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RECURRENCE OR PROGRESSION USING TRANSURETHRAL RESECTION OF BLADDER TUMOUR (TURBT)

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Abstract: The goals of transurethral resection of bladder tumour (TURBT) are to identify and eradicate visualized bladder tumour if technically safe and feasible and to obtain a specimen of satisfactory quality to enable accurate histological diagnosis. In the setting of high grade bladder tumour this generally entails the inclusion of detrusor muscle and assessment for the presence of associated carcinoma in situ (CIS), lymphovascular involvement or any variant form of bladder cancer. This will assist in determining risk stratification and prognostication of the bladder cancer and guides further treatment planning. Conversely, if suboptimal TURBT is performed there will be detrimental consequences on patient outcomes in regards to undergrading or understaging, increased recurrence or progression, and subsequently need for further treatments including more invasive interventions. This review article firstly summarises the key principles and complications of TURBT, as well as significance of re-TURBT.

Keywords: Transurethral resection of bladder tumour (TURBT); non-muscle invasive bladder cancer (NMIBC); carcinoma in situ (CIS).

Introduction

Bladder cancer is the fourth most common malignancy and eighth most common cancer risk deaths among men in the USA (1). Approximately 75% of patients present with non-muscle invasive bladder cancer (NMIBC) in which cancer involves only the urothelium or lamina propria without invasion to the detrusor muscle (2). It is also known to be the very costly cancer to treat due to high recurrence rate and its protracted course (3). One of the most likely explanations for this is thought to be due to suboptimal quality of transurethral resection of bladder tumour (TURBT) (4). While there are a range of investigative modalities to aid in diagnosis of bladder cancer, TURBT remains to be the cornerstone for diagnosis and treatment of bladder cancer. It allows to assess the local staging and grading of the tumour as well as relieving symptoms if present. It will provide information that will guide us to arrange the appropriate next line of investigations or therapy. Various guidelines emphasiz the key role of TURBT, in particular complete resection of all visible tumours when technically safe and feasible. Carcinoma in situ (CIS) is an exception, however, because it is often widespread

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or even inconspicuous with no definite demarcation of the tumour margins. Hence the role of endoscopic assessment and resection is to establish the diagnosis so that intravesical therapy can be instituted if deemed appropriate.

Preoperative considerations

It is important to take a focused history pertaining to haematuria, associated lower urinary tract symptoms, and risk factors of urothelial cancer such as smoking, occupational exposure, chronic inflammation/infection, history of pelvic radiation. Physical examination would entail the assessment of body habitus and abdomen and genitalia as well as digital rectal examination to assess the prostate in men. Investigations would include, but not limited to, basic blood and urine tests including cytology if high risk factors. Computed tomography intravenous pyelogram (CT IVP) is the imaging modality of choice to assess upper tract pathology. More recently, two meta-analyses calculated sensitivity of 87% and 92% and specificity of 79% and 87%, respectively, in distinguishing NMIBC from muscle invasive bladder cancer (MIBC), with multiparametric magnetic resonance imaging (mpMRI) (5,6). Although mpMRI of the Bladder before TURBT has been shown to differentiate MIBC and NMIBC (7) using Vesical Imaging-Reporting and Data System (VI-RADS), cystoscopy and bladder tumour resection remains the gold standard for diagnosis and initial management of bladder cancer. Bimanual examination is also still recommended by the guidelines, for clinical staging of bladder tumour, although its routine use is debated unless it appears invasive. The preoperative assessment should not only facilitate the assessment of risk of malignancy but ensure appropriate investigations are completed in order for patients to undergo TURBT safely under spinal or general anaesthetics. Furthermore, it would also minimise the risk of adverse events and avoid unnecessary overzealous resection in the setting of situations that are not aimed to cure (i.e., metastatic or palliative cancer).

