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En-bloc versus conventional transurethral resection of bladder tumors: prospective, comparative, and randomized evaluation on the impact of both techniques on postoperative complications, tumor staging and cancer outcomes

Alberto BREDA

Universitat Autònoma de Barcelona
Facultat de Medicina
Departament de Cirurgia

TESIS DOCTORAL

En-bloc versus conventional transurethral resection of bladder tumors: prospective, comparative, and randomized evaluation on the impact of both techniques on postoperative complications, tumor staging and cancer outcomes

Autor:
Alberto BREDA

Tutor de Tesis:
Prof. Joan Palou

Directores de Tesis:
Prof. Joan Palou
Dr. Óscar Rodríguez-Faba

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Resumen

Introducción

La resección transuretral del tumor de vejiga (TURBT) representa un paso crucial en el tratamiento del cáncer de vejiga. La TURBT convencional (cTURBT) puede conducir a una caracterización patológica subóptima, resección tumoral incompleta y aumento del riesgo de recidiva local debido a las limitaciones de la técnica quirúrgica.

La resección en bloque del tumor de vejiga (ERBT) podría proporcionar una mejor tasa del músculo detrusor y una resección más precisa y controlada.

El objetivo de esta tesis doctoral fue aportar evidencia sobre el papel de la ERBT en el tratamiento del cáncer de vejiga non musculo invasivo en términos de resultados patológicos, quirúrgicos y oncológicos.

Materiales y métodos

Después de realizar una revisión sistemática de la literatura, diseñamos un ensayo aleatorizado controlado prospectivo que compara cTURBT y ERBT utilizando diferentes fuentes de energía [monopolar (ERBT-m), bipolar (ERBT-b), láser al tulio (ERBT-l)]. Se inscribieron pacientes con sospecha de cáncer de vejiga, con un máximo de tres lesiones cada una inferior o igual a tres centímetros.

El endpoint primario del estudio fue la presencia de musculo detrusor en la pieza. Posteriormente, analizamos los outcomes de acuerdo con la fuente de energía utilizada durante la intervención.

Finalmente, se desarrolló una clasificación de la perforación endoscópica de vejiga (escala DEEP) durante la TURBT: 0" capa muscular visible sin grasa

perivesical; "1" fibras musculares visibles con pequeños puntos de grasa perivesical; "2" exposición de grasa perivesical; "3" perforación intraperitoneal.

Resultados

Nuestra revisión sistemática de la literatura llevó a la conclusión de que la ERBT representa un avance considerable en el manejo quirúrgico del cáncer de vejiga no musculo invasor.

Se incluyeron 300 pacientes consecutivos entre 04/ 2018 y 06/2021. Tasas similares de presencia de músculo detrusor (95% vs 94%, p=0.9) se encontraron en los grupos ERBT y cTURBT. La tasa de factibilidad de subestadificación T1 fue superior para ERBT (100% vs 80%, p=0.02). No hubo diferencia en los outcomes quirúrgicos, en la tasa de complicaciones intraoperatorias y postoperatorias (p=0.5).

Con una mediana de seguimiento de 15 meses (RIC 7-28 meses), los resultados oncológicos no mostraron ninguna diferencia entre los dos grupos en términos de recurrencia.

Se registraron 5 (10,2%), 10 (22,2%) y 0 casos de reflejo del nervio obturador (ONR) en los grupos ERBT-m, ERBT-b y ERBT-l, respectivamente (p=0.001). La conversión a cTURBT fue mayor por lesiones ubicadas en la pared anterior/cúpula/cuello (p<0.001).

Un total de 146/248 (58,9%), 56/248 (22,6%), 41/248 (16,5%), 5/248 (2,0%) pacientes presentaron grado DEEP 0, 1, 2 y 3, respectivamente. El sexo femenino [coeficiente-B=0.255 (IC del 95%: 0.001-0.513); p=0.05], localización tumoral [coeficiente-B=0.188 (0.026-0.339); p=0.015], y el ONR [coeficiente-B=0.503 (0.148-0.857); p=0.006] fueron predictores independientes de DEEP. La escala predijo complicaciones mayores independientes [Odd Ratio 2.221 (1.098-4.495); p=0.026], ausencia de instilación intravesical de quimioterapia postoperatoria [OR 9.387 (2.434-36.200); p = 0.001], mayor tiempo de riego [coeficiente-B = 0,299 (0.166-0.441); p < 0.001] y estancia hospitalaria [coeficiente-B = 0.315 (0.111-0.519); p=0.003].

Conclusiones

La ERBT demostró de no ser inferior a la cTURBT en la tasa de músculo detrusor en la pieza quirúrgica. La viabilidad de subestadificación de tumores T1 fue mayor en el grupo ERBT. La energía láser podría ser beneficiosa en las lesiones de la pared lateral para evitar la ONR. En ERBT, el electrocauterio podría preferirse al láser para las lesiones de la pared anterior/cúpula puesto que hay un riesgo de conversión del 25%. La escala DEEP demostró ser una herramienta visual para clasificar la perforación de la vejiga durante el TURBT, lo que puede ayudar a estandarizar los informes de complicaciones y planificar el manejo postoperatorio en consecuencia.

Abstract

Background

Transurethral resection of bladder tumor (TURBT) represents a crucial step in the clinical care pathway of non-muscle-invasive bladder cancer (NMIBC). Conventional TURBT (cTURBT) may lead to suboptimal pathological characterization and incomplete tumor resection due to the limitations of the surgical technique.

En-bloc resection of bladder tumor (ERBT) might provide more precise and controlled resection with a better detrusor muscle sampling, and reduced risk of tumor cell scattering.

The aim of this study was to provide highest level of evidence over the role of ERBT in the treatment of NMIBC in terms of pathological, surgical and oncological outcomes, stratifying by energy source.

Materials and Methods

After performing a systematic review of the current literature, we designed a prospective randomized controlled trial comparing cTURBT to ERBT. We enrolled patients with a maximum of three bladder lesions each smaller than three centimeters, that were randomly allocated to the ERBT or cTURBT group in a 3:2 ratio.

The primary endpoint of the study was the feasibility of pathological staging of bladder cancer.

Subsequently, we divided the patients in accordance with the energy source used (i.e., monopolar-ERBT [ERBT-m], bipolar-ERBT [ERBT-b] and thulium

laser-ERBT [ERBT-l]) and compared pathological, surgical, and postoperative outcomes between the groups.

Finally, we developed a classification of the depth of endoscopic bladder perforation (i.e., DEEP scale) during ERBT/cTURBT: “0” visible muscular layer with no perivesical fat; “1” visible muscle fibers with spotted perivesical fat; “2” exposition of perivesical fat; “3” intraperitoneal perforation. We investigated the predictors of high-grade perforations (DEEP 2–3) and assessing whether the DEEP scale independently predicted patients' postoperative outcomes.

Results

Our systematic review of the literature found that ERBT represents a considerable advancement in the surgical management of NMIBC.

A total of 300 consecutive patients were enrolled in the study between April 2018 and June 2021. Similar rates of detrusor muscle presence (95% vs 94%, p=0.9) were found in the ERBT and cTURBT groups. T1 substaging feasibility rate was significantly superior for ERBT (100% vs 84%, p=0.02). The two groups did not differ both in term of intra-operative and post-operative outcomes. ERBT was converted to cTURBT in 6 cases (4.3%).

With a median follow-up duration of 15 months (IQR 7-28 months), early oncological outcomes did not show any difference between the two arms in terms of recurrence.

Five (10.2%), 10 (22.2%) and 0 cases of obturator nerve reflex (ONR) were recorded in ERBT-m, ERBT-b, and ERBT-l groups, respectively (p=0.001). Conversion to cTURBT was higher for lesions located in the anterior wall/dome/neck (p<0.001), irrespective from the energy used.

A total of 146/248 (58.9%), 56/248 (22.6%), 41/248 (16.5%), 5/248 (2.0%) patients presented DEEP grade 0, 1, 2, and 3, respectively. Female gender [B coeff. 0.255 (95% CI 0.001–0.513); p=0.05], tumor location [B coeff. 0.188 (0.026–0.339); p=0.015], and obturator-nerve reflex [B coeff. 0.503 (0.148–0.857); p=0.006] were independent predictors of DEEP. The scale predicted independently major complications [Odd Ratio (OR) 2.221 (1.098–4.495); p=0.026], no post-operative chemotherapy intravesical instillation [OR 9.387 (2.434–36.200); p=0.001], longer irrigation time [B coeff. 0.299 (0.166–0.441); p<0.001] and hospital stay [B coeff. 0.315 (0.111–0.519); p=0.003].

Conclusions

ERBT is non-inferior to cTURBT in the rate of detrusor muscle sampling at final pathology. The T1 substaging feasibility was higher in ERBT group. Laser energy might be beneficial in lateral wall lesions to avoid ONR. Electrocautery might be preferred for lesions of the anterior wall/dome, since there is an increased risk of ERBT conversion to cTURBT (25%). The DEEP scale proved to be a visual tool for grading bladder perforation during TURBT, which can help physicians standardize complication reporting and plan postoperative management accordingly.

Index

Introduction: bladder cancer

Epidemiology

Bladder cancer (BC) is the 10th most common cancer worldwide, representing the 7th most commonly diagnosed cancer in males and the 17th in females, with an age-standardized incidence rate (per 100,000 person/year) of 9.5 for men and 2.4 for women. In the European Union the age-standardized incidence rate is higher for both men and women, being 20.0 for men and 4.6 for women. The worldwide BC age-standardized mortality rate (per 100,000 person/year) is 3.3 for men and 0.86 for women [1]. Bladder tumors appear especially in the elderly, with over 90% of cases occurring in patients over 55 years of age. Although with a low incidence, this cancer can also occur in young patients and even in children [2].

BC incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments [3]. The highest incidence of bladder tumors in Europe is recorded in Western Europe (23.6 in men, 5.4 in women) and in Southern Europe (27.1 in men, 4.1 in women), followed by Northern countries (16.9 in men, 4.9 in women), while the lowest incidence is observed in East European countries (14.7 in men, 2.2 in women) [2]. The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative agents [4]. While mortality caused by bladder cancer has decreased by 12–14% in most countries in the last 20 years, it has increased in some others, including Romania, Croatia, Poland, and Denmark [2].

The vast majority of patients with BC (approximately 75%) presents with a non-muscle-invasive bladder cancer (NMIBC), which is a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1); this percentage is even higher considering patients younger than forty years [5]. Patients with NMIBC have a high prevalence among BC patients due to their generally good long-term survival and lower risk of cancer-specific mortality compared to muscle-invasive bladder cancer (MIBC) [1].

Economic and social burden

The economic and social costs of managing bladder cancer patients are increasingly higher, and BC is characterized by one of the highest cost/patient ratio among all neoplasms. According to an American study published in 2003, the disease was reported to be the 5th most expensive cancer with regards to the total expenses of medical management, with a total cost of almost $3.7 billion in 2001 in the United States and a per-patient cost ranging from $96,000 to $187,000 [6].

Unfortunately, detailed data regarding the economic and social costs associated with bladder cancer diagnosis and treatment is scarce, but invasive and metastatic BC do not seem to be main culprit of the economic burden of the disease, with NMIBC being responsible for 58.9% of the costs involved in the management of patients with BC in Great Britain in 2001 [7]. A simple yet likely explanation for the high costs related to NMIBC is that many patients have a long life expectancy, which implies the need for a long-term follow up. Although cystoscopies seem to account only for the 13% of the cost related to BC [8], transurethral surgery is responsible for over 40% of the costs according to a

Swedish study [8], while TURBT accounts for almost 75% of the total costs of treatment of patients with different types of BC in Great Britain [6].

Considering that more than half of patients with NMIBC will present with one or more relapses during follow up, disease recurrence prevention appears to be crucial to limit treatment expenses, since every event require additional treatment and further follow-up [7].

Etiology and risk factors

Tobacco smoking contains aromatic amines and polycyclic aromatic hydrocarbons, which are renally excreted and appear to contribute to BC pathogenesis. It is the most important and well established risk factor for BC, as it seems to be implied in respectively the 50-65% of male and 20-30% of female cases [3, 9]. The risk of BC increases with smoking duration and intensity [10], and environmental exposure to tobacco smoke is recognized as well as a risk factor for BC [3]. The risk associated with electronic cigarettes is still not adequately assessed, even though carcinogens have been identified in urine of users [10].

Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons is the second most important risk factor for BC. Work-related cases account for 10% of all BC cases [3], and are generally reported in occupations in which dyes, rubbers, textiles, paints, leathers, and chemicals are implied [11]. In developed countries these risks have been reduced by work-safety laws, and workers in these sectors no longer show a higher incidence of BC compared to the general population [3, 12].

Increased rates of secondary bladder malignancies have been reported after external-beam radiotherapy for urogenital malignancies, with relative risks of 2-4 folds [13, 14].

In addition, there is a well-established relationship between schistosomiasis, a chronic endemic cystitis based on recurrent infection with a parasitic trematode, and urothelial carcinoma of the urinary bladder, which can progress to squamous cell carcinoma [15].

Finally, although family history seems to have little impact on the risk of developing BC [16], and no genetic variation appears to have a clear impact on BC pathogenesis, genetic predisposition has an influence on the incidence of BC via its impact on susceptibility to other risk factors [17]. This has been suggested to lead to familial clustering of BC with an increased risk for first- and second-degree relatives.

Pathology

Papillary tumors confined to the mucosa or invading the lamina propria and flat, high- grade superficial tumors confined to the mucosa (CIS) are collectively grouped under the term of non-muscle-invasive bladder cancer (NMIBC) on the basis that they can be generally treated as a first-line approach by transurethral surgery, eventually in combination with adjuvant intravesical instillation [18]. The term NMIBC represents a group of diseases of limited homogeneity, and each tumor should be characterized according to its stage, grade, and further pathological characteristics.

The following histopathological classification of BC, based on the 2004 WHO classification, is most commonly employed [19]:

- pure urothelial carcinoma (more than 90% of all cases);
- urothelial carcinoma with squamous differentiation;
- urothelial carcinoma with glandular differentiation;
- urothelial carcinoma with trophoblastic differentiation;
- micropapillary urothelial carcinoma;
- nested variant (including large nested variant)
- microcystic urothelial carcinoma;
- plasmacytoid, giant cell, signet ring, diffuse, undifferentiated;
- lymphoepithelioma-like;
- small-cell carcinoma;
- sarcomatoid urothelial carcinoma;
- neuroendocrine variant of urothelial carcinoma.

This is not an exhaustive classification, since other, extremely rare, variants exist which are not detailed. Most variants of urothelial carcinoma have a worse prognosis than pure urothelial carcinoma [20].

Nonepithelial tumors represent up to the 5% of primary tumors and may originate from connective, adipose, muscle, nervous, vascular, hematopoietic, or endocrine tissues. Thus, different types of benign or malignant tumors may develop in the urinary bladder, including squamous papillomas, squamous or villous carcinomas, adenomas or adenocarcinomas, paragangliomas, carcinoid tumors, and different types of mesenchymal tumors.

The urinary bladder is also the site where metastases appear through direct extension or distant dissemination. The most common neoplasms determining bladder metastases include the prostate, uterus, ovary, lung, breast, and stomach cancers, even though almost every type of cancer has been reported to be able to seldomly metastasize to the bladder. Melanomas, leukemias, and lymphomas may also determine bladder involvement.

Molecular markers and their prognostic role have been investigated, and patient stratification based on molecular classification has been proposed. However, This approach, however appealing and promising, is not yet suitable for routine application [21].

Grading

From the point of view of histological grading, urothelial carcinomas of the bladder are most commonly classified using the 2004/2016 WHO/ISUP classification [22], which provides a different patient stratification between individual categories compared to the older three-tiered 1973 WHO classification.

Fig. 1 - BC grading according to the WHO 1973 and 2004/2016 classifications.

The introduction of this new classification in 2004 has determined a significant shift of patients between the categories of the two systems, with an increase in the number of patients with an HG disease due to the inclusion in this category of some patients with a 1973 WHO G2 disease [23]. 1973 WHO G1 carcinomas have been reassigned to PUNLMP and LG carcinomas in the 2004 WHO classification, and G2 carcinomas to LG and HG carcinomas, while all G3 carcinomas have been reassigned to HG carcinomas.

A systematic review and meta-analysis failed to demonstrate the superiority of the 2004/2016 classification in comparison to the 1973 classification in terms of prediction of disease recurrence and progression [23]. In a large, multicentric study from the EAU NMIBC Guidelines Panel comparing the prognostic performance of the two grading systems, both classifications resulted predictive of progression but not recurrence. When compared, the WHO 1973 classification was a stronger prognosticator of progression in NMIBC than the WHO 2004/2016. However, a four-tier combination of both classification systems (LG/G1, LG/G2, HG/G2 and HG/G3) proved to be superior to either classification system alone, as it is able to divide the group of G2 patients into two subgroups (LG/HG) with distinct prognoses [24].

Finally, since a similar prognosis was found in patients with primary PUNLMP and Ta LG carcinomas, the continued use of PUNLMP as a separate grade category in the WHO 2004/2016 has been progressively losing value [25].

