REVIEW

Transurethral Resection of Bladder Tumor: Novel Techniques in a New Era

Shengkun Sun†, Hengen Wang†, Xu Zhang ,Guangfu Chen*

Department of Urology, Chinese PLA General Hospital

†These authors contributed equally to this work.

***Corresponding author:** Guangfu Chen: chenguangfu@301hospital.com.cn

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Abbreviation used: TURBT: transurethral resection of bladder tumor; ERBT: en-bloc resection of bladder tumors; NMIBC: non-muscle-invasive bladder cancer; ONR: obturator nerve reflex; WLC: white light cystoscopy; BLC: blue light cystoscopy; NBI: narrow-band imaging; PDI: photodynamic imaging; PC: partial cystectomy; MIBC: muscle-invasive bladder cancer; S-scope: super scope; STURBT: super transurethral resection of bladder tumor

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ABSTRACT

Transurethral resection of bladder tumor (TURBT) serves both diagnostic and therapeutic purposes in the management of bladder cancer. Attaining a high-quality TURBT is not always guaranteed due to various factors. *En-bloc* resection of bladder tumors (ERBT) holds promise to be a primary technique for removing bladder tumors in most non-muscle invasive bladder cancers. However, so far, no conclusive evidence indicates the superiority of any specific energy source used for ERBT. While laser energy can prevent the activation of obturator nerve reflex during ERBT, it poses challenges such as thermal injury and imprecise controllability. Needle-shaped electrodes offer high-level precision and controllability, without causing tissue deterioration or vaporization. The primary limitation of ERBT at present is the extraction/harvesting of large *en-bloc* specimens. Effective tools have been developed to overcome this limitation. Enhanced cystoscopy improves the detection of flat and small bladder tumors, allowing for better removal of cancerous tissues and significantly reducing recurrence rates. Advances in medical technology have brought forth a multitude of strategies to address the shortcomings of traditional TURBT. Appliances with large operating channel provide a platform for conducting laparoscopic procedures within the context of pneumocystoscopy, facilitating the execution of super TURBT and conferring comparable advantages to *en-bloc* resection. Moreover, the utilization of pneumocystoscopy enables the safe and effective performance of transurethral partial cystectomy for localized muscle-invasive bladder cancer. Novel techniques significantly improve the precision of the transurethral surgery and lower the risk of complications.

Keywords: transurethral resection of bladder tumor, bladder cancer, super TURBT, partial cystectomy

Bladder cancer represents one of the most prevalent cancers across the globe. Approximately, 75% of the cases fall into the category of non-muscle-invasive bladder cancer (NMIBC), which encompasses Ta, T1, and Tis (tumor *in situ*) [1]. The standard treatment for NMIBC is transurethral resection of bladder tumors (TURBT) plus adjuvant intravesical chemotherapy [2].

TURBT, which employs a wire loop, is regarded as the cornerstone and gold standard for staging and treating NMIBC since the 1910s [3]. Nevertheless, the piecemeal resection, the potential scattering of tumor cells, and the absence of detrusor muscle in the resected specimen are believed to be drawbacks of the conventional TURBT [4,5]. This resection technique is not in line with the fundamental principles of oncological surgery, *i.e.*, efficient diagnosis and treatment of bladder cancer. In recent years, advances in medical technologies, including surgical techniques and instruments, micro or small tumor imaging, have introduced multiple methods to tackle shortcomings of traditional TURBT.

1. *EN-BLOC* RESECTION

Both monopolar and bipolar TURBT involve piecemeal resection of the tumor in layers by repeatedly moving the cutting loop back and forth, which carries the risk of tumor seeding. A high-quality resection should be the first and foremost consideration in the primary management of NMIBC. Efforts to completely remove bladder tumors date as far back as 1980, when a polypectomy snare was first used [6]. *En-bloc* resection of bladder tumors (ERBT) is a more recent development that has been introduced to overcome the limitations of conventional TURBT. Complete *en-bloc* resection was not accomplished until

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the introduction of *en-bloc* resection techniques as described by Kawada *et al*. in 1997 [7].

1.1 EBRT provides high quality specimen

Several reasons can explain why EBRT allows for high-quality transurethral resection and precise pathological analysis: (1) enabling a more accurate and controlled resection that may reduce the incidence of complications; (2) providing better sample orientation for precise histopathological analysis; (3) obtaining the detrusor in the resected specimen, if necessary.