Factors that would affect recurrence and progression

Bladder cancer is associated with a high rate of recurrence among patients with NMIBC. A number of studies assessed the factors that might be associated with recurrence and progression of bladder cancer following TURBT. The majority of the studies were rated as low quality and no strong recommendations were made in the guidelines due to study heterogeneity and hence low grade evidence. Nevertheless, there were a number of factors that have been shown to significantly influence the outcomes. The largest randomised controlled trial (RCT) included 2,596 patients in seven European Organization for Research and Treatment of Cancer (EORTC) trials. It demonstrated recurrence rates ranging from 15%

to 61% and progression rates of less than 1% to 17% at one year. At five years, the probabilities of recurrence and progression ranged from 31% to 78% and from less than 1% to 45%, respectively *(table 1).* The risk of recurrence was linked to a number of clinicopathologic factors including size, multifocality, prior recurrence, stage, CIS and grade (8). The main drawbacks of the above EORTC tables were that most patients received intravesical chemotherapy and did not undergo second TURBT. Patients with CIS alone were also excluded. Subsequently the Spanish Urological Oncology Group (CUETO) developed a scoring model for Bacillus Calmette-Guérin (BCG)-treated patients that predict the short- and long-term risks of recurrence and progression (9). It showed that EORTC risk tables overestimated the risk of recurrence and progression in high risk patients likely due to a low percentage of patients receiving intravesical BCG.

More recently, prognostic factors were evaluated in NMIBC patients treated with 1–3 years of BCG therapy. NMIBC patients at high risk of recurrence and progression did poorly despite maintenance BCG. However, it was limited by lack of repeat TURBT and exclusion of CIS (10).

Table 1. Probability of recurrence according to total score

Recurrence score	Probability of recurrence at 1 year		Probability of recurrence at 5 years	
	%	95%CI	%	95%CI
0	15	10-19	31	24-37
1-4	27	21-26	46	42-49
5-9	38	35-41	62	58-65
10-17	61	55-67	78	7384

TURBT quality and its influence on outcomes

In addition to the above individual patient and tumour characteristics ‘good quality’ TURBT is of paramount importance as incomplete TURBT could lead to a higher rate of upstaging and inferior oncological outcomes. One of the key determinants at the time of TURBT is whether detrusor muscle was obtained. All the guidelines (EAU, NICE, NCCN and AUA) highlighted the importance of fully resecting all visible tumour and obtaining muscle at the time of TURBT particularly when high-grade disease is initially identified and, if no muscle was contained in the specimen, a further resection is recommended. Chamie *et al.* conducted

a retrospective study on 1,865 patients who underwent TURBT recorded in the Surveillance, Epidemiology and End Results (SEER) registry. They found that detrusor was reported to be present in only 52% of cases, irrespective of stage or grade. The absence of muscle translated into an adverse impact on five-year mortality (11). Mariappan *et al.* evaluated the outcomes following TURBT on two Scottish cohorts with bladder cancer (12). They showed a significant reduction in the recurrence rate at first cystoscopy following TURBT based on the presence of detrusor muscle in the specimen. (43% and 70% if muscle was absent compared to 18% and 39% if muscle was present). The presence of detrusor muscle in the specimen is considered as a surrogate for the resection quality except in low grade or non-invasive tumours.

Second TURBT (re-resection or re-look TURBT)

Repeat resection should be performed for any high grade or tumour involving the lamina propria (T1), or incompletely resected tumour, especially when detrusor muscle was not identified in the resected specimens (13). Despite further experience and education on the significance of high grade or T1 disease residual tumour was found in 17–72% of Ta and 33–78% of T1 tumours (14-18). In addition, the risk of under staging NMIBC is significant, with 15–30% of cases being upstaged to T2 at the second TURBT (17-19). The risk of upstaging (≥T2) increases up to 49% in patients with T1 disease if no muscle was obtained in the initial specimen (20).