Staging and T1 substaging

The most used and universally recognized staging classification is the 2009 TNM classification approved by the Union International Contre le Cancer (UICC), that was updated in 2017 with its 8th edition [26].

T - Primary tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Ta	Non-invasive papillary carcinoma	
Tis	Carcinoma *in situ*: 'flat tumour'	
T1	Tumour invades subepithelial connective tissue	
T2	Tumour invades muscle	
	T2a	Tumour invades superficial muscle (inner half)
	T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue	
	T3a	Microscopically
	T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall	
	T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
	T4b	Tumour invades pelvic wall or abdominal wall
N – Regional lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in common iliac lymph node(s)	
M - Distant metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastases

Fig. 2 - TNM classification of bladder cancer, 8th edition, 2017.

Since not all T1 tumors appear to behave in the same way, a T1 subclassification based on the depth and extent of invasion into the lamina propria has been proposed for prognostic and therapeutic purposes. Even though T1 substaging has been showed to have a prognostic value in retrospective cohort studies [27], and its use has been endorsed by the most recent 2016 World Health Organization (WHO) classification [22], the optimal T1 substage system remains to be defined, as both two-tiered and three-tiered classifications have been proposed [28].

Carcinoma *in situ* classification

CIS is a flat, high-grade, non-invasive urothelial carcinoma that can be frequently missed or misinterpreted as an inflammatory lesion during cystoscopy if not biopsied. Carcinoma in situ is often multifocal and can occur in the bladder, but also in the upper urinary tract, prostatic ducts, and prostatic urethra.

From the clinical point of view, CIS may be classified as [18]:

- Primary: isolated CIS with no previous or concurrent CIS or TaT1 tumors;
- Secondary: CIS detected during follow-up of patients with a previous tumor that was not CIS;
- Concurrent: CIS in the presence of any other urothelial BC.

Diagnosis

In case of primary bladder cancer, a painless and monosymptomatic haematuria is the most common clinical sign. Less common presenting symptoms and signs include dysuria, increased frequency or other disorders of the micturition, which are more frequently present in case of CIS or voluminous masses [18]. In more advanced cases, pelvic pain or upper urinary tract obstruction-related symptoms may be present. Physical examination, which consists of bimanual palpation, should include rectal and vaginal examination [29].

Urinary tests

The sensitivity of the examination of voided urine or bladder-washing specimens for exfoliated cancer cells varies according to tumor grade, as it reflects the more profound cytologic alteration that are present in HG masses. For this reason, urinary cytology has a notably high sensitivity in HG tumors (84%) and CIS (28-100%), but low sensitivity in LG tumors (16%) [30, 31].

Accordingly, urinary cytology appears to be most useful as an adjunct to cystoscopy in patients with HG disease. When interpreting the results from urinary cytology, it must be always considered that a positive voided urinary cytology can indicate an urothelial carcinoma anywhere in the urinary tract, and that a negative cytology does not exclude the presence of disease, since a low cellular yield, urinary tract infections, stones or intravesical instillations can hamper cytological evaluation [18].

To limit interobserver variability and provide more reliable and reproducible data, a standardized reporting system redefining urinary cytology diagnostic categories was published in 2016 by the Paris Working Group [32], which has been validated in several retrospective studies [33, 34]. The Paris Classification includes the following diagnostic categories:

- adequacy of urine specimens (Adequacy);
- negative for high-grade urothelial carcinoma (Negative);
- atypical urothelial cells (AUC);
- suspicious for high-grade urothelial carcinoma (Suspicious);
- high-grade urothelial carcinoma (HGUC);

Driven by the suboptimal diagnostic performance of urine cytology, numerous urinary tests have been developed [35], although none of these markers have been accepted in routine practice or clinical guidelines. These test usually have an higher sensitivity at the cost of lower specificity compared to urine cytology, and their result may be influenced by both benign conditions and previous BCG instillations.

Imaging

Ultrasound may be performed as an adjunct to physical examination in case of hematuria since it has moderate sensitivity to a wide range of conditions of the upper and lower urinary tract. It allows the detection and characterization of renal masses, hydronephrosis, and intravesical masses, but cannot rule out all potential causes of hematuria and replace CT urography [36].

CT urography may be used to detect papillary tumors in the urinary tract, indicated by contrast-enhancing masses, filling defects and/or hydronephrosis [37]. In case of MIBC suspicion, CT urography provides information about local, nodal and distant staging. BC may be incidentally detected in CT performed for other reasons, such as in case of follow up of others diseases. The necessity to perform a baseline CT once a bladder tumor has been detected is questionable if MIBC is not strongly suspected on the basis of endoscopic evaluation [38]. The incidence of a synchronous UTUC is low (1.8%), but increases to 7.5% in the case of trigonal tumors and multifocal, high volume disease, so that a baseline CT may be limited to these cases [38].

The role of multi-parametric MRI has not yet been established in BC diagnosis and staging, but a standardized methodology of MRI reporting in patients with BC (Vesical Imaging-Reporting And Data System, VI-RADS) has recently been published and requires validation [39].

Cystoscopy with biopsy

The definitive diagnosis of papillary BC ultimately depends on endoscopic examination of the bladder and sampling of abnormal tissue by cold-cup biopsy or loop resection with subsequent histological evaluation. Carcinoma in situ is diagnosed by a combination of cystoscopy, urine cytology, and histological evaluation of multiple bladder biopsies [40].

Cystoscopy is initially performed as an outpatient procedure. Especially in men, the use of a flexible instrument preceded by an intraurethral instillation of an anesthetic lubricant results in better compliance compared to a rigid instrument [41, 42]. An optimal cystoscopy should describe all the macroscopic features of the tumor (including localization using a bladder diagram, size, number and appearance) and all the mucosal abnormalities.

If a bladder tumor has been unequivocally visualized by imaging studies such as computed tomography, magnetic resonance imaging or ultrasound, diagnostic cystoscopy evaluation may be omitted, and the patient can proceed directly to TURBT for histological diagnosis and resection.

History of transurethral bladder surgery

Although bladder tumors were probably recognized since the antiquity, the first certain description of a bladder neoplasm by Lacuna dates back to 1551. The lack of valid diagnostic instruments meant that bladder tumors couldn't be systematically diagnosed in the patient presenting with macroscopic hematuria, and therefore could not be properly treated. Consequently, despite incidentally diagnosed bladder masses were occasionally excised during cystolithotomy, the first operations targeting bladder tumors were performed in the 16th and 17th centuries and were mainly limited to urethral or bladder neck tumors in women [43]. Up to the 18th century, bladder neoplasms were blindly excised through a dilated urethra or an open suprapubic (Billroth technique) or lateral perineal incision, using a variety of techniques encompassing ligatures, "*ecrasement*" (steel-wire loop), "*arrachement*" (tearing out), enucleation, or cauterization.

Early endoscopic era

Prior to cystoscopy the bladder was directly inspected through specula inserted into the dilated urethral meatus in women: surgeons attempted to seize pedunculated lesions through the urethra, tie the pedicle and blindly tear away as much tissue as possible, usually with unsatisfactory results.

In 1806 Philippe Bozzini, a German army surgeon, inaugurated the era of endoscopy through the invention of the *Lichleiter* (i.e., light conductor) [44]. He devised a device that consisted of aluminum tubes that were inserted into a body orifice and, using a system of angled mirrors and a candle as a light source, projected the image of internal cavities towards the examiner's eye [45]. The *Lichtleiter* was unsuccessful because the instrument was large and painful, reflected candlelight was a poor and uncontrollable light source, and there were no optics.

However, the term "endoscope" was introduced only in 1853 to describe an extensively modified version of Bozzini's *Lichtleiter* device developed by the French urologist Antonin Jean Desormeaux. Using an alcohol/turpentine lamp as a light source and a more focused mirror system that allowed a superior optical visualization, Desormeaux was able to perform the first endoscopic surgical intervention, reporting the excision of a urethral polyp, and cystoscopy became established as a practical, although difficult, means of clinical investigation [46, 47]. Twenty years later, in 1873, the French electric engineer Gustave Trouvé made a crucial contribution to cystoscopy moving the light source (a glowing hot platinum wire) to the inner tip of his instrument, termed *Polyscope*.

The operative cystoscope

The German urology professor Maximilian Nitze introduced the first direct-vision cystoscope in 1877, which markedly improved the visualization of the bladder walls through an innovative optical system that employed prisms and lenses to provide a much-improved visual field with magnified images, although it offered limited operating capability [48]. This instrument used a water-cooled electric platinum-filament lamp, but the heat generated by the filament proved to be a limiting factor in cystoscopy. Using a carbon filament in a vacuum, Thomas Alva Edison invented in 1878 his lamp, eventually resulting in mass production of a small incandescent lightbulb that could be incorporated in a cystoscope, as it was reliable and it would not damage the patient's bladder by heat. In 1883, David Newman effectively adapted this type of lamp as a light source for the cystoscope, greatly simplifying the production process and reducing its cost, leading to the widespread use of these instruments [45].

In 1881, the Austrian dermatologist Josef Grünfeld was the first to remove a bladder papilloma under direct visual control through endoscopic loop threaders, scissors and forceps that he devised, leading to the development of the *Polypenkneipe*, the first cystoscope specifically designed to remove tumors from the urethra and bladder [49]. From 1891 to 1894, professor Nitze designed and assembled the first practical operating cystoscope, through which he became the first to coagulate a bladder tumor using hot wire loops for galvanocautery. Nitze's improvements lead to an increase in the diagnostic accuracy and created the conditions for the systematic employment of the transurethral endoscopic treatment of bladder tumors, reporting a successful tumor excision from 150 patients with only 1 death and 20 recurrences [50].

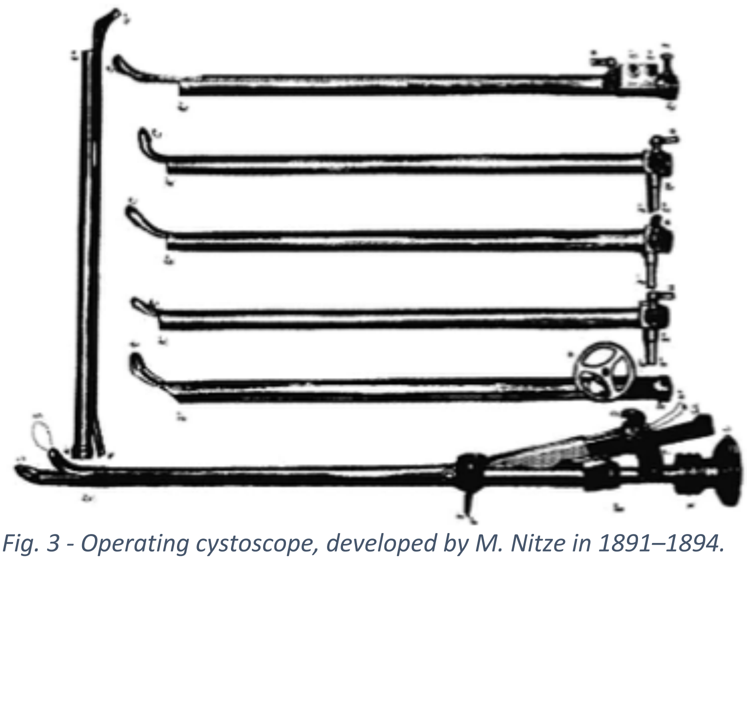

Fig. 3 - Operating cystoscope, developed by M. Nitze in 1891–1894.

Electrofulguration of bladder tumors

Nagelschmidt and Doyen were the first to advocate the use of electrically induced heat to treat cancerous growths, but it was the American urologist Edwin Beer who really established the concept of bladder electrosurgery. Convinced that Nitze's transurethral treatment of bladder tumors was superior to an open approach, in 1908 Beer conceived the idea to endoscopically coagulate bladder tumors using a high-frequency electric current. He used a catheterizing-cystoscope, a modified two-channel Nitze cystoscope with a channel for a 6F copper electrode and the other used for bladder irrigation, through which he directly applied a monopolar current to papillary tumors for 15-30 seconds, while the bladder was distended with sterile water. Beer concluded that coagulation was simpler than loop treatment, and in 1910, he published his work in a landmark article, claiming fulguration to be "proven effective in the cure of bladder papilloma" [51]. Beer's innovative approach revolutionized the treatment of papillary bladder tumors, and although the urologists, especially in Europe, were at first skeptical, they were soon convinced of the effectiveness of this approach and endorsed electrofulguration of bladder tumors.

In 1911, Ernst Frank together with Edward Lawrence Keyes experimented with bipolar electrocoagulation of bladder neoplasms, although at last Keyes abandoned bipolar coagulation in 1916 in favor of the more destructive high-frequency monopolar current.

Transurethral resection of bladder tumors (TURBT)

Even though electrofulguration was used all around the world to destroy bladder papillomas, it was clear that not all bladder masses behaved in the same way in terms of both recurrence and progression, and electrocoagulation was not always effective in treating these masses. In the 19th century, thanks to marked advancements in the knowledge of bladder tumor pathology based on histologic structure, it was already clear that papillary fungoid type of growth behaves very differently from solid cancerous tumors. Definition of these two categories of bladder masses, now described as low-grade papillary tumors and high-grade solid tumors, was highly relevant because early endoscopists seemed able to successfully treat only the more common papillary forms [52].

By 1935, Edwin Beer himself became pessimistic about the efficacy of endoscopic diathermy because it was applicable only to tumors of limited dimension, it seemed to be unable to prevent disease recurrences, and was ineffective against more aggressive cancerous forms. The optimism around this approach faded and it became clear that a more effective means to remove bladder tumors was needed to obtain better outcomes.

The Stern-McCarthy resectoscope

Finally, in 1926, an American urologist named Maximilian Stern introduced the resectoscope, a new instrument that summarized all the available innovation in urological endoscopy and condensed them in a revolutionary fashion. The resectoscope consisted of a sheath and a working element comprising a direct vision telescope, a light carrier, a channel for irrigation and an electric cutting loop that was maneuvered by a manually controlled gear mechanism that moved back and forth a tungsten wire through an opening in the sheath itself. Since this instrument was designed to resect obstructing prostatic tissue, it was cumbersome to use for bladder tumor resection because it was difficult to engage the neoplastic bladder tissue in the opening of the sheath. However, the cutting loop offered the obvious advantage of removing rather than simply cauterizing bladder tumors [53].

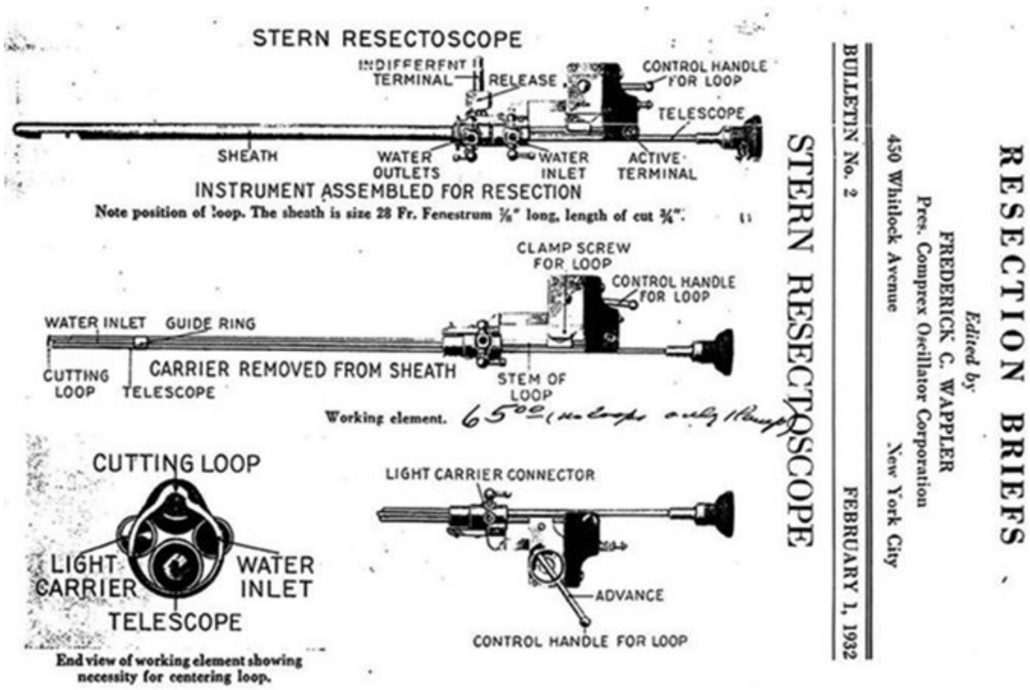

Fig. 4 - The first resectoscope, developed by Maximilian Stern, 1926

Some years later, in 1931, Theodore Davis, who had been an electrical engineer before entering the field of urology, improved Stern's resectoscope by using a larger tungsten wire and providing better insulation, and working with Bovie, was able to combine cutting and coagulation diathermy, inventing a duel-foot pedal allowing him to switch between either current during surgery.

