 2006; Arends et al. 2014). Currently these methods have not been popularised and further large scale studies are required to confirm their efficacies.

11.4 Role of Second TURBT

Conventionally, TURBT is performed in a piecemeal manner with a top-down approach. Whether the bladder tumor is completely resected is dependent on the operating surgeon's judgement intra-operatively. Unfortunately, this judgement is prone to error and relies greatly on the surgeons' resection technique and past experiences. In a prospective study (Mariappan et al. 2012) comparing between senior surgeons (including consultant and trainees in year 5 or 6) and junior surgeons (trainees below year 5), senior surgeons were more likely to obtain detrusor muscle in the specimen (OR = 4.9, 95% CI 2.3–10.7, $p < 0.001$) and were associated with a lower recurrence rate at the first follow up cystoscopy (OR = 5.3, 95% CI 2.1–12.9, $p < 0.001$). This highlighted the importance of quality control in performing TURBT (Herr and Donat 2008).

Second TURBT following an initial 'complete tumour resection' has been advocated in selected groups of patients with NMIBC. There are several goals in performing second TURBT. First, we aim to resect any residual Ta or T1 disease. In patients with Ta high-grade disease, residual disease could be detected in 37.9–59.5% of them upon second TURBT (Lazica et al. 2014; Gendy et al. 2016); in patients with T1 disease, residual disease could be detected in 25.7–71.3% of them upon second TURBT (Gendy et al. 2016; Hashine et al. 2016; Vasdev et al. 2012; Gontero et al. 2016; Divrik et al. 2010). Second, we aim to detect any under-staged T2 disease. In patients with Ta high-grade disease, upstaging of disease is rare and was only reported in up to 2.7% of them (Lazica et al. 2014; Gendy et al. 2016). However, in patients with T1 disease, upstaging of disease was reported in up to 14.6% of them (Vasdev et al. 2012; Gontero et al. 2016; Hashine et al. 2016; Gendy et al. 2016; Divrik et al. 2010). In particular, for patients with T1 disease without detrusor muscle in the first TURBT, upstaging of disease was much higher than those with detrusor muscle (25% vs. 4.5%) (Gendy et al. 2016). To a certain extent, the presence of detrusor muscle in the specimen reflects whether appropriate depth of resection has been achieved during TURBT and it is important for local staging of the disease. Third, we aim to enhance the efficacy of intravesical BCG. In a retrospective study on 1021 patients with NMIBC receiving intravesical BCG (Sfakianos et al. 2014), patients with a single TURBT had a recurrence rate of 44.3% compared to 9.6% in patients with second TURBT being performed.

Second TURBT has become the cornerstone in the management of NMIBC. In the only randomized controlled trial investigating the role of second TURBT in patients with T1 disease, second TURBT has been shown to improve recurrence-free survival, progression-free survival and disease-specific survival. Second TURBT is indicated in patients with incomplete tumour resection during first TURBT, in patients with T1 disease, and when there is no detrusor muscle in the first TURBT specimen with the exception of Ta low-grade tumours and primary carcinoma-in-situ (Babjuk et al. 2017). When indicated, second TURBT should be performed within 2–6 weeks after first TURBT, as a delay in second TURBT has been shown to be a risk factor of both disease recurrence and progression (Baltaci et al. 2015).

11.5 New Developments that May Improve the Treatment Outcomes of TURBT

A number of new developments have been investigated and applied to our clinical practice in the past decade. They include the use of enhanced imaging during TURBT, use of alternative energy sources and en bloc resection of bladder tumour.

11.5.1 Enhanced Imaging During TURBT

Undetected bladder tumour upon TURBT may lead to 'early disease recurrence'. In order to facilitate bladder tumour detection, the use of photodynamic diagnosis (PDD) and narrow-band imaging (NBI) have been investigated in high-quality studies previously.

11.5.1.1 Photodynamic Diagnosis

The principle of PDD is based on the preferential accumulation of a photosensitizing compound in neoplastic cells that emits a fluorescence upon blue-violet excitation (Kausch et al. 2010). This can be achieved after intravesical instillation of 5-aminolevulinice acid (ALA) or hexaminolevulinic acid (HAL) for 1 h and using violet light during cystoscopy.

A number of studies have investigated the role of PDD in the management of NMIBC. Concerning the use of ALA during TURBT, meta-analyses have shown that it could significantly reduce residual disease and improve recurrence-free survival when compared to white light alone (Kausch et al. 2010; Mowatt et al. 2011). However, two subsequent randomized controlled trials failed to demonstrate any significant benefit of ALA in recurrence-free survival and progression-free survival (Stenzl et al. 2011; Schumacher et al. 2010). Concerning the use of HAL, a meta-analysis based on raw data from prospective studies showed that HAL could significantly reduce recurrence rate when compared to white light alone (Burger et al. 2013). One subsequent randomized controlled trial on the use of HAL-assisted TURBT showed similar benefit (Mariappan et al. 2015), but another trial showed no significant reduction in disease recurrence (O'Brien et al. 2013). Further trials are needed to investigate the value of PDD, be it ALA or HAL, in particular for important outcomes including progression-free survival and disease-specific survival. One should also be aware of the possible false-positive results due to inflammation, recent TURBT and BCG therapy (Draga et al. 2010; Ray et al. 2010).

11.5.1.2 Narrow-Band Imaging

In NBI, white light is being filtered into two bandwidths of 415 and 540 nm, which can only penetrate urothelium superficially and are strongly absorbed by hemoglobin. This can therefore enhance the contrast between normal urothelium and hypervascular cancer tissue and facilitate detection of subtle urothelial abnormalities.