A RCT conducted by Divrik *et al.* also showed improved oncological outcomes in patients with T1 disease who underwent second TURBT (21). Recurrence-free survival (RFS), progression-free survival (PFS) and cancer-specific survival (CSS) were 52% *vs.* 21% (P=0.0001), 93% *vs.* 76% (P=0.0001) and 83.3% *vs.* 68.6% (P=0.038), respectively. Similarly, Tseng *et al.* demonstrated improved RFS and PFS following second TURBT in patients with T1 disease (22). The 2-year RFS rates were 74.6% and 60% and the PFS rates were 91.2% and 87.5% in groups 1 and 2, respectively (23). These results emphasize the importance of second TURBT in T1 bladder cancer not only for restaging but also for therapeutic benefit (24). Improved CCS and overall survival (OS) were also demonstrated (25). Although the rate of upstaging is significantly lower in patients with T1 disease in the presence of muscle in the initial resection, second TURBT is still recommended due to a potential for progression in 1–14% of cases (18,20). It would help achieve a higher rate of clear resection, more accurate staging, and improved treatment selection (i.e. immediate radical cystectomy *vs.* intravesical therapy) and prognostication. While the majority of the

studies showed that the greatest benefit from reTURBT was achieved in patients with T1 disease, patients with Ta high grade tumours fared the worst in terms of recurrence and progression rates, highlighting the significance of high grade disease regardless of its depth of invasion (26). Therefore, all guidelines (AUA, EAU, NCCN and NICE) recommend re-TURBT for these indications within 2–6 weeks due to the high incidence of residual tumour and understaging (27). It is critical to resect all visible papillary tumours, especially T1 lesions, as intravesical BCG is used to treat CIS and does not treat residual T1 papillary tumours. However, Gontero *et al.* showed that, while second TURBT had a positive impact on recurrence, progression, CSS and OS in the presence of muscle in the primary specimen, it did not improve the outcome for any of the oncological endpoints (28). It is also important to consider possible impact on potential complications, resource allocation and healthcare costs that are associated with second TURBT. With ongoing technical refinements and advances second TURBT might not be necessary in all of these patients in the future. We would require further high quality studies which could identify factors that could be used as a predictive tool for better selection of patients for second TURBT while avoiding an unnecessary surgery with possible risks and costs (29).

Factors that affect resection quality

Surgeon experience

Studies showed that resection quality depends on surgeon experience. It is influenced by education and experience of surgeon as well as surgical resection technique. Although it is perceived to be relatively straightforward endoscopic procedure, satisfactory resection of bladder tumours requires significant technical skill and 3-dimentional orientation skills to achieve accurate pathologic diagnosis.

A retrospective review of 463 TURBTs demonstrated there was a significantly less likelihood of containing detrusor muscle among high-risk patients when TURBT was performed by residents (P=0.006) (30). Huang *et al.* reported similar findings (31). These studies were in agreement with Mariappan *et al.*, who demonstrated surgeon experience (year 5 trainee or higher) to be independently associated with the presence of detrusor muscle in TURBT specimen. Both the absence of detrusor muscle and resection by junior surgeons were associated with an increased recurrence rate at first follow-up cystoscopy (12). Rouprêt and colleagues evaluated 340 patients with T1 bladder cancer and corroborated the above findings (32). The detrusor muscle was found in 73% of cases undertaken by senior surgeons compared to 61% by junior surgeons (P=0.02). There was 31% recurrence rate at first

cystoscopy if detrusor was present and 53% if it was absent (P=0.01). They also showed that recurrence rate was independently associated with junior surgeons, regardless of the presence of detrusor muscle. Herr and Donat further supported this conclusion and proposed that fractionated wide resection of all tumours and re-resection could be used to improve the quality of TURBT (20). Complete resection with detrusor present, carried out by experienced surgeons, would be considered to be an essential benchmark for TURBT.

Conversely, Shoshany *et al.* found no significant difference in the presence of detrusor muscle based on surgeon experience (33). This discrepancy in the rate of detrusor muscle based on surgeon seniority would indicate several factors such as training environment, supervision, and educational techniques. While it is imperative to maintain high quality TURBT for optimal patient outcomes with improved efficacy and efficiency it must be balanced with further opportunity for quality surgical education and training for trainee surgeons. Of many proposed avenues simulation training model has been widely utilized in a number of surgical procedures. Although there are several proposed simulation programs that have been studied, there is a need for the development of validated simulation program that is associated with excellent transferability of skills to good quality TURBT. This will need to be incorporated into standard training curriculum (34).