In the same year, Joseph McCarthy made significant improvements to the resectoscope: he added a lens system that widened the visual field, used a nonconducting Bakelite sheath, added a rack-and-pinion lever mechanism to control the working element, incorporated separate currents for coagulation and cutting and, most importantly, moved the wire loop and cutting window to the tip of the instrument. Furthermore, differently from the Stern resectoscope, the working element of the McCarthy resectoscope was used to cut the tissue towards the operator, so that the instrument was better adapted to resect vesical neoplasms because it was easier to engage bladder tumors and to cut the tissue under direct visual control [54]. The Stern-McCarthy resectoscope, as it became known, was the first practical cutting-loop resectoscope, and it quickly replaced electrofulguration to become the dominant method used to diagnose and treat bladder neoplasms for the rest of the 20th century.

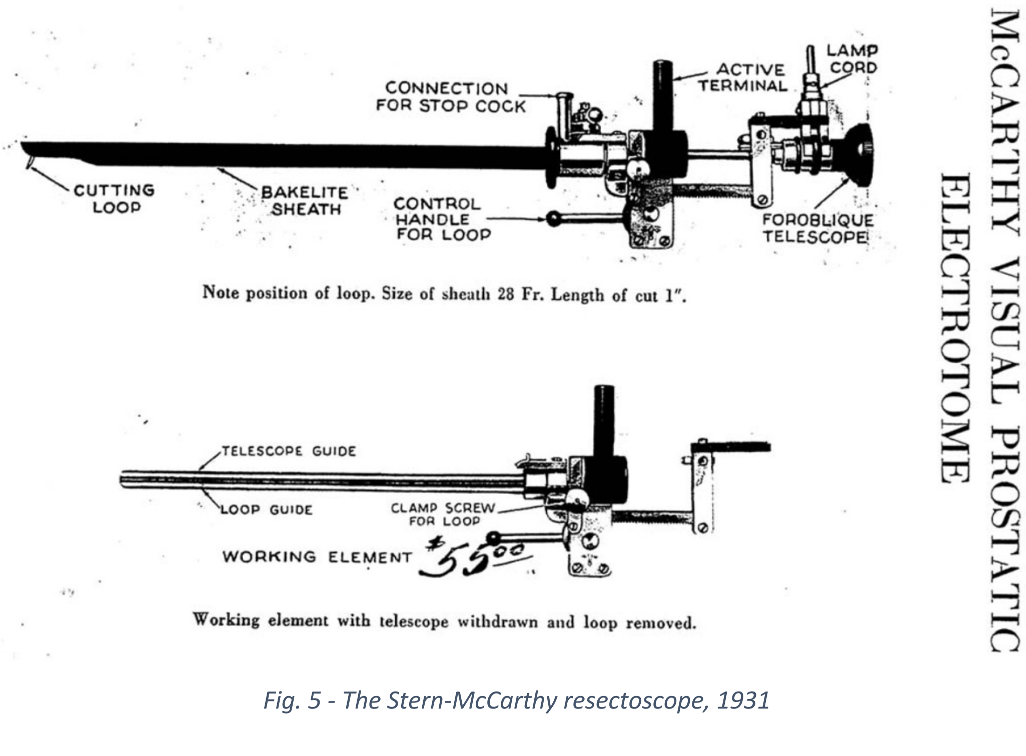

Fig. 5 - The Stern-McCarthy resectoscope, 1931

The Nesbit one-handed resectoscope

The Stern-McCarthy resectoscope underwent to numerous modifications through the years, but they were all based on its original concept and design. The most significant of these modifications is the one-handed resectoscope devised by Reed Nesbit in 1938 [55], who introduced a novel rotating thumb hole that maneuvered the cutting element, which was equipped with a spring that drove it back to its resting position. With this configuration the instrument could be used by the surgeon with only one hand, leaving the other free to elevate the bladder base through the rectum or apply suprapubic pressure to lower the bladder dome and to expose the anterior wall of the bladder, in order to bring tumors located in this area within the reach of the resectoscope itself. Furthermore, he shortened the opening in the sheath for the cutting element, for it to extend 1 cm beyond the tip of the instrument to release the resected tissue.

For these reasons, Nesbit's one-handed resectoscope became the forerunner to current modern resectoscopes, which all maintain the same basic concepts although different configurations of the working element are available, the most common of which are the Baumrucker and Iglesias configurations. The Baumrucker element has a spring mechanism which extends the electrode to its resting position beyond the sheath, so that the cutting element must be actively moved to cut or coagulate tissue during transurethral surgery (active element), while in the Iglesias element the electrode has to be actively extended into the bladder and the spring mechanism passively retracts the electrode into the sheath while applying the cutting or coagulating current (passive element).

The Iglesias continuous flow resectoscope

With the widespread diffusion of transurethral surgery, urologists became progressively concerned with its possible complications and how to prevent and manage them. It soon became clear that overfilling of the bladder could lead to postoperative complications related to irrigation fluid reabsorption such as uremia and other serious events, as Charles D. Creevy first pointed out in 1947 showing that "sterile water used as an irrigating fluid during transurethral resection could enter the prostatic veins and produce hemolysis, thus damaging the kidney exactly as does a transfusion with incompatible blood" [56]. In the same year, Baumrucker described a pressure gauge incorporated into his resection setup to alert him of increasing intravesical pressures. Using radioisotopes, Madsen was able to establish that an intravesical pressure of 30 mmHg was the threshold for fluid reabsorption during transurethral resection of the prostate [57]. These findings finally led to the development of low-pressure resection systems.

In 1975 the Cuban urologist José Iglesias presented his continuous flow resectoscope as a practical solution to this problem [58]. He devised an instrument that allowed simultaneous irrigation and evacuation of the bladder through an additional sheath that created two separate conduits for the inflow and outflow of the irrigation solution. Since clear fluid is constantly flowing in front of optics to irrigate the operative field before being evacuated via the outflow conduit, this resectoscope introduced several advantages over traditional instruments, such as a superior endoscopic vision, a reduced operative time by eliminating the necessity of interrupting the procedure to evacuate the bloody irrigation fluid with the subsequent need for reorientation, and the ability to control the amount of distension of the bladder by regulating the inflow and outflow of the solution while maintaining a bladder pressure around 10 mmHg, which is able to decrease venous bleeding without the risk of irrigation fluid reabsorption.

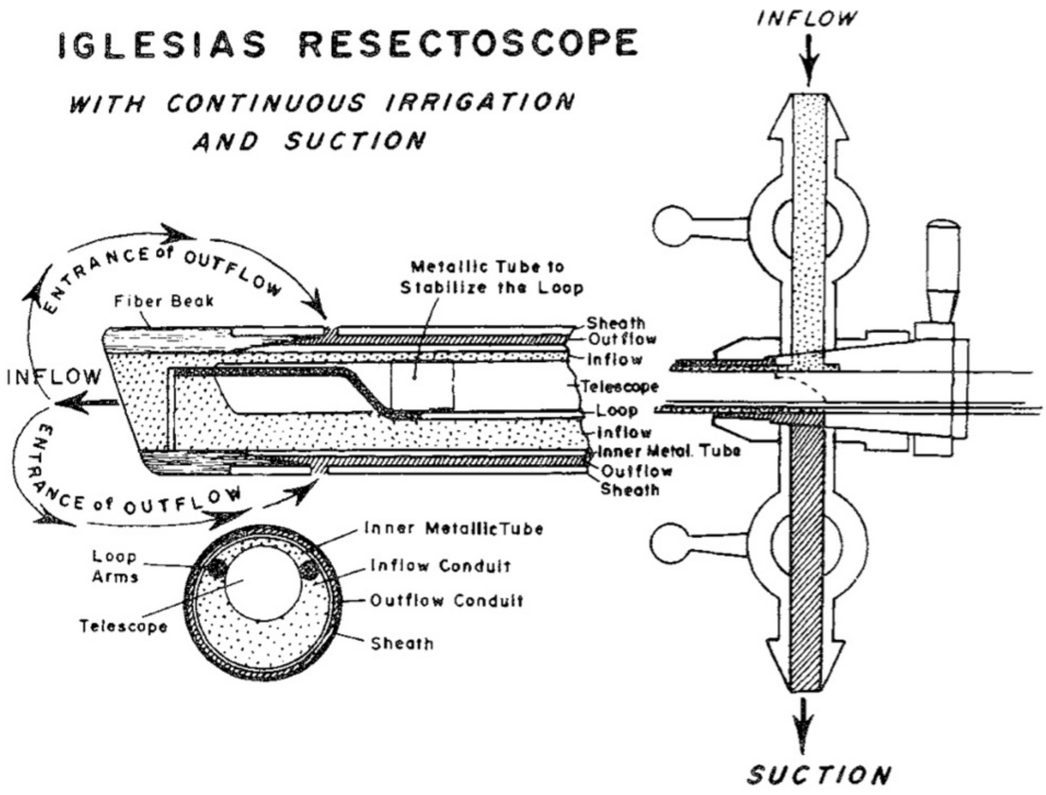

FIG. 1

Fig. 6 - The Iglesias continuous flow resectoscope, 1975

Nowadays, the continuous flow resectoscope is considered the standard of care for transurethral surgery, and modern-day instruments are based on modifications derived from the original Iglesias concept.

Principles of TURBT

Goals of TURBT

Transurethral resection of bladder tumor (TURBT) represents a surgical procedure which is crucial for the diagnosis, staging, risk stratification and treatment of most primary or recurrent bladder tumors.

The aims of endoscopic resection in the management of NMIBC are [18]:

- diagnosis, by obtaining a specimen for histological examination and pathological characterization, that allows the definitive diagnosis of bladder cancer and establishes the histopathological category of the disease;
- grading, by acquiring information about the grade of differentiation of the bladder tumor and its aggressiveness, evaluating both histological and cytological features;
- staging, by determining the presence, depth, and type of tumor invasion in the bladder wall structure (T stage and T1 substaging);
- treatment, by resecting all visible tumors.

The information acquired during TURBT are essential for risk stratification of NMIBC patients [25], because the stage, grade, extension (lesion number and size), and pattern of the tumor growth are decisive for choosing eventual complementary treatments, determining the follow up schedule, and establishing the prognosis of these patients.

The absence of detrusor muscle in the pathological specimen is associated with a significantly higher risk of residual disease, early recurrence, and risk of tumor understaging [59]. Therefore, the presence of detrusor muscle in the specimen is considered as the surrogate criterion of the resection quality and is required by the EAU NMIBC guidelines except for TaG1/LG tumors [18].

Achieving all the previously mentioned goals is essential for the correct management of NMIBC. An incorrect risk stratification (i.e., understaging) may lead to an inadequate subsequent treatment, with direct implications on the disease progression and consequently on the survival of patients.

Even though TURBT is a basic urological procedure, it should not be regarded as an easy one, since it does not always provide the expected results, and its failure may have noteworthy repercussions on the outcomes of the patient.

II-look resection

Since a significant risk of residual disease has been demonstrated after primary TURBT [60], a second resection (second look TURBT) has been proposed to detect residual disease and reduce the risk of understaging of an high-risk tumor. Although this risk is present even in case of Ta tumors, it is especially true in tumor infiltrating the lamina propria (T1 stage), which according to a systematic review showed an 8% risk of understaging and a 51% risk of disease persistence, with most of the residual tumors located at the original resection site [61].

Another metanalysis showed that the rate of residual tumor (58%) and upstaging to invasive disease (11%) after repeat TURBT remained high in the subgroup of patients with presence of the detrusor muscle in the pathological specimen, in which the resection could be deemed as appropriate [62].

For these reasons, a repeat TURBT, performed 2 to 6 weeks after initial resection, has been introduced and it has been demonstrated to improve outcomes after BCG treatment and increase recurrence-free survival, progression-free survival and overall survival, especially in patients without detrusor muscle in the specimen of the primary TURBT [63].

Procedure standardization

Transurethral resection of the bladder should be performed systematically in individual steps [18], since standardization of all phases of the procedure are necessary for the intervention to succeed [64, 65].

According to the EAU guidelines on NMIBC [18], the operative steps necessary to achieve a successful TURB include:

- determination of clinical stage (bimanual examination under anesthesia with assignment of cT stage);
- identification and recording of all information required to risk-stratify the patient, including the tumor number, size, multifocality, characteristics (sessile, nodular, papillary or flat), concern for the presence of CIS, recurrent vs. primary disease;
- evaluation of the adequacy of the resection (macroscopically complete resection, visualization of muscle at the resection base);
- documentation of eventual complications (intraoperative bleeding, assessment for perforation) and other peculiarity (involvement of ureteral orifices).

Resection strategies

Different approaches and techniques are available to effectively resect bladder tumors, that can be summarized in two basic technical variants:

- conventional resection (cTURBT), also deemed piecemeal resection, with separate resection of the exophytic part of the tumor, the underlying bladder wall, and the edges of the resection area [66];
- *en-bloc* resection (ERBT), using a variety of energy sources, such as monopolar or bipolar current, Thulium-YAG or Holmium-YAG laser, to resect and extract the entire tumor as a single piece [67].

Conventional resection

The standard conventional resection technique consists in maintaining the resectoscope in a fixed position, placing the loop behind the tumor and resecting the mass while withdrawing the working element toward the instrument's sheath to completely separate the resected tissue from the bladder wall.

The extended standard technique implies the concomitant movement of both the working element and the resectoscope itself, to obtain larger tumor fragments during endoscopic resection.

A variant of the extended standard resection consists in withdrawing the loop to approximately 1 cm from the resectoscope's sheath, after which the resection continues by moving the resectoscope while maintaining the working element in a fixed position: in this way the resecting loop is maintained close to the tip of the resectoscope, where the flow of the irrigation solution is higher, to obtain the best possible visibility in case of heavy bleeding.

This variety of basic conventional resection technique can be combined into different resection strategies that allows the surgeon to effectively approach tumors with different characteristics and methodically resect the bladder mass to increase resection efficiency.

Staged resection

Staged resection is a strategy first described by Milner in 1949 [68] and refined by Koloszy in 1991 [69]. This technique, that results particularly suitable in case of large tumors, consists in separating tumor resection in a staged fashion, starting with the exophytic part of the mass, followed by the subjacent resection bed together with the detrusor muscle, and, finally with the margins of the resected area.

The tumor fragments are stored in different recipients to allow the pathologist to separately examine the specimens obtained at the tumor base and to more accurately assess the tumor stage and its eventual infiltration of the detrusor muscle. Several variants for applying staged resection have been described, including parallel and vertical resection.

Stalk resection

Pediculated tumor with a clearly visible and easily approachable tumor stalk can be very effectively resected if the stalk is divided at the level of the surrounding mucosa by a series of horizontal or oblique cuts, and hemostasis at the level of the resection bed can be rapidly achieved [70].

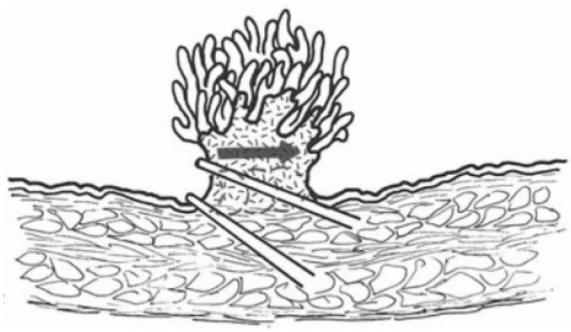

Fig. 7 - Stalk resection. W. Mauermayer, 1983.

Parallel resection

Parallel or horizontal resection is a strategy described by Reed Nesbit in 1943 that consists in resecting the neoplastic tissue layer by layer, parallel to the base of the tumor.

After filling the bladder to approximately half of its maximum capacity, resection starts from the lateral edge of the tumor and extends across all its surface. After finishing a layer, the next deeper layer is approached until the base of the tumor is reached. As in other staged resection strategies, complete resection of the exophytic mass is followed by resection of the underlying base of the tumor into the bladder wall, that is sent separately for histological examination.

This type of resection allows a better highlighting of the base of the tumor by gradually reaching the normal bladder mucosa around the tumor. The use of parallel resection is limited by the difficulties regarding resection of tumors located at the level of the dome, and by the bleeding that is caused in high-volume masses by resecting the entire surface of the tumor, since blood vessels cannot be effectively coagulated until the base of the tumor is reached [70].

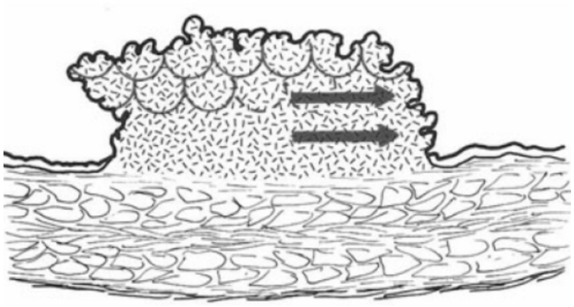

Fig. 8 - Parallel resection. W. Mauermayer, 1983.

Vertical resection

Vertical resection consists in resecting progressively deeper layers of a segment of a voluminous bladder mass, to completely remove a section of the tumor up to the bladder wall, and consequently obtain hemostasis.

This resection technique could avoid potential injuries of the bladder wall adjacent to the tumor, and at the same time ensures a better hemostasis. However, it can be occasionally difficult to maintain the orientation during the procedure, since adjacent residual neoplastic tissue floats into the way [70].