The *en-bloc* technique involves making an incision on the surrounding mucosa with a safety margin to detach the tumor in one piece. Teoh *et al*. conducted a review of 10 randomized controlled trials that compared ERBT with TURBT [8]. Their findings indicated that ERBT was associated with a longer operation time than TURBT, but a shorter irrigation time and lower risk of bladder perforation. In a comparative study, classical TURBT in combination with ERBT using hydrodissection were both assisted by photodynamic diagnosis using hexaminolevulinate [9]. The study reported a higher presence of detrusor muscle in the resected specimen in the *en-bloc* group (86% vs. 63%). Kramer *et al*. compared electrocautery (monopolar or bipolar) and laser (holmium or thulium) ERBT and found no significant difference between the two approaches in terms of clinically-relevant complications, availability of detrusor muscle, irrigation time, or catheterization time [10].

1.2 Oncological effect of ERBT compared with conventional TURBT

ERBT can decrease the likelihood of tumor seeding onto normal urothelium caused by tumor fragments. Three relatively small studies have reported a decreased recurrence rate with ERBT as compared to conventional TURBT at 3 to 39 months of follow-up [11,12,13]. However, three other comparative studies failed to find any significant difference in the recurrence rate at 3 to 18 months of follow-up [14,15,16]. It is worth noting that the evaluation of recurrence is subject to a wide array of factors, such as heterogeneous risk stratification, intravesical treatment regimens, and follow-up protocols. The initial pathological studies suggested a higher inter-observer concordance and longer analysis time for ERBT specimens than for their TURBT counterparts, along with the possibility of improved sub-staging in T1 disease [17]. Additionally, a second translational study reported a higher level of circulating tumor cells following TURBT compared to ERBT [18]. Various techniques such as loop modifications, laser techniques, and water-jet-based enucleation have been suggested as potential options [19,20,21,22]. However, the superiority of any particular energy source in ERBT over others has not been definitively confirmed.

1.3 Laser energy during ERBT

Several laser subtypes have been utilized for ERBT, and, as aforementioned, no clear superiority has been established amongst them. Literature search identified no instances of obturator nerve reflex (ONR) [23,24,25]. Additionally, various comparative studies have reported a statistically significant reduction in the occurrence of ONR and bladder perforation rates with the use of laser against conventional TURBT [26,27]. The utilization of laser energy sources may suppress activation of ONR, thus allowing for the safe resection of lesions via a lateral-wall approach.

While laser fiber is a valuable tool for TURBT, it has some shortcomings that must be addressed. At first, the limited availability of adequate tissue for pathological examination presents a major limitation to the laser treatment of bladder cancer, which restricted its application in the treatment of bladder tumor. However, with the advent of holmium laser technology, *en-bloc* resection of bladder tumors is now feasible, providing sufficient tissue for histological examination. Specifically, holmium and thulium lasers are most suitable for ERBT procedures due to their shallow penetration depths (0.4 mm and 0.2 mm, respectively) and excellent hemostatic property [28]. Another shortcoming of laser fiber during TURBT is its potential to cause thermal injury to the surrounding tissue. The high temperatures generated by the laser fiber can cause tissue damage, leading to complications such as bleeding, perforation, and scarring [29]. Furthermore, laser fibers are less effective in removing larger tumors, which may entail multiple surgeries or additional treatment. In addition, the end-firing laser fiber can be cumbersome to manipulate during the excision process.

1.4 Needle-shaped electrode during ERBT

The use of needle-shaped electrodes during ERBT can offer a high degree of controllability and precision, allowing for accurate orientation of the extracted specimen [30]. This application may also increase the likelihood of obtaining detrusor muscle samples, resulting in more accurate pathological staging. What is more, the transurethral needle electrode resection involves removal of the tumor base from the periphery to the center, with bleeding vessels coagulated during the process.

Electric energy is widely used in TURBT. However, the use of electric energy can elicit the obturator nerve reflex and cause related injury, which has been deemed a major obstacle during the procedure. A number of methods have been reported to address this issue [31,32,33]. Nonetheless, despite the endeavor, up till now, no reliable methods have been found to completely eliminate the obturator nerve reflex. Though reports suggested several advantages of bipolar TURBT, such as a reduction in obturator nerve related injury [34], we have observed occurrences of ONR in treating tumors nested in the lateral bladder wall. Furthermore, a recent systematic review and meta-analysis comparing bipolar and monopolar TURBT did not find any statistically significant differences between them in the rates of obturator nerve reflex, bladder perforation, and transfusion [35].