Another more practical approach was suggested by Zainfeld and colleagues. They proposed an “intermittent resection technique”. There was no increase in cautery artefact or decreased quality of resections. It would allow trainees to perform resection using short intermittent cuts rather than single large swipes. This would provide an enhanced opportunity for feedback to trainees which will enable them to adjust depth or direction of resection without compromising outcomes. There was no increase in cautery artefact or decreased quality of resections (35).

In addition to surgeon’s experience a number of measures have been developed to achieve more satisfactory TURBT. It begins with the implementation of a perioperative bladder tumour checklist and bladder diagram (16,36). A checklist can be used to ensure that all of the necessary equipment is available and thus avoid delays while the patient is under anaesthesia. The use of a bladder diagram was developed to document the location of all tumours and could lower recurrence rate (37). Jurewicz *et al.* also proposed to incorporate clinical photograph into operation report (16).

Key steps and principles of TURBT

After induction of anaesthesia patient is placed in the dorsal lithotomy position. The procedure can be performed either under spinal or general anaesthetics. General anaesthetics would be preferred if neuromuscular blockade is indicated to prevent stimulation of obturator nerve reflex (ONR) during the resection of lateral wall tumours. Bimanual examination of the bladder under anaesthesia is performed before resection. The prostate should also be assessed for men. The TURBT is undertaken after a detailed pancystoscopic evaluation using both 30- and 70-degree lenses for optimal assessment of the urethra, prostate and bladder including the bladder neck. Alternatively, a retroflexion manoeuvre using a flexible cystoscope can also be utilized. The anterior wall and the dome of the bladder might require suprapubic pressure for better visualisation.

If indicated a barbotage urine sample using normal saline irrigation can be obtained after inspection of the bladder. It is important not to overfill the bladder during tumour resection to avoid inadvertent perforation. Bimanual examination of the bladder under anaesthesia is also performed after resection for staging. Thickening of bladder wall might indicate MIBC, while palpable or mobile mass could suggest cT3 disease and fixed mass cT4 disease. Complete eradication of tumour is the key step of TURBT. If there are widespread red velvety flat lesions suggestive of CIS it would not be prudent to resect the entire lesions but instead selective biopsy would suffice with a view to intravesical therapy. If muscle is not confidently included in the specimen or concerned about cautery artefact cold cup biopsy of the base could also be performed to ensure accurate staging and the absence of invasion to detrusor muscle. Conventionally, large tumours are resected in a piecemeal fashion. This staged resection is often performed in a series of different layers until detrusor muscle is obtained. Judicious use of cautery would be employed to avoid potential cautery artefact on the specimen which would make it difficult for pathological interpretation of grading or staging of tumour.

Complications of TURBT

Although TURBT has been the technique of choice over decades with relatively low morbidity, it is far from perfect due to risk of complications as well as compromise in oncological outcomes from thermal damage to specimen margin, the absence of detrusor, tumour seeding, incomplete resection, and subsequently inaccurate pathological assessment. Complication rates are approximately 4–6% of which urinary tract infections and significant haematuria are most common. Bladder perforation and ONR are major complications and

every measure should be taken to avoid these serious complications from both anaesthesia and surgery.

Challenging situations

Tumours at the ureteral orifices

Coagulation close to the ureteral orifices should be avoided as it may cause scarring and lead to ureteric obstruction (38). However, tumours that involve the ureteral orifices can be resected judiciously under pure cutting settings. This would be particularly beneficial as satisfactory renal function can be facilitated if cisplatin-based neoadjuvant chemotherapy is considered for MIBC. Although it may result in vesicoureteric reflux and would be uncommon to cause stricture, a temporary ureteric stent placement between 2 and 6 weeks can further reduce the risk. A form of imaging such as renal ultrasound, CT urogram or Diethylenetriamine Pentaacetic Acid (DTPA) renal scan after resection is recommended.

Tumours on the lateral and anterior walls

Resection of lateral wall tumours may result in stimulation of ONR resulting in increased risk of perforation (39). Strategies that have been shown to reduce the likelihood of ONR would include (I) avoidance of bladder overfilling, (II) reduced cutting current, (III) use of short intermittent burst current (‘Stacatto’), (IV) use of bipolar electrocautery, and (V) use of neuromuscular blockade (40).