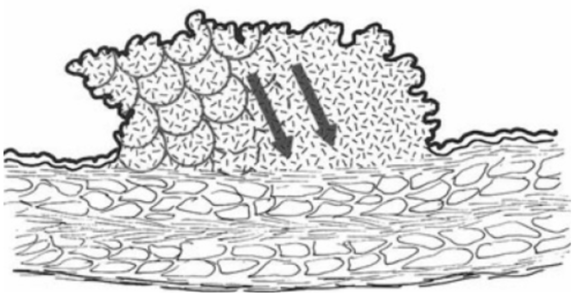

Fig. 9 - Vertical resection. W. Mauermayer, 1983.

En-bloc resection

En-bloc resection of bladder tumor (ERBT) is a resection technique that consists in the removal of the bladder tumor in its entirety, without cutting through neoplastic tumor with the working element and obtaining a specimen that contains both the whole tumor and the subjacent muscle layer [67].

This technique was first described by the Japanese urologist Kenya Kitamura in 1980 [71]. Even though in his report a polypectomy snare was used to rudimentarily resect the exophytic part a bladder tumor, and the resection of the base of implantation had to be concluded with a conventional approach, his pioneering work inaugurated the era of ERBT. The technique was properly described for the first time by Wolfgang Mauermayer [72] in 1981, who reported the use of a cutting current applied with a straight electrode to circularly dissect the tumor from the bladder wall, but its application remained anecdotical.

In 2000, Ukai [73] theorized the use of a short, curved needle electrode to excise the whole tumor with the surrounding tissue in one piece in order to improve the quality of histological diagnosis. Finally, ERBT started its slow diffusion, and Lodde [74] described in 2003 its application using a flat electrode in 37 patients, treating 62 lesions under 2.5 cm and reporting a single perforation.

Principles

This technique has been initially proposed to uphold the basic principle of oncological surgery of dissecting through normal tissue while avoiding cutting across neoplastic tissue, to maintain tumor integrity and avoid a potential spread of floating tumor cells that could be responsible for the considerable rate of recurrences in patients with NMIBC [75].

While in cTURBT the specimen is fragmented in many resection chips, in the case of ERBT the pathologist receives the whole tumor in its integrity, including the surrounding normal tissue. As such, since the orientation and the structure of the tumor can be preserved for pathological examination, and the neoplastic tissue results less compromised by surgical artifacts, a better evaluation of the depth of penetration of the neoplasia into the different bladder wall structures ought to be possible, possibly reducing the risk of disease understaging and enabling T1 substaging in a higher proportion of cases because of a better *muscolaris mucosae* visualization. Moreover, resection radicality may be evaluated by histological means rather than the surgeon's judgement alone.

Finally, since the resection process is more precise and controlled, as it is performed under direct visual control, the complication profile, in particular the risk of bladder perforation, may be reduced [67].

Patient selection

The goal of an en bloc resection is to completely resect the tumor mass, ensuring the presence of detrusor muscle in the specimen and guaranteeing a proper local staging of the disease, with tumor-free resection margins and without cutting into the neoplastic mass to reduce the risk of reimplantation and recurrence [67].

To respect these principles ERBT was historically indicated for lesions up to 3cm in order to avoid the fragmentation of the specimen during its extraction through the resectoscope sheath, that would negate the core concept of the ERBT itself [76]. The location of the lesion was also reported as a limitation to the application of ERBT, since some authors emphasized that an anterior wall or dome location could be demanding from a technical point of view and could lead to an increased risk of bladder perforation. For the same reason, ERBT cannot be safely applied in case of intradiverticular masses.

A recent systematic review including a two-round Delphi survey and a consensus meeting, summarized the available evidence and established the current indications for ERBT [67]. According to this report, ERBT should always be considered for treating NMIBC.

As reported in this work, size of bladder tumor is still a major limitation in performing ERBT, since for tumors > 3 cm it might be difficult to extract the specimen in one piece, even though the resection procedure itself could still be technically feasible and the potential benefits of ensuring proper staging and complete resection of NMIBC can still be preserved. Therefore, the panel members concluded that ERBT should be regarded as a feasible surgical approach even for bladder tumors larger than 3 cm. If the bladder tumor is too large for retrieval, dividing the specimen into two to three pieces can be considered. Special extraction methods (graspers, baskets) can be alternatively considered in retrieving large ERBT specimens.

The number of bladder tumors is not a major limitation in performing ERBT, even though most studies used four bladder tumors as a cut-off for patient selection for ERBT. Even though it might be time consuming and it might require more effort, ERBT is still feasible in a reasonable amount of time even in case of more than four tumors.

Regarding tumor location, it was agreed that ERBT can be applied irrespective of tumor location; although bladder dome tumors might be more technically difficult to resect, ERBT is still a feasible approach in such situations in experienced hands by allowing more time for resection

Surgical technique

To perform ERBT, the bladder should be distended enough, but not overdistended, to facilitate the dissection of the tumor from the bladder while avoiding bladder perforation [77].

The planned circumferential margin should be marked first to demarcate the area to be resected prior to any manipulation that could alter the surrounding mucosa and cause any false images. Sometimes it can be difficult to visualize the area located posteriorly to the tumor, so that the surgeon must be careful to maintain a safety margin that ensures complete resection. A margin of normal mucosa of at least 5 mm from any visible tumor should be kept to ensure complete resection and not to damage the neoplastic tissue during the procedure [67]. If multiple bladder tumors are adjacent to each other (i.e., satellite lesions), en-bloc resection of the cluster of tumors as a whole can be considered.

The incision should be continued deeply until the detrusor muscle fibers are clearly recognized, so that a part of the muscle can be included in the resected specimen. As ERBT specimens can provide comprehensive information regarding the depth of tumor invasion and resection margins, additional biopsy of the tumor base and edge of resection should not be performed routinely after ERBT [67]. If there is any doubt regarding resection radicality, additional resection of tumor base and edge should be performed and sent for histopathological examination separately.

In order to make the resection easier, the tumor can be tilted backward with the help of the sheath, and bluntly dissected from the detrusor muscle by the mechanical action of the resectoscope's sheath itself. The angle between the bladder wall and the tumor is increased in this way, allowing a precise dissection of the lesion during the procedure under direct visual control. The previously demarcated area is isolated by progressive incision at the level of the detrusor muscle. Tumor resection is subsequently completed, followed by coagulation of the base of the tumor with the preferred electrode or an alternative energy.

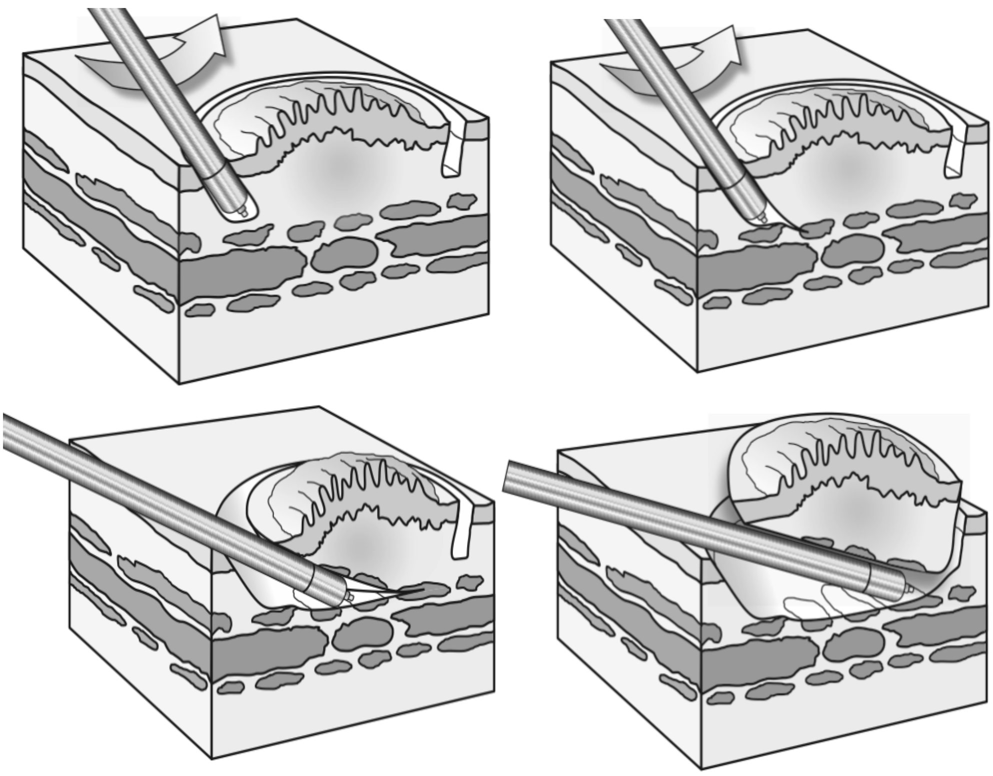

Fig. 10 - The en-bloc resection concept. Kramer, 2014

It is technically feasible to employ a wide variety of energy sources in the procedure, including monopolar energy, bipolar energy, holmium laser, thulium laser, and hydro dissection. A clear advantage of one energy source over the others has not been demonstrate, but monopolar and bipolar ERBT can be easily converted to cTURBT if any technical difficulty is encountered, while the employment of laser energy sources eliminates the risk of obturator nerve reflex stimulation during the procedure. Concerning hydro dissection, it implies a higher risk of residual disease and understaging due to its nature [78].

Outcomes

A recent systematic review and metanalysis of the 10 RCT currently available in the literature analyzed and reported the principal intraoperative and postoperative outcomes of ERBT in comparison with cTURBT [67].

As expected, ERBT was reported to have a longer operative time than cTURBT, even though the absolute difference is limited (mean difference 9.07 min, 95% CI 3.36–14.79, I2 = 86%, $p = 0.002$; very low certainty evidence), and a shorter irrigation time than TURBT (mean difference –7.24 h, 95% CI –9.29 to –5.20, I2 = 85%, $p < 0.001$; moderate certainty evidence), but there were no significant differences in the catheterization time and hospital stay (mean difference –1.32 d, 95% CI –2.71 to 0.06, I2 = 97%, $p = 0.06$; low certainty evidence).

Regarding complications, there was no significant difference in the rate of obturator nerve reflex stimulation (RR 0.19, 95% CI 0.03–1.22, I2 = 79%, $p = 0.08$; very low certainty evidence), but ERBT was reported to have a lower bladder perforation rate in comparison to cTURBT (RR 0.30, 95% CI 0.11–0.83, I2 = 1%, p = 0.02; moderate certainty evidence).

Concerning pathological and oncological outcomes, the rate of detrusor muscle presence in the pathological specimen was similar between ERBT and cTURBT (RR 1.11, 95% CI 0.40–3.11, I2 = 77%, p = 0.84; very low certainty evidence). No significant differences in 0–12 months (RR 0.82, 95% CI 0.56–1.19, I2 = 12%, p = 0.29), 13–24 months (RR 0.79, 95% CI 0.44–1.42, I2 = 0%, p = 0.43), and 25–36 months (RR 0.89, 95% CI 0.65–1.22, I2 = 47%, p = 0.47) recurrence rates were reported (all very low certainty evidence).

Quality of evidence

The most complete and methodologically robust systematic review of the available ERBT evidence up to date identified 10 RCTs directly comparing ERBT and TURBT; however, only four of them were published as full-text articles.

A significant variation in the reporting of outcomes was noticed both across RCT and non-RCT, with occasionally missing data on important outcomes for ERBT, such as detrusor muscle presence in the resection specimen.

Additionally, the authors reported a high-to-moderate risk of bias for most included studies, concerning primarily selection bias (randomization, allocation) and reporting bias (selective reporting), with a wide variation in the quality of the included studies that lead to very low to moderate certainty of evidence for most measured outcomes. The collected data did not allow the authors to stratify the results according to patient and disease factors, so that some results of the effectiveness review (i.e., recurrence rates) have to be interpreted with caution.

As such, high-quality data is scarce and does not consent to formulate robust recommendation for ERBT. For this reason, the EAU NMIBC guidelines do not advise to perform ERBT over cTURBT, leaving the choice to the surgeon [18].

Standardization on data reporting and outcome measures is important to clarify the role of ERBT in the management of NMIBC. Results from high-quality RCTs are needed to determine whether ERBT should replace cTURBT as the standard of care, and, subsequently, long-term real-world data will determine the impact of ERBT implementation in NMIBC management.

Intraoperative complications

Despite TURBT is a very common surgery in urology, it is not devoid of complications. Bleeding and bladder perforation (BP) are typical complications [79]. Moreover, the absence of BP is considered a quality indicator of TURBT, on par with the presence of detrusor muscle in the specimen [80]. Although BP is considered uncommon, reaching a 2.5–5% risk during procedure [81], several studies showed a non-negligible underdiagnosis and underreporting rates leading to a real frequency ranging up to 58.3% [82]. The absence of standardized methods to report intraoperative adverse events has been recognized as a major issue by the European Association of Urology, which created an ad hoc Complication Guideline Panel to propose a dedicated classification [83]. This may help identifying proper measures of benchmarking, to compare surgeons, institutions, and surgical techniques, to characterize surgical morbidity and report it accurately to patients [83]. Moreover, a universal standard reporting system of intraoperative adverse events is being developed through a Delphi Consensus

(ICARUS project) [84]. In TURBT, the resection depth is the most conditioning factor, either intraoperatively or postoperatively. Depending on resection depth, the surgeon may decide to interrupt the procedure and/or to avoid immediate intravesical instillation of chemotherapy to limit drug extravasation [82]. Thus, a standardized classification of resection depth is necessary to identify the preoperative risk factors and analyze the post-operative consequences.

Experimental design and results

Background

Transurethral resection of bladder tumor (TURBT) is the gold standard for the diagnosis, staging and conservative treatment of bladder cancer (BC) [18]. Even though it is often regarded as a basic urological procedure, it represents a crucial step in the clinical care pathway of non-muscle-invasive bladder cancer (NMIBC), enabling the histopathological diagnosis and characterization of BC, including grading and staging of the disease. Moreover, it allows the urologist to obtain all the information needed to define the patient's risk class and his prognosis, thus informing the need for a repeat TURBT, adjuvant intravesical therapies or radical surgery, and defining the subsequent follow-up schedule [18].

Conventional TURBT (cTURBT) is normally performed by piecemeal resection of the bladder mass, employing a monopolar or bipolar electrical current. Complete resection is achieved according to a resection strategy that is chosen on the basis of tumor location and characteristics, such as the staged resection strategy with a parallel or vertical approach [70].

Since the urologist has to cut through neoplastic tissue to reach the base of implantation of the mass and complete the resection, cTURBT implies the violation of one of the core principles of oncologic surgery, raising some concerns on the risk of tumor cell scattering and seeding and, thus, local recurrence [75].

Moreover, it is well-known that the presence of the detrusor muscle in the resection specimen is crucial to avoid the risk of understaging of the disease and it is related to a lower risk of residual disease and early recurrence [59]. Even though it can be considerate as a surrogate criterion of the resection quality and is required in all resection specimen except in Ta G1/LG tumors [18], it can be absent in a noteworthy proportion of the cTURBT specimens [85].

Finally, since the resection specimen obtained through cTURBT is fragmented, non-orientable and damaged by coagulation artefacts, with loss of both the internal structure of the tumor and its relationship with the bladder wall, the pathologist may be unable to provide reliable information about disease staging and T1 substaging [76].

In an attempt to obtain better surgical, pathological and oncological outcomes, en-bloc resection of bladder tumor (ERBT) was described in the 80' [71, 72] and has progressively gained popularity, being finally presented as an option along cTURBT in the EAU NMIBC guidelines [18]. In ERBT, the bladder tumor is dissected from the bladder wall as a single piece, that is comprehensive of both its exophytic and endophytic parts along with the surrounding unaffected tissue [67].

ERBT supposedly presents with many advantages over cTURBT, including the reduction of the tumor cell scattering risk, a more precise and controlled resection with a reduced risk of bladder perforation, a better sampling of the underlying detrusor muscle and the retrieval of a more informative pathological specimen that could provide more helpful and reliable prognostic data [76].

In the last decades many studies with low-to-intermediate quality of evidence have suggested some advantages of EBRT over cTURBT [76]. Recently, an International Collaborative Consensus Statement on ERBT including a metanalysis of the available RCTs confirmed the safety and feasibility of ERBT in most cases but failed to demonstrate a substantial advantage of ERBT in comparison with cTURBT. Most importantly, the Consensus underlined the need for high-quality, adequately powered and unbiased evidence, since the metanalysis showed very low to moderate certainty of evidence for most of the evaluated outcomes and did not allow the authors to stratify the results according to patient and disease factors [67].

Therefore, results from high-quality RCTs are needed to determine whether ERBT should replace cTURBT as the standard of care in the management of NMIBC.

Objectives

The aim of our work is to directly compare cTURBT with ERBT to analyze surgical, pathological, and oncological outcomes of these two techniques, performed employing different energy sources, to provide high-quality evidence that can contribute to clarify the role of ERBT in the management of NMIBC.