The needle-shaped electrode resection includes blunt dissection to the muscularis layer, followed by dissection within the muscularis layer using retrograde or combined retrograde-antegrade approaches, by means of energy and/or blunt dissection. With this technique, the crucial step is to insert the needle tip into the muscle layer, detach the muscle bundles away from the lateral bladder wall, and then cut them using the electroresection, to fully eliminate ONR. This dissection continues until the tumor is lifted free of the base *en-bloc*. The needle-shaped electrode resection seems to enhance the quality of TURBT since it is in compliance with the oncological principle of excising malignant tissue '*en-bloc*' while ensuring a tumor-free resection margin. In particular, the presence of detrusor muscle (except in TaG1/LG tumors) is a vital determinant of the quality of resection and serves as a surrogate marker for this purpose. The needle-shaped electrode can achieve a single intact specimen containing lamina propria ± muscularis propria fibers [30].

1.5 Tumor Retrieval after ERBT

The primary limitation of ERBT, at present, is the inability to extract large *en-bloc* specimens. Several techniques have been employed to address this limitation. For small-sized tumors (less than 3 cm), evacuation can be done through the resectoscope sheath, or by using a standard Ellik evacuator [36,37,38]. However, retrieval of larger specimens (3-4 cm in size) can be challenging, entails division within the bladder prior to extraction, and may require use of special tools to retrieve via a nephroscope sheath by using laparoscopic forceps or an Endo-catch specimen retrieval bag [39,40].

We have developed a reliable and effective device for tumor retrieval used in bladder surgery. The device, named β basket, is composed of four memory nitinol steel wire silks that can stretch out to a diameter of 5 cm inside the bladder. By using the β basket, tumors cut free can be captured with ease [41]. *En-bloc* retrieval is possible with small tumors, but for larger-sized tumors, it is not feasible due to the narrow urethral passage during transurethral resection. In such cases, the tumors can be split into two to three pieces by pulling the basket, thereby allowing for sub-en-bloc retrieval. This method provides a more efficient and reliable option for tumor removal. Although subdividing large tumors may not be as easy as removing them intact, it is still a strategy that is superior to traditional TURBT, where the tumor is chopped into numerous small pieces by using a loop. In the cases where large and solid tumors are difficult to divide, they can be fragmented using a pulverizator, which may damage the tumor's structure. However, the tumor base can still be conserved and retrieved through the sheath for further pathological analysis.

2. ENHANCED CYSTOSCOPY: A PROMISING WAY TO DECREASE THE RECURRENCE RATE

Bladder cancer is a malignancy notorious for its high recurrence rates, which can reach up to 80% [42]. This high frequency of recurrence often necessitates retreatment, resulting in lifetime treatment and a financial burden that is among the highest of all cancers [43]. The biological features of bladder cancer, such as multiple foci, can contribute to this high recurrence rate. However, it is also important to consider the potential role of various diagnostic steps in this process. Further investigation into the factors that contribute to the high recurrence rate of bladder cancer is warranted, as it may inform the development of more efficacious treatment strategies for this disease. Regular white light cystoscopy (WLC) carries the risk of missing mainly flat lesions [44], which may result in vital tumor going undetected and untreated, eventually leading to progression of the disease. Inadequate tumor clearance can lead to early recurrence and inaccurate staging of the cancer, which highlights the need to improve techniques to ensure complete resection of the tumor. The development of new visualization and detection techniques is of paramount importance since tumors composed of hundreds of tumor cells that are beyond the detection limits of current techniques may re-emerge within several months after operation.