Tumours on the anterior wall could be challenging to resect and may require suprapubic depression by an assistant as well as proper resectoscope angles. More effective resection might be achieved by using open-angled loops.

Tumours in bladder diverticulae

Tumours within bladder diverticula are also considered to be difficult to obtain complete clearance due to suboptimal access and resection in particular if the diverticular neck is narrow and lack of muscularis propria layer. This would pose an increased risk of perforation and the inherent limitations in the assessment of the depth of tumour invasion. In view of this, while small, low grade tumours can be carefully resected, diverticulectomy, partial or radical cystectomy is considered to deal with large, high grade tumours in the diverticulum (38).

Random biopsy

Random bladder biopsy usually involves removal of bladder specimens with a cold cup forceps, sampling mostly mucosa and lamina propria layers with the intention to identify CIS in grossly normal-appearing areas. There is no strong evidence to support the routine use. Its main indications are in patients with negative cystoscopy but positive cytology, or with a

history of high grade and non-papillary tumours to further investigate the presence or the extent of CIS involvement. Biopsies should be taken from the trigone, dome, right, left, anterior and posterior bladder wall according to the EAU guidelines (41). This method of biopsy is therefore also known as site-directed biopsy. The incidence of positive random biopsies in areas of normal mucosa ranges from 1.5% to 14.5% which seem to influence management in 8% of patients (41,42). Additionally, photodynamic diagnosis (PDD) or narrow band imaging-based cystoscopy have shown promising results and may substitute some of the indications for random biopsy, although no high level evidence is available to date. These enhanced imaging technologies will be discussed in details in the later section of this review article. Prostatic urethra biopsy

Prostatic urethra biopsy could also serve as an important aspect of staging and should be performed in patients with negative cystoscopy but positive cytology or in patients with CIS to assess its extent. The incidence of CIS was noted to be 11.7% in patients with T1 high grade urothelial cancer of the bladder (43). It could be very superficial and confined to the urethra but extend more deeply into ducts, acini or stroma of the gland. The risk of prostatic urethral involvement increases with higher stage, grade, bladder tumour located at the trigone or bladder neck and multiple tumours (44). If prostatic urethral biopsy is not performed in the first resection it should be included in the subsequent biopsy. Precollicular areas carry the largest concentration of prostatic ducts and hence should be obtained with the resection loop at 5 and 7 o'clock positions. Cold cup biopsy can be employed if superficial disease only is suspected. If there is confirmed presence of CIS or T1 disease in the prostatic urethra, these patients should undergo a formal transurethral resection of the prostate (TURP) for more accurate staging, and so they can get maximal benefit from intravesical BCG therapy. More recently, advances in enhanced cystoscopic imaging technologies in the form of fluorescence cystoscopy for PDD, narrow-band imaging (NBI) have shown more accurate assessment and treatment of NMIBC. *En bloc* resection of bladder tumour technique (EBRT) has also been gaining increasing popularity due to its ability to include detrusor muscle, with less risk of seeding and complications. Further details are discussed in another section.

Current and future perspectives

ERBT seems to be a safe and effective resection technique. A new envisaged goal is also to decrease the number of second TURBTs. It can be facilitated by achieving higher rate of detrusor in the initial specimen and minimal tumour fragmentation using the correct ERBT technique. Large randomised prospective multicentre comparative trials are needed to clarify

outcomes and to further assist in identifying suitable patients for this technique. This will enable us to offer more personalized approach to management of patients with bladder cancer. Moreover, it would be important to acquire appropriate instruments and dedicated surgical team as well as genitourinary pathologist who are familiar with the procedure.

Conclusions

TURBT remains a gold standard for the evaluation and management of bladder cancer. Quality of resection has a direct impact on patient outcomes. Conventional TURBT has several limitations. These include suboptimal pathological assessment, perioperative morbidities, in particular ONR and bladder perforation, and high recurrence and progression rates. Modifications in resection technique (i.e., ERBT) and enhanced cystoscopy in the form of PDD and NBI demonstrated promising results to address some of these inherent limitations of conventional TURBT for diagnosis and treatment of bladder cancer. Future seems to be promising but ongoing research will be required to further define the role of these novel techniques and technologies.

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