Materials and methods

This doctorate project led to the publication on peer-reviewed journals of 4 different articles. First of all, a systematic review of the literature was conducted to assess the current evidence of en-bloc technique in bladder tumor resection. Afterwards, the outcomes of a single-center were assessed in a randomized control trial, stating the non-inferiority of en-bloc resection when compared conventional TURBT. Subsequently, a sub-analysis of the RCT population was conducted to compare the resection's outcomes using different energies intraoperatively to state which energy to use according to tumor's location, proposing a patient-tailored approach in daily practice. Finally, within the RCT study, a visual-assessed endoscopic perforation scale (i.e., DEEP scale) was described, to offer surgeons a new tool to identify risk factors for intraoperative perforation and to esteem its impact on clinical and oncological outcomes. Below, a summary of each work's materials and methods is reported.

Study 1: introduction

The first article, entitled "En bloc resection of bladder tumors: indications, techniques, and future directions", was published on *Current Opinion on Urology* (Curr Opin Urol. 2020 May;30(3):421-427. doi: 10.1097/MOU.0000000000000737. PMID: 32205806., I.F.=2.3).

Study 1: design and endpoints

A MEDLINE search for studies published in the last 2 years (2018 and 2019) was performed using the keywords 'en bloc resection of bladder tumor', 'conventional transurethral resection of bladder tumor', 'non-muscle-invasive bladder cancer', and 'lasers in urologic surgery'. The following studies were considered for inclusion in this review: prospective and randomized studies, retrospective well designed studies, systematic reviews, and meta-analyses in the English language. Abstracts, technical notes, case reports, series shorter than 10 cases, comprehensive reviews, and articles written in languages other than English were not considered valuable for the review. The reference lists of the eligible articles were reviewed by two authors. PRISMA criteria used for this article are shown in Fig. 11.

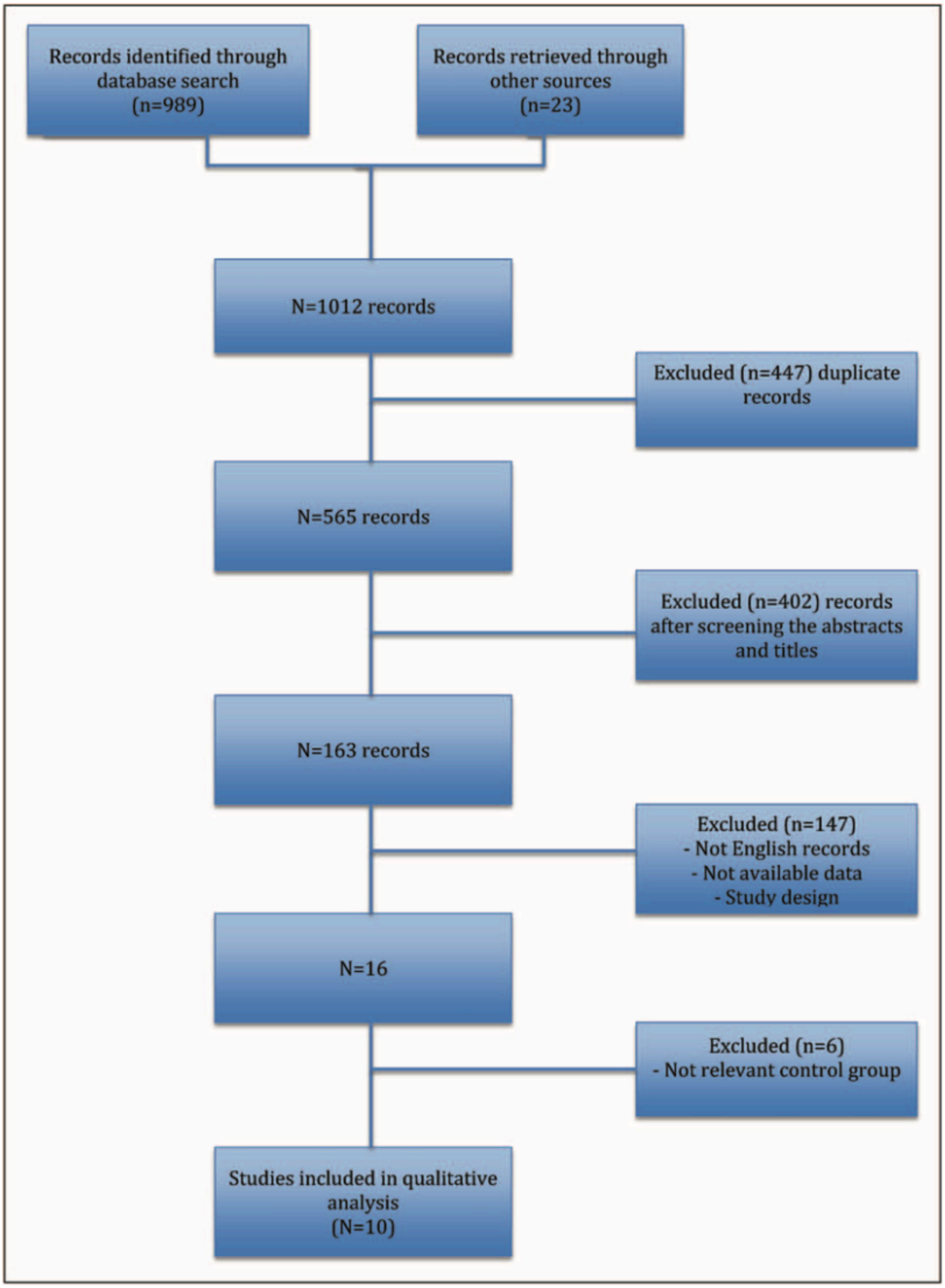

Fig. 11 – PRISMA flowchart for studies' selection

Study 2: introduction

The second article, entitled "En Bloc Versus Conventional Transurethral Resection of Bladder Tumors: A Single-center Prospective Randomized Noninferiority Trial", was published on European Urology Oncology (Eur Urol Oncol. 2022 May 23:S2588-9311(22)00068-2. doi: 10.1016/j.euo.2022.05.001. Epub ahead of print. PMID: 35618567, I.F.=8.2).

Study 2: design and endpoints

We designed a prospective randomized controlled trial (RCT) comparing cTURBT to ERBT using different energy sources. All the patients who respected the inclusion and exclusion criteria during the study period were prospectively enrolled and randomized to receive the allocated treatment, either ERBT using monopolar (ERBT-m), bipolar (ERBT-b) or thulium laser (ERBT-tl) energy or cTURBT using monopolar (cTURBT-m) or bipolar (cTURBT-b) energy.

The primary endpoint of the study was the feasibility of pathological staging and grading of bladder cancer according to the American Joint Committee on Cancer/Union for International Cancer Control TNM system [26] and the World Health Organization classification [22].

Secondary endpoints included surgical, pathological, and oncological outcomes. Surgical outcomes included operative time, postoperative irrigation and catheterization time, the rate of adjuvant one-shot instillation of mitomycin/epirubicin, hospital length of stay, obturator nerve reflex stimulation, bladder perforation and post-operative complications scored according to the Clavien-Dindo classification [86]. Regarding pathological outcomes, they included the rate of feasibility of T1a/b/c subclassification according to the depth of invasion in the lamina propria and its relationship to the *muscularis mucosae* and vascular plexus layer [27] and the presence of artifacts in the resection specimen. Finally, only early oncological outcomes were considered and analyzed, with comparison of the three-months and overall recurrence rate.

This study was carried out according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board (2017/09c). All participants were adequately informed and signed a written consent. The study was registered on *ClinicalTrials.gov* (NCT04712201).

Study 2: population and treatment allocation

The target population included all consecutive patients undergoing TURBT at the *Fundació Puigvert* (Barcelona, Spain) for the diagnosis and treatment of a primary or recurrent bladder cancer according to the EAU guidelines [18].

We included patients affected by primary or recurrent bladder cancer, located anywhere in the bladder, with at most three different tumors, each with a maximum size of three centimeters. Candidates were excluded from the study in case of preoperative evidence of MIBC, nodal and metastatic extension of the disease, or in case of synchronous UTUC.

Population numerosity to reach statistical significance for the primary endpoint was estimated on the basis of the data currently available in the literature, which showed that cTURBT and ERBT were suitable to ensure correct staging respectively in the 80% [85] and 97% of the cases [87]. Accepting an alpha risk of 5% and a beta risk of 20% in a two-sided test, and allowing a drop-out rate of 13%, the population size was estimated to be 300 patients.

Patients were allocated to the ERBT or cTURBT group in a 3:2 ratio using computer-generated randomization tables during surgical schedule planning on the day before surgery. In particular, 180 patients were randomized to the ERBT test group (60 patients each for the ERBT-m, ERBT-b and ERBT-tl subgroups) and 120 to the cTURBT control group (60 patients each for the cTURBT-m and cTURBT-b subgroups).

Preoperative evaluation included patients' anthropometric variables, smoking habits, comorbidities, medications, history of urothelial cancer, and urine cytology. An abdominal computed tomography (CT) scan was performed in case of suspicion of muscle-invasive bladder cancer (MIBC) or upper urinary tract (UUT) involvement.

Study 2: surgical procedure

Every procedure was performed with the patient in the standard lithotomy position under spinal or general anesthesia, using a 28*Ch.* resectoscope (*Karl Storz*, Tuttlingen, Germany) and saline or glycine solutions as irrigation solutions.

At the start of the procedure, inclusion and exclusion criteria were verified as the bladder was carefully inspected. In case of discrepancies between intraoperative endoscopy and preoperative data that disagreed with the inclusion criteria (i.e., presence of more than three tumors not described at the outpatient cystoscopy or tumor growth to a size bigger than three centimeters), the drop-out was recorded and the patient was excluded from the per-protocol analysis.

cTURBT was performed according to the conventional technique and the surgeon's preferred resection strategy on the basis of tumor's characteristics, using standard monopolar or bipolar loop electrodes.

Monopolar needle electrodes were used for ERBT-m, while bipolar rectangular electrodes were employed for ERBT-b. ERBT-tl was performed using a 550 µm fiber connected to a thulium laser generator (*Revolix Duo, LisaLaser,* Katlenburg-Lindau, Germany) set to 10-20 W power. Regardless of the energy source, ERBT was achieved through a circular incision around the tumor base, cutting through healthy mucosa with a safety margin of 5 mm from the tumor base. The incision was deepened until detrusor muscle fibers were clearly visible, and the tumor was dissected from the bladder wall at the desired depth [67].

In both cases, hemostasis of the resection bed was obtained by coagulation with the same energy used for the resection. The resection specimen was extracted using a glass Toomey evacuator or grabbing it with the electrode. If the specimen was too large to pass through the resectoscope sheath, the lesion was subsequently cut in two or three pieces for extraction [67].

At the end of the procedure, a 20-22 ch three-way Couvelaire-tipped bladder catheter was positioned, and continuous bladder irrigation was started. Early one-shot instillation of 40 mg mitomycin C or 50 mg epirubicin was administered according to current guidelines [18]. Impossibility to proceed with the adjuvant instillation due to bladder wall perforation or excessive bleeding was recorded. Patients followed the postoperative care pathway and follow-up protocols of our institution, which is in line with current EAU NMIBC guidelines.

The resection specimen was processed for pathological evaluation according to a standard internal protocol. All samples were examined by a single expert uropathologist. In case of a tumor infiltrating the *lamina propria*, T1a-b-c substaging was performed if feasible. The presence of artifacts was recorded and graded as focal or extensive.

Study 2: statistical analysis

Descriptive statistical analysis was performed with SPSS v26 (*IBM Corp.*). Absolute frequencies and percentages were used to describe the categorical variables, while median and IQR were used for continuous variables. Differences between study groups were assessed with the Chi-square test for categorical variables and with the Mann-Whitney test for continuous variables. For the pathological outcomes, both a per-patient and a per-lesion analysis were performed. Kaplan-Meier curves were generated to assess disease-free survival and overall survival. All the tests were conducted at a significance level p=0.05.

Study 3: introduction

The third article, entitled "Energy source comparison in en-bloc resection of bladder tumors: sub analysis of a single-center prospective randomized study", was published on World Journal of Urology (World J Urol. 2022 May 31:1–7. doi: 10.1007/s00345-022-04042-y. PMID: 35639159; PMCID: PMC9152642., I.F.=3.66). This study is a sub analysis of the previously described RCT, so part of the materials and methods (i.e., "study population and treatment allocation" and "surgical procedure") are the same. Below, the specific subsections.

Study 3: endpoints

Primary endpoint of the sub analysis was the comparison between energies in term of 156 pathological analysis (detrusor muscle (DM) presence, staging feasibility, and presence of artifacts). Secondary endpoints were intra operative (obturator nerve reflex (ONR), hemoglobin (Hb) drop, and bladder wall perforation) and post-operative (the rate of post-operative intravesical instillation feasibility after BC resection in patients meant to receive it according to the European Association of Urology (EAU) guidelines1, irrigation and catheterization time, hospital stay, and post-operative complications scored according to the Clavien-Dindo classification (10) outcomes.

Study 3: statistical analysis

Statistical Analysis Data were complemented by descriptive statistical analysis. Categorical variables were reported as frequencies and percentages (%), and continuous variables as means and standard deviations (SD). Differences between study groups in baseline variables were analyzed with ANOVA for continuous variables or chi-square test for categorical ones. All the tests were conducted at a significance level p=0.05. Statistical analyses were performed using SPSS v.26 (IBM Corp., Armonk, NY).

Study 4: introduction

The fourth article, entitled “The DEpth of Endoscopic Perforation scale to assess intraoperative perforations during transurethral resection of bladder tumor:

subgroup analysis of a randomized control trial", was published on World Journal of Urology (World J Urol. 2022 Jun 4:1–7. doi: 10.1007/s00345-022-04052-w. Epub ahead of print. PMID: 35665840; PMCID: PMC9166183, I.F.=3.66).

This study is a sub analysis of the previously described RCT, so part of the materials and methods (i.e., "study population and treatment allocation" and "surgical procedure") are the same. Below, the specific subsections.

Study 4: the DEpth of Endoscopic Perforation (DEEP) scale

Four grades of vesical endoscopic perforation during TURBT were defined (Fig. 12). Grade 0 indicates that, after the resection, the vesical muscular layer is visible with no sign of perivesical fat. In grade 1, the vesical muscular layer is visible with some spots of perivesical fat. Grade 2 identifies those cases where the muscular layer was completely resected with the exposition of the perivesical fat (extraperitoneal perforation). Grade 3 indicates the resection of muscular layer, perivesical fat and peritoneum (intraperitoneal perforation). Grade 2 (extraperitoneal) and grade 3 (intraperitoneal) perforations were defined as high-grade complications as they could significantly affect the postoperative course of patients.

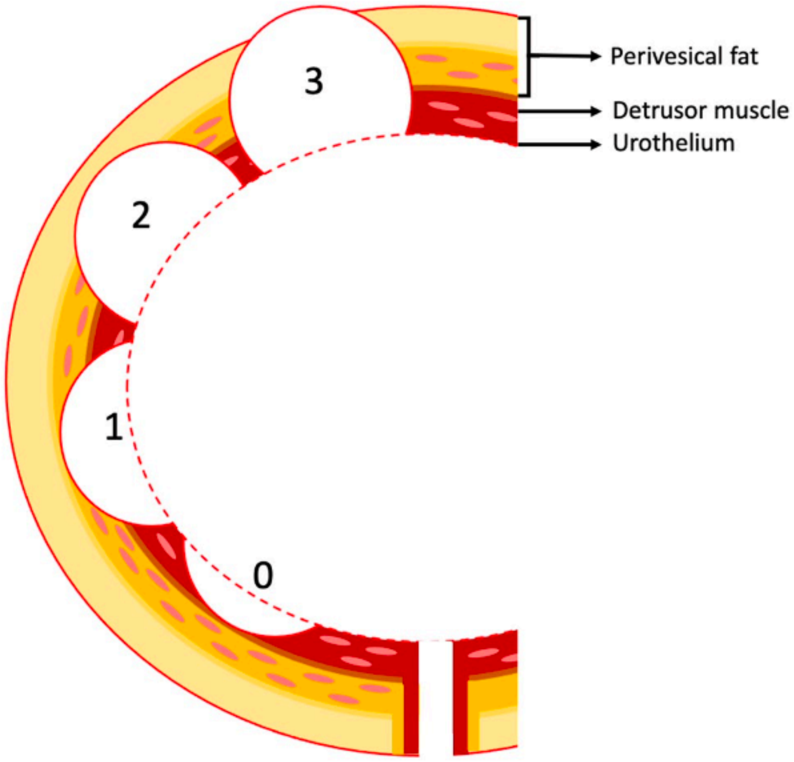

Fig. 12 – Grades of DEEP scale: (0) vesical muscular layer is visible with no sign of perivesical fat, (1) the vesical muscular layer is visible with some spots of perivesical fat, (2) the muscular layer is completely resected with the exposition of the perivesical fat (extraperitoneal perforation) (3) muscular layer, perivesical fat and peritoneum are perforated (intraperitoneal perforation)

Study 1: results

Indications

TURBT using white light cystoscopy (WLC) continues to represent the gold standard treatment for primary NMIBC according to the 2019 EAU Guide- lines. The goal is complete resection of the lesion, which is essential to a good prognosis, and this may be achieved by either a fractionated resection or an en-bloc resection [88]. The goal of an en-bloc resection is to resect the tumor mass, ensuring the presence of detrusor muscle in the specimen, with tumor-free resection margins and without cutting into the neoplastic mass: this facilitates the reading by the pathologist and reduces the risk of seeding and reimplantation of neoplastic cells.