Enhanced cystoscopy may include procedures such as blue light cystoscopy (BLC), narrow-band imaging (NBI), and other methods that utilize contrast agents to visualize abnormal areas in the bladder. Enhanced cystoscopy has been shown to improve the detection of bladder cancer, particularly for flat and small tumors that may be missed during traditional cystoscopy [45,46]. NBI or BLC is often used in conjunction with WLC to improve detection of bladder tumors, ensuring the resection of all macroscopic lesions, including overlooked small tumors. NBI and BLC rely on distinct light wavelengths that accentuate various aspects of bladder tissues, facilitating the identification of abnormal regions that may have been missed with use of WLC alone. Studies have demonstrated that the use of these techniques, primarily BLC, improves the detection rate of smaller tumors and reduces the rate of recurrence, thereby achieving more favorable outcomes for bladder cancer patients. NBI works by restricting the bandwidth of the emitted light to penetrate different depths. By allowing only the wavelengths 415 and 540 nm to permeate, NBI enhances the contrast between the superficial mucosa and microvascular structures [47]. According to a meta-analysis by Xiong *et al*., NBI has been found to improve tumor detection rates relative to WLC, with a pooled additional detection rate of 9.9% [48]. Another meta-analysis by Kang *et al*. revealed that NBI-guided TURBT had a pooled recurrence rate (RR) of 4.6% and 26.0% at month 3 and 12 months, respectively. In contrast, patients who underwent WLC-guided TURBT yielded a pooled recurrence rate of 16.7% and 38.6% during the same time intervals [49]. Geavlete and colleagues demonstrated that the specificity of identifying *in situ* carcinoma was significantly higher with NBI compared to WLC (53.8% versus 15.4%). However, a potential risk of over-treatment associated with the use of NBI was also reported by Geavlete BF. The rate of false positive biopsies, for Ta as well as T1 tumors (pTa: 14.3% vs. 9.6% and pT1: 8.1% vs. 5.1% respectively), was elevated by the use of NBI [50]. Additionally, some experimental approaches such as optical coherence tomography [51], confocal laser endomicroscopy [52], and red-green-blue analysis of WLC [53], are under investigation, with attempts to improve detection accuracy.

The latest advances in intraoperative imaging include photodynamic imaging (PDI), which have shown some promising results. Currently, two substances have been confirmed to act as a photosensitizer, namely 5-aminolevulinic acid and its derivative hexaminolevulinate, with only the latter receiving approval for clinical application. These substances accumulate within the tumor cells and metabolize to protoporphyrin IX, resulting in the tumor fluorescing red under blue light [54]. It is recommended to employ enhanced cystoscopic techniques, whenever available, as they may assist in achieving complete resection of the tumor. Similar to NBI, PDI is also associated with a higher false positive rate, leading to additional unnecessary TUR biopsies. In a study by Gallagher *et al*., 153 out of 345 patients received a "good quality" WLC-TURBT, while 192 underwent a "good quality" PDI-TURBT. The time to recurrence was significantly longer in PDI group compared to WLC group (PDD: 52.9 vs. WLC: 42.4 months, P=0.001), and the recurrence rate (RR) after one year was significantly lower with PDI compared to WLC (21.5% vs. 38.9%, P=0.001), and three years later (39.0% vs 53.3%, P=0.02) [55].

3. TRANSURETHRAL PARTIAL CYSTECTOMY (PC) FOR LOCALIZED MIBC

Although maximal or complete TURBT is frequently discussed, there are no significant differences between these techniques and traditional TURBT in essence. The efficacy of TURBT cannot be compared to that of PC, which is mainly used to remove the tumor and its surrounding tissues according to pathological conditions, such as lesion size and infiltration range [56,57]. PC has been gaining attention as a potential alternative to radical cystectomy for T1 high-grade and sometimes T2 bladder cancer. PC may have several advantages over more radical surgical interventions. It may result in improved psychological well-being and reduced risk of complications, such as urinary incontinence and sexual dysfunction, as compared to radical cystectomy. Furthermore, with progression of in surgical techniques and technologies, it may be a viable option for selected patients seeking to preserve bladder function.

Formerly, PC experienced a resurgence. However, careful patient selection, surgical expertise, and postoperative management are required to ensure optimal outcomes and to minimize complications. A growing body of literature has argued that PC might be a viable alternative to RC for select muscle-invasive bladder cancer (MIBC) patients [58,59]. However, some critics of PC proclaimed that PC was an incomplete cancer operation that carries a significant risk of recurrence for MIBC patients and may lead to the missing of the best treatment timing [60,61]. Conventional partial cystectomy involves making skin incisions and necessitates further mobilization of the bladder. Despite its effectiveness, its efficacy is not as good as that of radical cystectomy, but is comparable to that of TURBT. In contrast to TURBT, patients who undergo partial cystectomy may experience postoperative discomfort and urinary dysfunction, which can exert an unfavorable impact on their quality of life. For these reasons, PC was not utilized frequently, accounting for 7% to 10% of all cystectomies according to the studies of the National Cancer Database [62].