A meta-analysis showed that NBI cystoscopy could yield a higher diagnostic accuracy than white light cystoscopy (Zheng et al. 2012). More recently, a multi-centre randomized trial comparing between NBI-assisted TURBT versus white light imaging-assisted TURBT has been conducted (Naito et al. 2016). In this randomized trial, 965 patients were included, with 481 patients in the NBI group and 485 patients in the white light group. Overall, no significant differences in the 1-year recurrence rates were detected between the two groups. However, upon the subgroup analysis on low-risk patients, NBI-assisted TURBT was found to significantly improve 1-year recurrence rate from 27.3% to 5.6% ($p = 0.002$). Therefore, NBI can be considered to assist TURBT in patients with presumably low-risk features. Compared to PDD, NBI can be performed more conveniently as no intravesical instillation is necessary before hand.

11.5.2 Bipolar TURBT

Conventionally, TURBT is performed using monopolar energy. However, when monopolar energy is applied, the electrical resistance creates a high temperature up to 400 degrees with collateral tissue damage (Singh et al. 2005). This results in a significant charring effect which may hinder further resection of the adjacent tissue. This led to the utility of bipolar energy in performing TURBT. By converting the conductive medium into a plasma field of highly ionized particles, organic molecular bonds can be disrupted readily and resection can be achieved in a more precise manner (Teoh et al. 2016).

There are three well-designed randomized controlled trials evaluating the use of bipolar energy in performing TURBT. When compared to monopolar TURBT, bipolar TURBT has been shown to be associated with higher detrusor sampling rate, fewer incidence of cautery artifacts, shorter catheterization time and shorter hospital stay (Venkatramani et al. 2014; Del Rosso et al. 2013; Teoh et al. 2017). In a recent meta-analysis (Zhao et al. 2016), bipolar TURBT has also been shown to be associated with less blood loss, fewer incidence of obturator nerve reflex and bladder perforation. In addition, bipolar TURBT could result in a lower recurrence rate at 2 years (Zhao et al. 2016). Therefore, the use of bipolar energy can be considered in patients undergoing TURBT.

The use of bipolar system requires additional costs and resources. However, in a propensity score-matched comparative study (Sugihara et al. 2014), taking into account the type of operation being performed, the peri-operative complications and duration of hospital stay, the calculated mean costs were USD 4628 for one bipolar TURBT procedure and USD 4727 for one monopolar TURBT procedure. The cost reduction following bipolar TURBT was 1.1% and it was statistically significant ($p = 0.034$). The authors concluded that the use of bipolar TURBT could reduce cost in treating patients with bladder tumours.

11.5.3 En Bloc Resection of Bladder Tumour

Due to the size limitation of the urethra, TURBT is conventionally performed in a piecemeal manner. However, this renders histological assessment of resection margin impossible. Complete tumour resection as judged by the operating surgeon is often inaccurate, and residual disease may lead to 'early disease recurrence'. Moreover, piecemeal resection causes tumour fragmentation. Floating tumour cells may re-implant into the bladder wall causing multiple early tumour recurrences. While the recurrence rates of NMIBC following TURBT were high, ranging from 15% to 61% at 1 year and 31% to 78% at 5 years, the concept of en bloc resection has been proposed in the hope of ensuring complete tumour resection and minimizing chance of tumour re-implantation (Ukai et al. 2000).

A number of energy sources including monopolar electrocautery, bipolar electrocautery, holmium laser, thulium laser and HybridKnife system have been used in performing en bloc resection (Kramer et al. 2015; Islas-Garcia et al. 2016); neither of them has shown superiority over the other in clinical trial settings. Based on the authors' experiences, there are a few potential differences between the energy sources. For example, using bipolar energy allows a more precision incision and may be technically easier than monopolar energy in performing en bloc resection. The occurrence of obturator nerve reflex may be reduced by using bipolar energy, and can be completely eliminated by using holmium or thulium laser. HybridKnife system may allow easier identification of the dissection plane by lifting up the mucosal with saline injection. However, whether such maneuver has any impact on detrusor muscle sampling and its potential implications are unknown. While more studies are needed to define the best energy source for en bloc resection, the availability of resources and the operating surgeons experiences and preferences are probably more important.

As en bloc resection aims to remove the bladder tumour in one piece via the urethra, there is a limitation in the maximal size of bladder tumour that can be handled. Based on the authors' experiences, bladder tumours with maximal dimension of 3 cm can be removed readily, although removal of tumour up to 4.5 cm has been reported (Naselli et al. 2012). On the other hand, as en bloc resection is intended to treat NMIBC, most of them are smaller tumours which should be amenable to this approach. Therefore, despite its limitation, en bloc resection should be a technically feasible option for most patients with bladder tumours.

A meta-analysis showed that en bloc resection was associated with shorter catheterization time and hospital stay, lower incidence of obturator nerve reflex and bladder perforation, and lower recurrence rate at 24 months. However, among the seven studies being included, there was only one single-centre randomized controlled trial, and other studies were either retrospective or prospective non-randomized studies. There was another single-centre randomized controlled trial comparing between thulium laser en bloc resection and TURBT, which failed to demonstrate significant differences in disease recurrence. Large-scale multi-centre randomized controlled trial are needed to investigate whether the theoretical benefits of en bloc resection could translate into clinical significance in terms of disease recurrence, progression and survival outcomes.

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