According to the literature, ERBT is performed for lesions up to 3 cm of size [76], in order to avoid its later fragmentation during specimen retrieval, and without omitting the 'one piece concept' [89].

The localization of the lesion can also represent a limit to the indications for the en bloc technique. Same authors emphasized as the tumor location at the anterior and/or posterior bladder wall may potentially result in the risk of peritoneal damage [74] [90]. On the other hand, in different bladder areas (i.e., bladder dome) the en-bloc resection can be demanding from a technical point of view [91].

Tumor visualization and detection

An optimal view of a neoplastic lesion is essential for correct diagnosis and treatment. WLC is currently the gold standard for the treatment of bladder tumors; nevertheless, additional tumor visualization methods can improve the recognition of small lesions and flat lesions as carcinoma in situ.

Photodynamic diagnosis (PDD) is a technique that aims to improve the endoscopic recognition of a tumor based on the intravesical instillation of 5-aminolevulinic acid or hexaminolevulinic acid. These products are metabolized into protoporphyrin IX, which gives the neoplastic cells a red fluorescent appearance when excited by violet light. PDD appears to increase the tumor detection rate and to decrease the residual tumor rate [92] and is the most widespread additional tumor visualization method to be used [93].

Narrow-band imaging (NBI) technology uses wavelengths that are strongly absorbed by hemoglobin so that it enhances the surface capillary visualization and the contrast between normal urothelium and hyper vascular cancer tissue. Unlike PDD, which increases the cost of the procedure, NBI slightly increases the duration of the procedure, but the costs are comparable with those of WLC. Some studies have claimed that NBI improves the tumor detection rate [94] and that there is a reduction in recurrence risk if NBI is used during TURBT [95].

Confocal laser endomicroscopy (CLE) is an emergent in-vivo high-resolution optical imaging technique that uses a fluorescein dye that may enable real-time differentiation between high-grade and low-grade urothelial cancer. Liem et al. [96] used CLE to better characterize bladder lesions in 73 patients and found agreement between CLE imaging and histopathological results in 76 and 70% of low- grade and high-grade urothelial cancers, respectively. CLE could be used to identify, in the en-bloc resection, the presence or absence of lesion-free margins and could serve as the basis for the decision on whether to extend the resection margins within the same operative session, but to date this technique has not been used routinely in clinical practice.

Technique of resection and energy sources

Regardless of the technique used in the en-bloc resection, a circumferential incision is made with a safety margin of a few millimeters from the tissue that is macroscopically evaluated as a tumor with the aim of avoiding positive margins. The resection then proceeds deep into the muscular layers until progressive detachment of the lesion is achieved and until it floats in the bladder lumen. Subsequently, the tissue is recovered to be sent for analysis.

TURBT was traditionally performed with monopolar energy, which determines the passage of the energy itself between the resectoscope and the grounding pad applied to the patient's body. Subsequently, the use of bipolar energy was introduced for this type of procedure. The use of bipolar energy should theoretically reduce the risk of excitation of the obturator nerve, and therefore, reduce both the risk of bladder perforation, even if the literature data on these two points are conflicting [97] [98] [99]. In recent years, laser energies, including holmium, thulium, and KTP, have entered the arsenal for the execution of bladder resection procedures [100, 101] (Fig. 2). En bloc resection using monopolar or bipolar current, thulium-YAG, or holmium-YAG laser is feasible in selected exophytic tumors [18]. Other emerging resection techniques use KTP laser and water jet as energy sources.

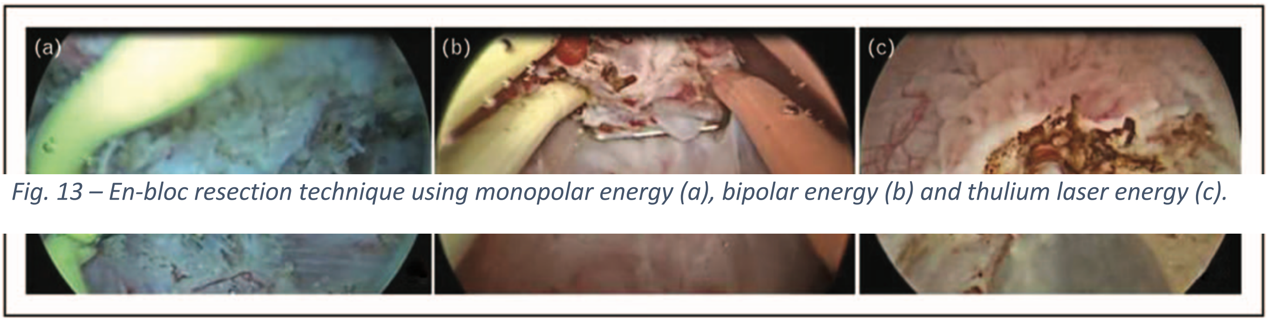

Fig. 13 – En-bloc resection technique using monopolar energy (a), bipolar energy (b) and thulium laser energy (c).

Energy sources

Zhang et al. [99] evaluated the safety and efficacy of the bipolar button electrode for ERBT of NMIBC. In their study of 82 patients, the authors concluded that this technique guarantees accurate resection of the tumor, reduces postoperative irrigation and the period of catheterization, shortens postoperative hospital stay, is associated with a trifling number of intraoperative and postoperative complications, and provides good oncological outcomes. To overcome the limitation that performing a procedure with a new technique requires a learning curve, Teoh et al. [102] conceived a porcine training model for performance of transurethral piecemeal and en bloc resection as an easy-to-build and low-cost model for training purposes worldwide.

In 2018 Balan et al. [97] conducted a clinical comparison to evaluate whether bipolar ERBT or standard monopolar TURBT is the best way to treat medium-sized superficial papillary bladder tumors. The patients treated with en-bloc bipolar resection showed a lower frequency of obturator nerve reflex, a reduction in the average operating time, catheterization time, a decrease in hemoglobin levels, and a minor hospital stay. Furthermore, the authors emphasized that the specimens obtained from patients treated with en-bloc resection had a well-represented muscular layer with minimal cauterization artifacts, making evaluation of the tumor depth easier for the pathologists (Table 1). Cheng et al. [78] compared the submucosal en-bloc resection technique with the hybrid knife for treatment of NMIBC with conventional TURBT. The former technique uses a multifunctional probe that combines a water jet system and electrosurgical technology, allowing injection of solution into the sub-mucosa to create a fluid cushion to facilitate en-bloc resection with a single instrument. For the hybrid knife technology, the authors reported a longer average operating time for tumors greater than 3 cm diameter. Postoperative irrigation time, catheter indwelling time, and hospital stay were shorter in the hybrid knife group. The overall complication rate of TURBT was much higher than that of endoscopic submucosal dissection. Preoperative and postoperative changes in hemoglobin showed no significant differences between the two groups. Compared with conventional TURBT, application of the hybrid knife led to a decrease in complications and the rate of recurrence and offered a safer and more effective approach for NMIBC. In their study, Hayashida et al. [103] used a combined technique consisting of transurethral endoscopic mucosal resection using a polypectomy snare (EMR) and en-bloc resection in 39 patients with tumors at least 1.5cm in diameter and compared the results with those in a group of patients with the same characteristics who were treated with conventional TURBT. They found no difference between the two techniques in terms of operative time, incidence of severe complications, blood transfusion, risk of recurrence, urinary catheterization, or recurrence rate. Nevertheless, the pathologists were able to assert the presence or absence of invasive disease in all specimens from patients who underwent en-bloc surgery, with a statistically significant difference compared with the other group.

Tab. 1- Comparison between conventional TURBT and different en-bloc resection techniques

	Bipolar	Laser (thulium)	KTP	Water jet	EMR with en bloc
Bălan *et al.*	↓ Obturator nerve reflex ↓ Average operating time ↓ Decrease in haemoglobin ↓ Catheterization time ↓ Duration of hospital stay ↑ Representation of muscular layer in the specimen ↓ Cauterization artifacts ↓ Recurrence rate				
Cheng *et al.*				↑ Operating time in tumors more than 3 cm ↓ Postoperative irrigation time ↓ Catheter indwelling time ↓ Duration of hospital stay ↓ Overall complication rate ↓ Recurrence rate	
Hayashida *et al.*					↑ Possibility of evaluating the presence or not of invasive disease in the specimen
Liang *et al.*			↑ Identification of muscularis mucosae		
Li *et al.* (compared with plasmakinetic transurethral resection)		↓ Operating time ↓ Hospitalization time ↓ Postoperative irrigation time ↓ Catheterization time ↑ Representation of muscular layer in the specimen			

EMR, endoscopic mucosal resection; KTP, potassium titanyl phosphate.

Histological findings

The latest findings considered in our review suggest that, although further studies are needed, the en-bloc resection technique can offer significant advantages. First of all, from an anatomopathological point of view, the technique results in a noticeable improvement in the quality of collected samples in terms of representation of muscle layers, with a reduction in cauterization artefacts [97] [103] [104]. Furthermore, the possibility of obtaining a good sample of the underlying layers of the mucosa could lead to different therapeutic decisions compared with samples of more superficial layers [105] [106] [107]. Kardoust

Parizi et al. [106] confirmed that T1 substaging, according to the relationship between muscularis mucosae and tumor, is of prognostic value as it is associated with prognostic outcomes of bladder cancer. In 2019, Liang et al. [107] suggested that, although further confirmation needs to be obtained in larger studies, ERBT using KTP green-light laser improves the identification of muscularis mucosae in the specimen, which may facilitate accurate identification of the T1 substage.

Many concerns are related to the oncological outcomes. Particularly, some authors [97] [78] have also found a reduction in the recurrence rate in patients treated with en-bloc resection compared with patients who underwent conventional resection.

Surgical outcomes

The reviewed studies not only indicate that ERBT improves the histological sample but also contain interesting results on the surgical outcomes of ERBT compared with the conventional procedure. As regards operating times, some authors have reported a reduction [108] [97] whereas others have reported an increase for larger lesions [78]. Improvements in length of hospital stay, postoperative irrigation time, catheterization time, hemoglobin loss, obturator reflex, and overall complication rate have been reported with en-bloc resection [108] [97] [78]. In a retrospective comparison of thulium laser en-bloc resection and plasma kinetic transurethral resection, no difference in complications or recurrence-free rates were noted [108], but the authors did report shorter operative, hospitalization, post- operative irrigation, and catheterization times in those patients who underwent thulium laser en-bloc resection. Hurle et al. [109]

evaluated the role of en-bloc resection in patients who had previously undergone en-bloc resection for high-risk NIMBC and concluded that ERBT appears to be a feasible, well tolerated, and effective procedure with a low rate of complications.

Study 2: results

A total of 300 consecutive patients met the inclusion criteria and were enrolled in the study between April 2018 and June 2021. The study was suspended between March 2020 and September 2020 due to SARS-CoV-2 pandemic.

Fifty-two patients (17,3%) were excluded after treatment allocation because they did not meet inclusion criteria at the moment of the surgical procedure (*see fig. 14*). 248 patients were included in the analysis, 140 in the ERBT and 108 in the cTURBT group. Among the patients excluded for technical issues, one patient had a stenosis of the urethra, another a flat lesion deemed unsuited for ERBT, and the remaining four patients did not undergo ERBT because of surgeon's preference.

Population characteristics are summarized in Table 2. The two population did not differ in a statistically significant way in all the analyzed variables.

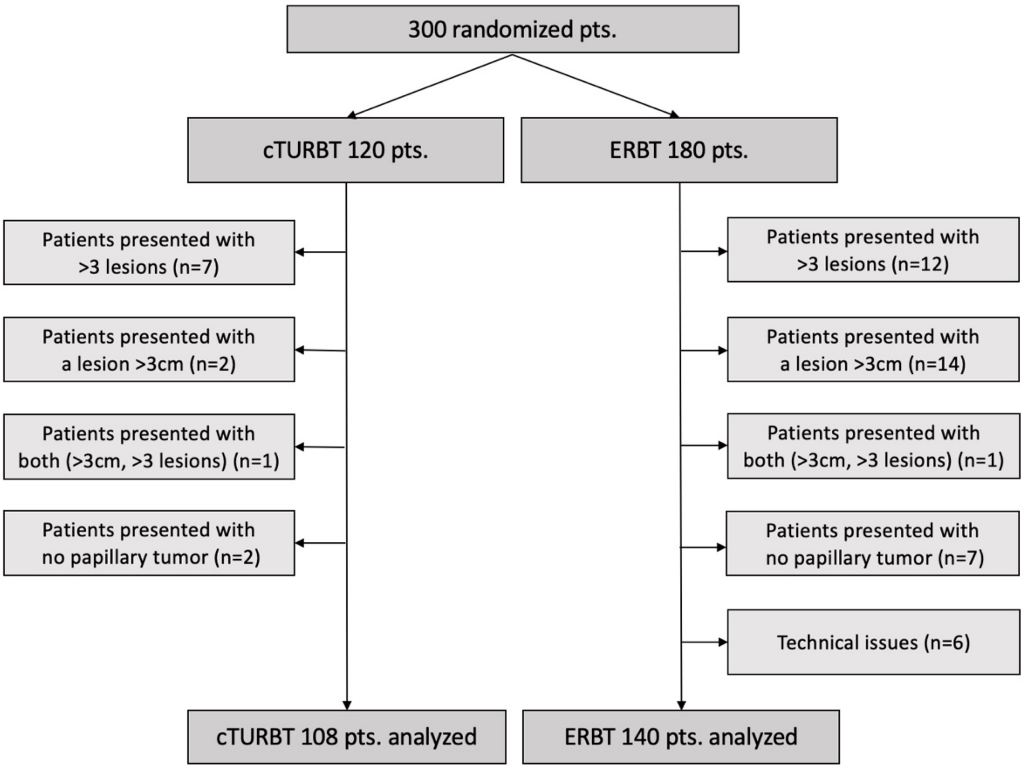

Fig. 14 - Patients flowchart

Tab. 2 - Patient population

	overall	**c-TURBT**	**ERBT**	**p-value**
Patients, n(%)	248	108 (43.5)	140 (56.5)	
Gender, n (%)				
Male	200 (80.6)	91 (84.3)	109 (77.9)	0.206
Female	48 (19.4)	17 (15.7)	31 (22.1)	
Age, median (IQR)	72 (64-80)	73 (65-78.75)	72 (61.25-80)	0.727
Hemoglobin, median (IQR)	143 (133-154)	142 (129-154)	144 (135-154)	0.564
Smoking habit, n (%)				
Active smoker	82 (33.1)	33 (30.6)	49 (35)	0.762
Former smoker	73 (29.4)	33 (30.6)	40 (28.6)	
Never smoker	93 (37.5)	42 (38.8)	51 (36.4)	
Hypertension, n (%)				
Yes	139 (56)	63 (58.3)	76 (54.3)	0.524
No	109 (44)	45 (41.7)	64 (45.7)	
Diabetes, n (%)				
Yes	62 (25)	28 (25.9)	34 (24.3)	0.767
No	186 (75)	80 (74.1)	106 (75.7)	
Myocardial infarction, n (%)				0.460
Yes	32 (12.9)	12 (11.1)	20 (14.3)	

No	216 (87.1)	96 (88.9)	120 (85.7)	
Stroke, n (%)				
Yes	11 (4.4)	6 (5.6)	5 (3.6)	0.452
No	237 (95.6)	102 (94.4)	135 (96.4)	
Anticoagulant, n (%)				
Yes	31 (12.5)	14 (13)	17 (12.1)	0.846
No	217 (87.5)	94 (87)	123 (87.9)	
Antiaggregant, n (%)				
Yes	44 (17.7)	19 (17.6)	25 (17.9)	0.957
No	204 (82.3)	89 (82.4)	115 (82.1)	
Radiation cystitis, n (%)				
Yes	5 (2)	4 (3.7)	1 (0.7)	0.097
No	243 (98)	104 (96.3)	139 (99.3)	
Bladder cancer history, n (%)				
LG BC history	59 (23.8)	28 (25.9)	31 (22.1)	0.488
HG BC history	45 (18.1)	21 (19.4)	24 (17.1)	0.641
Pre-op. cytology, n (%)				
Positive	38 (15.3)	18 (16.7)	20 (14.3)	
Negative	193 (77.8)	84 (77.8)	109 (77.8)	0.859
Suspicious	12 (4.8)	4 (3.7)	8 (5.7)	
Not performed	5 (2.1)	2 (1.9)	3 (2.1)	

Surgical outcomes

Intra- and post-operative data are shown in Table 3.

ERBT conversion to cTURBT was necessary in 6 cases (4.3%) due to the impossibility to safely or completely resect the tumor with the *en-bloc* approach (i.e., bladder neck tumors).

In the ERBT group, the specimen was extracted inside the resectoscope sheath in 90.7% (127/140) cases, while in the remaining cases it was extracted either by extracting it with the entire resectoscope or by splitting of the tumor.

The two groups did not differ both in term of intra-operative and post-operative outcomes. We reported similar median surgery duration, bladder wall perforation and obturator nerve stimulation (except for the ERBT-tl group).