3.1 Large work channel scope

Advanced imaging techniques and specialized equipment have revolutionized the identification of small tumors, resulting in better outcomes and a reduced risk of recurrence. However, these techniques are often of limited value in the context of bladder cancer due to the narrow channel of traditional transurethral appliances. Further advancements in imaging and surgical techniques may facilitate improving the effectiveness of TURBT and enhance the prognosis of bladder cancer.

The diameter of current instrument channel hampers the use of cutting-edge diagnostic and therapeutic tools in transurethral surgery. However, by optimizing the layout of the components and releasing the channel space as much as possible, we worked out a new transurethral diagnosis and treatment platform dubbed Super scope (S-scope) [41]. This new platform is designed to be compatible with advanced instruments, allowing for the maximization of the diagnostic and therapeutic capabilities of TURBT (**Figure 1**). The incorporation of laparoscopic surgical instruments and energy platforms into transurethral surgery through S-scope can potentially improve and optimize the current transurethral diagnosis and treatment techniques. By utilizing the minimally invasive transurethral natural cavity, S-scope can provide a safe and efficient approach for transurethral surgery, expanding the possibilities for transurethral bladder surgery.

3.2 Pneumocystoscopy

Fluid extravasation is a common complication of traditional transurethral surgery and can be a source of discomfort and morbidity in patients. Likewise, cell seeding is a major concern for patients with malignant tumors, as it increases the risk of metastasis and reduces the efficacy of therapy. Historically, pneumocystoscopy was employed for diagnosing hematuria [63]; however, due to the limited availability of instruments, it was not feasible to perform surgical procedures by using this method. Recent studies have demonstrated the potential of pneumocystoscopic resection as a promising approach for mitigating the risks of fluid extravasation and cell seeding in bladder surgery [41].

3.3 Transurethral PC

At present, traditional PC was performed open or laparoscopically with a disadvantage of high complication. Appliances with large operating channel and pneumocystoscopy provide the possibility to perform transurethral laparoscopic partial cystectomy.

Figure 1. The pattern diagram of S-scope.

Our team has recently developed a new surgical technique called super transurethral resection of bladder tumor (STURBT), providing a transurethral approach for conducting partial cystectomy [41]. This technique utilizes a resectoscope with a large working channel, through which laparoscopic tools, such as an ultrasound scalpel, can be used in the bladder. As a novel technique for partial cystectomy, STURBT has been shown to have numerous advantages in the surgical treatment of localized MIBC bladder tumors. Firstly, the utilization of carbon dioxide to fill the bladder during STURBT allows for the removal of the full thickness of the bladder wall and even tissues outside the bladder wall without the risk of fluid extravasation. Secondly, the ultrasonic scalpel generates mechanical energy for the resection of the bladder tumor, providing a more precise and controlled approach. This kind of energy can work freely inside the bladder without the concern for obturator nerve reflex. Thirdly, minimal bleeding during resection, which is particularly notable in comparison to traditional resection approaches. Even with mild bleeding, it is not liable to cause blurred vision. Fourthly, STURBT does not require the use of lavage fluid, which not only saves fluid during the operation but also eliminates the risk of tumor spread and planting. This minimizes the risk of complications and renders the procedure in line with the principle of freedom from tumor. Since STURBT is an *en-bloc* resection technique, it offers similar advantages to en-bloc resection.

STURBT utilizes a combination of different forms of energy as well as laparoscopic instruments to achieve the best possible surgical effect. STURBT may also possess various advantages, including less postoperative pain, and improved patient satisfaction, since it does not require incisions and can attain improved cosmetic outcomes compared with laparoscopic PC. As research in this field continues to move forward, it is likely that this technique may serve as an attractive alternative to traditional open or laparoscopic partial cystectomy in selected cases.

4. CONCLUSIONS

TURBT is a minimally invasive procedure that utilizes a single port and natural orifice to access the bladder. In the new era, TURBT can accomplish higher accuracy, increased safety, and better outcomes compared to other treatment options for bladder cancer. The development of new appliances in the field of laparoscopy presents an opportunity to fully tap the benefits of TURBT. Intergration of different laparoscopic tools can potentially further enhance the effectiveness of TURBT. However, continued research and development are warranted to maximize the utility of these new techniques.

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