Adjuvant treatment was planned in 49.3% and 39.8% of cases in ERBT and cTURBT (p=0.1) and was actually administered in a higher percentage of cases in the ERBT group, even though the data is not statistically significant (94.2% vs 86.0%; p=0.141).

Regarding post-operative outcomes and complications, we described similar irrigation and catheterization time and hospital length of stay.

Complications were reported in 20.7% and 24.1% of cases in the ERBT and cTURBT groups, respectively (p=0.5). Clavien-Dindo >2 complications were 4.3% vs 2.8% for and ERBT and cTURBT (p=0.5). Only two patients from the cTURBT group received a blood transfusion.

Tab. 3- Surgical outcomes

	overall	**c-TURBT**	**ERBT**	**p-value**
Patients, n (%)	248	108 (43.5)	140 (56.5)	
Operative time, median (IQR)	30 (20-40)	30 (20-35)	30 (20-40)	0.129
Obturator reflex, n (%)	22 (8.9)	7 (6.5)	15 (10.7)	0.245
Perforation, n (%)				
Grade 0	146 (58.9)	64 (59.3)	82 (58.6)	
Grade 1	56 (22.6)	26 (24.1)	30 (21.4)	0.905
Grade 2	41 (16.5)	16 (14.8)	25 (17.9)	
Grade 3	5 (2)	2 (1.9)	3 (2.1)	
Planned Instillation, n (%)				
Yes	112 (45.2)	43 (39.8)	69 (49.3)	0.137
No	136 (54.8)	65 (60.2)	71 (50.7)	
Performed instillation, n (%)				
Yes	102 (91.1)	37 (86.0)	65 (94.2)	0.141
No	10 (8.9)	6 (14.0)	4 (5.8)	
Complications, n (%)				
Clavien 0	193 (77.8)	82 (75.9)	111 (79.3)	
Clavien 1	13 (5.2)	7 (6.5)	6 (4.3)	0.715
Clavien 2	33 (13.3)	16 (14.8)	17 (12.1)	
Clavien 3	9 (3.6)	3 (2.8)	6 (4.3)	

Post-op Hb, median (IQR)	137 (121-145)	137 (119-147)	137 (123-144)	0.976
Blood Transfusion, n (%)	2 (0.8)	2 (1.9)	0 (0)	0.206
Irrigation, median (IQR)	0.5 (0.5-1)	0.5 (0.5-1)	0.5 (0.5-1)	0.143
Catheterization, median (IQR)	2 (2-3)	2 (2-3)	2 (1-3)	0.236
Hospitalization, median (IQR)	2 (2-2)	2 (2-2)	2 (1.25-2)	0.629

Pathological outcomes

The two groups were similar in terms of tumor dimension, focality and localization. In the per-lesion analysis, similar rates of detrusor muscle presence (92.8% vs 93.2%, p=0.9), Tx tumors (6.2% vs 4.1%, p=0.39) and artifact presence (7.2% vs 8.1%, p=0.74) were found in the ERBT and cTURBT groups (Table 3).

T1 substaging feasibility rate was significantly superior in the ERBT vs cTURBT group (100% vs 84.2%, p=0.02). These findings were confirmed in per-patient analysis that showed a statistically significant higher T1 substaging feasibility rate in favor of ERBT (100% vs 80%, p=0.02).

Tab. 1 - Pathological outcomes, per-lesion

	overall	**c-TURBT**	**ERBT**	**p-value**
Number of lesions, n (%)	341	147 (43.1%)	194 (56.9%)	
Tumor dimension, n (%)				0.075
< 10 mm	176 (51.6)	84 (57.1)	92 (47.4)	
10-30 mm	165 (48.4)	63 (42.9)	102 (52.6)	
Tumor location, n (%)				0.717
Trigon	48 (14.1)	24 (16.3)	24 (12.4)	
Posterior wall	55 (16.1)	26 (17.7)	29 (14.9)	
Right wall	78 (22.9)	27 (18.4)	51 (26.3)	
Left wall	99 (29)	43 (29.3)	56 (28.9)	
Anterior wall	19 (5.6)	8 (5.4)	11 (5.7)	
Dome	22 (6.5)	10 (6.8)	12 (6.2)	
Bladder neck	20 (5.9)	9 (6.1)	11 (5.7)	
Tumor location, n (%)				0.686
Trigon	48 (14.1)	24 (16.3)	24 (12.4)	
Posterior wall	55 (16.1)	26 (17.7)	29 (14.9)	
Lateral walls	177 (51.9)	70 (47.7)	107 (55.2)	
Anterior wall/dome	41 (12.1)	18 (12.2)	23 (11.9)	
Bladder neck	20 (5.9)	9 (6.1)	11 (5.7)	
Artefacts, n (%)				0.237

Absent	315 (92.4)	135 (91.8)	180 (92.8)	
Limited	11 (3.2)	3 (2)	8 (4.1)	
Extensive	15 (4.4)	9 (6.1)	6 (3.1)	
Detrusor muscle, n (%)				0.929
Present	317 (93)	137 (93.2)	180 (92.8)	
Absent	24 (7)	10 (6.8)	14 (7.2)	
Tumor grade, n (%)				0.936
Low grade	169 (49.6)	75 (51)	94 (48.5)	
High grade	132 (38.7)	56 (38.1)	76 (39.2)	
CIS	11 (3.2)	5 (3.4)	6 (3.1)	
T0	29 (8.5)	7 (7.5)	18 (9.2)	
Tumor Stage, n (%)				0.805
Tx	18 (5.3)	6 (4.1)	12 (6.2)	
CIS	7 (2.1)	3 (2)	4 (2.1)	
Ta	225 (66)	101 (68.7)	124 (63.9)	
T1	49 (14.4)	19 (12.9)	30 (15.5)	
T2	14 (4.1)	7 (4.8)	7 (3.6)	
T0	28 (8.2)	11 (7.5)	17 (8.8)	
T1 substage feasibility, n(%)				**0.025**
Yes	46 (93.9)	16 (84.2)	30 (100)	
No	3 (6.1)	3 (15.8)	0 (0)	
T1 substage, n (%)	46	16	30	**0.140**
T1a	34 (69.4)	11 (30)	23 (75)	
T1b	10 (20.4)	3 (30)	7 (25)	
T1c	2 (4.1)	2 (20)	0 (0)	

Pathological outcomes

Median follow-up duration was 15 months (IQR 7-28 months). Disease recurrence rates at three months were similar between cTURBT vs ERBT groups (0% vs 0.7%, p=1). Similarly, overall recurrence rates were not statistically different between the two groups (17.6% vs 12.9%, p=0.3), and the Kaplan-Meier curves failed to demonstrate any statistically significant difference between ERBT and cTURBT regarding the recurrence-free survival, both overall and after stratifying for the grade of the disease (Figure 14).

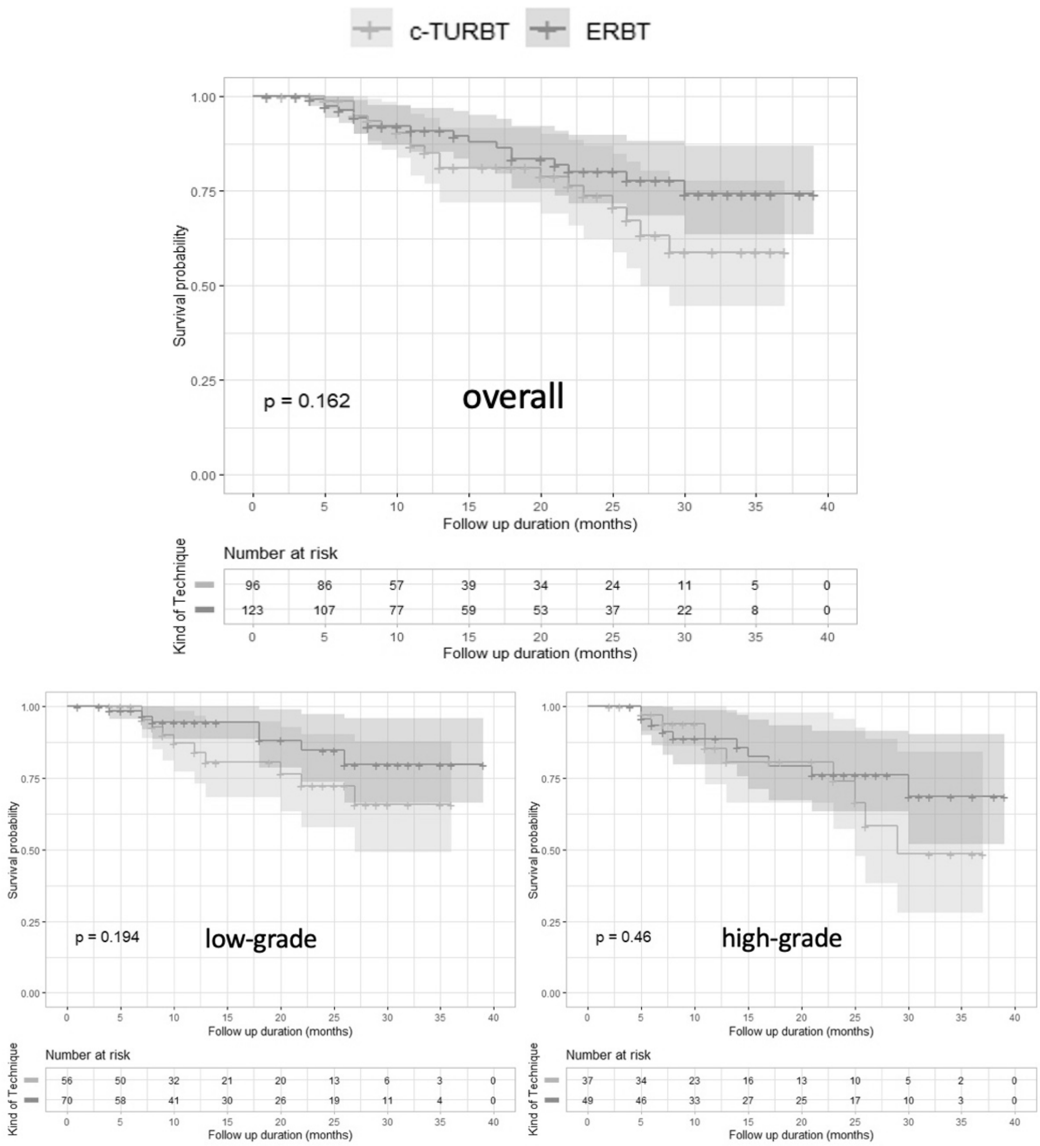

Fig. 14 - Kaplan-Meier estimates for RFS

Study 3: results

A total of 180 participants were enrolled between April 2018 and June 2021. Forty (22.2%) patients were subsequently excluded because they did not meet inclusion criteria. One hundred and forty patients were included in the final analysis: 49 (35%) m-ERBT, 45 (32.1%) b-ERBT, and 46 (32.9%) l-ERBT. One-hundred nine (77.9%) patients were male and mean age was 71 years (±11.8). Each energy group were similar in terms of patient and tumor characteristics (Tables 4 and 5), except for the baseline number of tumor which was higher in the l-ERBT patients (1.62 ± 0.59) than patients who underwent m-ERBT (1.24 ± 0.48) and b-ERBT (1.3 ± 0.78; p = 0.009). Pathological tumor staging was as follow: 11 T0 (7.8%), 6 Tx (4.3%), 2 CIS (1.4%), 90 Ta (64.3%), 20 T1a (14.3%), 5 T1b (3.6%), 6 T2 (4.3%) tumors. Tables 6 and 7 show the intra- and post-operative outcomes by either energy source employed (m-ERBT, b-ERBT, and l-ERBT) or by bladder walls (group 1: trigone and the posterior wall; group 2: right and left lateral walls; and group 3: anterior wall, dome, and bladder neck), respectively. In total, DM was present in 133 pathological specimens (95%). The rate of DM presence was comparable between the energies used (p = 0.796) or the location of the lesion (p = 0.662). The rate of DM presence was similar between residents and attendings (96.4 vs. 94% p = 0.702). While no case of ONR occurred in the l-ERBT group, five (10.2%) and ten (22.2%) cases were recorded in the m-ERBT and b-ERBT patients, respectively (p = 0.001). The over- all length of postoperative catheterization was 2.4 days (± 1.8) and was significantly shorter in the m-ERBT group (p = 0.034). As shown in Table 5, conversion from EBRT to cTURBT was found to be higher for lesions located in the anterior wall, dome or bladder neck, reaching 22.7% (5/22; p < 0.001). The presence of artifact in the pathological specimen ($p = 0.030$) was higher for lesions located to the posterior wall and trigone (17.9%; 7/39, $p = 0.03$). Overall complication rate and major complication rate was 12.2/2%, 26.7/8.9%, and 23.9/2.2% for m-ERBT, b-ERBT, and l-ERBT, respectively. Subgroup analysis comparing the energy used per bladder wall is provided in Tables 8 and 9. In case of anterior wall lesions, the rate of conversion from ERBT to cTURBT was significantly higher for both monopolar ($p = 0.031$) and laser energy ($p = 0.027$); the occurrence of ONR, recorded only in the lateral walls, was significantly higher when we used monopolar and bipolar electrocautery energies ($p = 0.016$ and $p < 0.001$, respectively).

Tab.4 - Population demographics

	Patients
Number of patients	140
Gender, n (%)	
Male	109 (77.9)
Female	31 (22.1)
Age, mean (SD)	71 (11.8)
Hemoglobin, mean (SD)	142.2 (17.5)
Tobacco, n (%)	
Active smoker	49 (35)
Former smoker	40 (28.6)
Non-smoker	51 (36.4)
Hypertension, n (%)	
Yes	76 (54.3)
No	64 (45.7)
Diabetes, n (%)	
Yes	34 (24.3)
No	106 (75.7)
History of myocardial infarction, n (%)	
Yes	20 (14.3)
No	120 (85.7)
History of stroke, n (%)	
Yes	5 (3.6)
No	135 (96.4)
Anticoagulant therapy, n (%)	
Yes	17 (12.1)
No	123 (87.9)
Antiplatelets therapy, n (%)	
Yes	25 (17.9)
No	115 (82.1)
Urine culture prior to surgery, n (%)	
Positive	5 (3.6)
Negative	135 (96.4)
Radiation induced cystitis, n (%)	
Yes	1 (0.7)
No	139 (99.3)
History of BC, n (%)	50 (35.7)
History of LG BC	31 (22.1)
History of HG BC	24 (17.1)
Pre-operative urine cytology, n (%)	
Positive	20 (14.3)
Negative	109 (77.8)
Suspicious	8 (5.7)
Not performed	3 (2.1)

*Tab.5 - Data and analysis per-patient of the pathological outcome endoscopic resection divided by energy source (monopolar, bipolar, and laser). *Patients are stratified according to the EAU 2018 guidelines risk categories. Abbreviations: low grade (LG); high grade (HG) carcinoma in situ (CIS); Analysis of variance (ANOVA).*

Energy employed	Overall	Monopolar	Bipolar	Thulium Laser	ANOVA or Fisher Exact test (p value)
Number of patients, n (%)	140 (56.5)	49 (19.8)	45 (18.1)	46 (18.5)	-
Bladder systematic mapping Stage					
Tx					
Ta	3 (13.6)	1 (14.3)	1 (16.7)	1 (11.1)	0.896
CIS	1 (4.6)	1 (14.3)	0 (0)	0 (0)	
	18 (81.8)	5 (71.4)	5 (83.3)	8 (88.9)	
Bladder systematic mapping Grade					
LG					
HG	2 (9.1)	1 (14.3)	1 (16.7)	0 (0)	0.684
CIS	1 (4.6)	1 (14.3)	0 (0)	0 (0)	
Unspecified	18 (81.8)	5 (71.4)	5 (83.3)	8 (88.9)	
	1 (4.6)	0 (0)	0 (0)	1 (11.1)	
Lesion dimension, n (%)					
<1 cm	63 (45)	25 (51)	19 (42.2)	19 (41.3)	0.581
>1cm	77 (55)	24 (49)	26 (57.8)	27 (58.7)	
Number of lesions, mean (SD)	1.39 (0.64)	1.24 (0.48)	1.3 (0.78)	1.62 (0.59)	**0.009**
Tumor Stage, n (%)					
Tx	6 (4.3)	2 (4.1)	1 (2.2)	3 (6.5)	
Tis	2 (1.4)	0 (0)	2 (4.4)	0 (0)	
Ta	90 (64.3)	32 (65.3)	29 (64.4)	29 (63)	0.657
T1	25 (17.9)	9 (18.4)	8 (17.8)	8 (17.4)	
T2	6 (4.3)	3 (6.1)	0 (0)	3 (6.5)	
T0/Benign/other	11 (7.8)	3 (6)	5 (11.1)	3 (6.5)	
T1 substage, n (%)					
1a	20 (80)	9 (100)	6 (75)	5 (62.5)	0.146
1b	5 (20)	0 (0)	2 (25)	3 (37.5)	
1c	0 (0)	0 (0)	0 (0)	0 (0)	
Tumor grade, n (%)					
Low grade	70 (50)	26 (53.1)	20 (44.4)	24 (52.2)	
High grade	55 (39.3)	20 (40.8)	16 (35.6)	19 (41.3)	0.243
CIS	4 (2.9)	0 (0)	4 (8.9)	0 (0)	
T0/Benign/other	11 (7.8)	3 (6)	5 (11.1)	3 (6.5)	
Risk Category*					
Low	11 (7.9)	3 (6.1)	3 (6.7)	5 (10.9)	
Intermediate	71 (50.7)	15 (30.6)	18 (40)	14 (30.4)	0.751
High	47 (33.6)	28 (57.1)	19 (42.2)	24 (52.2)	
T0/Benign/other	11 (7.9)	3 (6.1)	5 (11.1)	3 (6.5)	

Tab.6 - Intra-operative and post-operative outcome divided by energy source (monopolar, bipolar, and laser) and ANOVA or Fisher exact test analysis of the overall distribution between the three groups and pair comparisons.

Energy employed	Overall	Monopolar	Bipolar	Thulium laser	ANOVA or fisher exact test (*p* value)	Monopolar vs bipolar	Monopolar vs thulium laser	Bipolar vs thulium laser
Number of patients, *n* (%)	140	49 (35)	45 (32.1)	46 (32.9)	–	–	–	–
Lesion location, *n* (%)					0.505	–	–	–
Posterior/trigone	39 (27.9)	15 (30.6)	15 (33.3)	9 (19.6)				
Lateral walls	79 (56.4)	25 (51)	25 (55.6)	29 (63)				
Anterior/dome/neck	22 (15.7)	9 (18.4)	5 (11.1)	8 (17.4)				
Surgery duration, mean (SD)	33.4 (17.5)	31.8 (16.9)	34.7 (17.6)	33.8 (18.3)	0.72	–	–	–
Conversion to cTURBT, *n* (%)	6 (4.3)	2 (4.1)	2 (4.4)	2 (4.3)	1	–	–	–
Obturator nerve reflex, *n* (%)	**15 (10.7)**	**5 (10.2)**	**10 (22.2)**	**0 (0)**	**0.001**	0.159	**0.056**	**< 0.001**
Perforation, *n* (%)	28 (20)	7 (14.3)	13 (28.9)	8 (17.4)	0.193	0.129	0.781	0.221
Planned early CT instillation, *n* (%)	69 (49.3)	26 (53.1)	22 (48.9)	21 (45.7)	0.633	–	–	–
Performed early CT instillation of planned, n (%)	65 (94.2)	26 (100)	20 (90.9)	19 (86.4)	0.494	–	–	–
Complications, *n* (%)					–	–	–	–
No complications	111 (79.3)	43 (87.8)	23 (73.3)	35 (76.1)				
Clavien-dindo 1–2	23 (16.4)	5 (10.2)	8 (17.8)	10 (21.7)				
Clavien-dindo 3	6 (4.3)	1 (2)	4 (8.9)	1 (2.2)				
Overall complications, *n* (%)	29 (20.7)	6 (12.2)	12 (26.7)	11 (23.9)	0.172	0.114	0.182	0.812
Major complications, *n* (%)	6 (4.3)	1 (2)	4 (8.9)	1 (2.2)	0.282	–	–	–
Artifacts	11 (7.9)	2 (4.1)	6 (13.3)	3 (6.5)	0.253	–	–	–
Detrusor muscle					0.796	–	–	–
Yes	133 (95)	47 (95.9)	42 (93.3)	44 (95.7)				
No	7 (5)	2 (4.1)	3 (6.7)	2 (4.3)				
T1 substage feasibility					1	–	–	–
Yes	25 (100)	9 (100)	8 (100)	8 (100)				
No	0 (0)	0 (0)	0 (0)	0 (0)				
Length of irrigation, mean (SD)	0.9 (0.9)	0.9 (0.9)	1 (0.9)	0.9 (0.8)	0.692	–	–	–
Length of catheterization days, mean (SD)	**2.4 (1.8)**	**1.9 (1.3)**	**2.5 (1.8)**	**2.8 (2.1)**	**0.034**	0.162	**0.033**	0.779
Length of stay, mean (SD)	2.1 (1.2)	2.1 (1.4)	2.4 (1.3)	2.1 (0.9)	0.525	–	–	–
Post-op hemoglobin, mean (SD)	9 (9.4)	6.8 (8.8)	9.7 (9.8)	10.7 (9.3)	0.167	0.374	0.166	0.891

cTURBT conventional transurethral resection of bladder tumor, *SD* standard deviation, *CT* chemotherapy, *ANOVA* analysis of variance

Tab.7 - Intra-operative and post-operative outcome divided by bladder walls (posterior/trigone, lateral walls, and anterior/dome/neck) and ANOVA or Fisher exact test analysis of the overall distribution between the three groups and pair comparisons.

Energy employed	Overall	Posterior/trigone (1)	Lateral walls (2)	Anterior/dome/neck (3)	ANOVA or fisher exact test (*p* value)	1 vs. 2	1 vs. 3	2 vs. 3
Number of patients, *n* (%)	140	39 (27.9)	79 (56.4)	22 (15.7)	–	–	–	–
Energy, *n* (%)					0.285	–	–	–
Monopolar	39 (27.9)	15 (38.5)	25 (31.6)	9 (40.9)				
Bipolar	79 (56.4)	15 (38.5)	25 (31.6)	5 (22.7)				
Thulium laser	22 (15.7)	9 (23)	29 (36.8)	8 (36.4)				
Surgery duration, mean (SD)	33.4 (17.5)	29.6 (16.8)	35.2 (16.4)	33.6 (21.9)	0.261	–	–	–
Conversion to cTURBT, *n* (%)	**6 (4.3)**	**1 (2.6)**	**0 (0)**	**5 (22.7)**	**< 0.001**	0.33	**0.019**	**< 0.001**
Obturator nerve reflex, *n* (%)	15 (10.7)	3 (7.7)	13 (16.5)	0 (0)	0.071	0.257	0.547	0.065
Perforation, *n* (%)	28 (20)	8 (20.5)	16 (20.3)	4 (18.2)	1	–	–	–
Planned early CT instillation, *n* (%)	69 (49.3)	16 (41)	42 (53.2)	11 (50)	0.461	–	–	–
Performed early CT instillation of planned, *n* (%)	65 (94.2)	15 (38.5)	40 (50.6)	10 (45.5)	0.787	–	–	–
Complications, *n* (%)					–	–	–	–
No complications	111 (79.3)	31 (79.5)	65 (82.3)	15 (68.2)				
Clavien-dindo 1–2	23 (16.4)	6 (15.4)	11 (13.9)	6 (27.3)				
Clavien-dindo 3	6 (4.3)	2 (5.1)	3 (3.8)	1 (4.5)				
Overall complications, *n* (%)	29 (20.7)	8 (20.5)	14 (17.7)	7 (31.8)	0.357	–	–	–
Major complications, *n* (%)	6 (4.3)	2 (5.1)	3 (3.8)	1 (4.5)	1	–	–	–
Artifacts	**11 (7.9)**	**7 (17.9)**	**3 (3.8)**	**1 (4.5)**	**0.03**	**0.014**	0.238	1
Detrusor muscle					0.662	–	–	–
Yes	133 (95)	36 (92.3)	76 (96.2)	21 (95.5)				
No	7 (5)	3 (7.7)	3 (3.8)	1 (4.5)				
T1 substage feasibility					1	–	–	–
Yes	25 (100)	6 (100)	18 (100)	2 (100)				
No	0 (0)	0 (0)	0 (0)	0 (0)				
Length of irrigation, mean (SD)	0.9 (0.9)	0.8 (0.6)	0.9 (0.9)	1.3 (1.2)	0.069	0.671	0.057	0.152
Length of catheterization days, mean (SD)	2.4 (1.8)	2.1 (1.4)	2.5 (1.8)	2.6 (2.3)	0.382	–	–	–
Length of stay, mean (SD)	2.1 (1.2)	1.9 (0.9)	2.3 (1.3)	2.4 (1.5)	0.275	–	–	–
Hemoglobin drop, mean (SD)	9 (9.4)	7.2 (6.7)	8.8 (9.2)	12.1 (12.4)	0.203	0.746	0.182	0.349

cTURBT conventional transurethral resection of bladder tumor, *SD* standard deviation, *CT* chemotherapy, *ANOVA* analysis of variance

Tab.8 - ANOVA for ERBT energies (monopolar, bipolar, laser) divided per bladder wall. Abbreviations: standard deviation (SD); analysis of variance (ANOVA)

Variable	Walls	Overall	Monopolar N= 49	Bipolar N=45	Thulium Laser N=46	ANOVA / Fisher exact test	Monopolar Vs Bipolar	Monopolar Vs Thulium Laser	Bipolar Vs Thulium Laser
Obturator nerve reflex, n (%)	Trigone & Posterior	3/39 (7.7)	1/15 (6.7)	2/15 (13.3)	0/9 (0)	0.778	-	-	-
	Lateral walls	**13/79 (16.5)**	**5/25 (20)**	**8/25 (32)**	**0/29** (0)	**0.002**	0.520	**0.016**	**<0.001**
	Anterior wall & dome	0/22 (0)	0/9 (0)	0/5 (0)	0/8 (0)	**-**	-	-	-
Length of catheterization, mean (SD)	**Trigone & Posterior**	**2.1 (1.4)**	**1.4 (0.8)**	**2.4 (1.6)**	**2.7 (1.5)**	**0.044**	0.102	0.069	0.885
	Lateral walls	2.5 (1.8)	2.2 (1.5)	2.6 (1.8)	2.7 (2.1)	0.630	-	-	-
	Anterior wall & dome	2.6 (2.3)	1.8 (1.1)	2.8 (2.4)	3.4 (2.9)	0.353	-	-	-

Tab.8 - ANOVA for bladder wall divided per ERBT energies. Abbreviations: conventional transurethral resection of bladder tumor (cTURBT); analysis of variance (ANOVA).

Variable	Energy source	Overall	Posterior Trigone (1) N=39	Lateral walls (2) N=79	Anterior Dome/Neck (3) N=22	ANOVA / Fisher exact test	1 vs. 2	1 vs. 3	2 vs. 3
Conversion to cTURBT, n (%)	**Monopolar**	**2/49 (4.1)**	**0/15 (0)**	**0/25 (0)**	**2/9 (22.2)**	**0.031**	1	0.130	0.064
	Bipolar	2/45 (4.4)	1/15 (6.7)	0/25 (0)	1/5 (3.6)	0.085	-	-	-
	Laser	**2/46 (4.3)**	**0/9 (0)**	**0/29 (0)**	**2/8 (25)**	**0.027**	1	0.205	**0.042**
Artifacts, n (%)	Monopolar	2/49 (4.1)	1/15 (6.7)	0/25 (0)	1/9 (11.1)	0.234	-	-	-
	Bipolar	6/45 (13.3)	4/15 (26.7)	2/25 (8)	0/5 (0)	0.262	-	-	-
	Laser	3/46 (6.7)	2/9 (22.2)	1/29 (3.4)	0/8 (0)	0.167	-	-	-

Study 4: results

A total of 140 patients underwent en-bloc TURBT and 108 conventional TURBT. Population and operative characteristics are summarized in Table 1. After resection, 146/248 (58.9%), 56/248 (22.6%), 41/248 (16.5%), 5/248 (2.0%) patients presented a DEEP grade 0, 1, 2, and 3, respectively. All cases of intraperitoneal bladder perforation were treated conservatively with prolonged catheterization (5–7 days) and no surgical repair was ultimately required.

Tab.9 - Demographic and operative characteristics of the total cohort of patients, stratified for DEEP grade and compared using Chi-square or Kruskal–Wallis test

Variable	Total cohort (*n* = 248)	DEEP grade 0 (*n* = 146)	DEEP grade 1 (*n* = 56)	DEEP grade 2 (*n* = 41)	DEEP grade 3 (*n* = 5)	*P*
Gender, *n* (%)						
Male	200 (80.6)	122 (83.6)	44 (78.6)	32 (78)	2 (40)	0.093
Female	48 (19.4)	24 (16.4)	12 (21.4)	9 (22)	3 (60)	
Median (IQR) age, *years*	72 (64–80)	73 (64–80)	69.5 (64–76)	72 (65–78)	82 (76–85)	0.33
Median (IQR) preoperative hemoglobin, *g/L*	143 (133–154)	144 (133–154)	143 (132–155)	144 (135–150)	141 (136–143)	0.68
Tobacco, *n* (%)						
Active smoker	82 (33.1)	47 (32.2)	18 (32.1)	17 (41.5)	0	0.8
Former smoker	73 (29.4)	45 (30.8)	18 (32.1)	8 (19.5)	2 (40)	
Non-smoker	93 (37.5)	54 (37)	20 (35.8)	16 (39)	3 (60)	
History of bladder cancer, *n* (%)						
Yes	98 (39.5)	64 (43.8)	19 (33.9)	12 (29.3)	3 (60)	0.21
No	150 (60.5)	82 (56.2)	37 (66.1)	29 (70.7)	2 (40)	
Surgeon, *n* (%)						
Senior urologist	134 (52)	84 (57.5)	26 (46.4)	22 (53.7)	2 (40)	0.7
Resident	114 (48)	62 (42.5)	30 (53.6)	19 (46.3)	3 (60)	
Median (IQR) surgery duration, min	30 (20–40)	27.5 (20–40)	30 (20–40)	35 (30–40)	40 (30–45)	0.013
Systematic random biopsies, *n* (%)						
Yes	195 (78.6)	119 (81.5)	39 (69.6)	34 (82.9)	3 (60)	0.18
No	53 (21.4)	27 (18.5)	17 (30.4)	7 (17.1)	2 (40)	
Tumor diameter, *n* (%)						
< 1 cm	118 (47.6)	70 (47.9)	28 (50)	19 (46.3)	1 (20)	0.88
≥ 1 cm	130 (52.4)	76 (52.1)	28 (50)	22 (53.7)	4 (80)	
Tumor location, *n* (%)						
Trigone/posterior	79 (31.9)	58 (39.7)	11 (19.6)	9 (22)	1 (20)	0.059
Lateral walls	130 (52.4)	68 (46.6)	35 (62.5)	23 (56)	4 (80)	
Anterior/dome /neck	39 (15.7)	20 (13.7)	10 (17.9)	9 (22)	0	
Tumor number, *n* (%)						0.94
Single	178 (71.8)	106 (72.6)	40 (71.4)	29 (70.7)	3 (60)	
Multiple	70 (28.2)	40 (27.4)	16 (28.6)	12 (29.3)	2 (40)	
Technique of resection, *n* (%)						
cTURBT	108 (43.5)	64 (43.8)	26 (46.4)	16 (39)	2 (40)	0.91
EBRT	140 (56.5)	82 (56.2)	30 (53.6)	25 (61)	3 (60)	
Surgeon, *n* (%)						
Urologist	134 (54)	84 (57.5)	26 (46.4)	22 (53.7)	2 (40)	0.49
Resident	114 (46)	62 (42.5)	30 (53.6)	19 (46.3)	3 (60)	
Obturator nerve reflex, *n* (%)						
Absent	226 (91.1)	138 (94.5)	49 (87.5)	35 (85.4)	3 (60)	0.017
Present	22 (8.9)	8 (5.5)	7 (12.5)	6 (14.6)	2 (40)	
No. of planned postoperative CT instillations, *n* (%)						
Yes	112 (45.2)	71 (48.6)	25 (44.6)	13 (31.7)	3 (60)	0.25
No	136 (54.8)	75 (51.4)	31 (55.4)	28 (68.3)	2 (40)	
No. of postoperative CT instillations performed, *n* (%)						
Yes	102 (91.1)	71 (97.3)	24 (92.3)	7 (70)	0	
No	10 (8.9)	2 (2.7)	2 (7.7)	3 (30)	3 (100)	< 0.001

IQR Interquartile Range, *cTURBT* Conventional TransUrethral Resection of Bladder Tumor, *ERBT* En bloc Resection of Bladder Tumor, *CT* chemotherapy, *CD* Clavien–Dindo

Pre-operative variables distributed by DEEP grades are shown in Table 10. High-grade DEEP (grade 2–3) were more frequent in case of tumors located at the lateral walls (17.7% and 3.1% for grade 2 and 3, respectively) of the bladder and anterior wall/dome/neck (23.1% and 0% for grade 2 and 3, respectively) in respect to lesions found in the trigone and posterior walls (11.4% and 1.3% for grade 2 and 3, respectively). A linear regression analysis was performed to investigate the pre- and intra-operative variables that could be correlated with higher grade of DEEP scale (Table 10). At MVA, female gender [B coeff. 0.255; 95% CI 0.001–0.513; p = 0.05], tumor location [B coeff. 0.188 (0.026–0.339); p = 0.015], and obturator nerve reflex [B coeff. 0.503(0.148–0.857); p = 0.006] were independent predictors of higher DEEP grades.

Tab.10 - Linear regression analysis: preoperative and intraoperative predictors of high-grade perforation according to the DEEP scale (2–3)

	Univariate analysis		Multivariate analysis	
	B coeff. (95% CI)	*P*	*B* coeff. (95% CI)	*P*
Age	0.002 (– 0.007 to 0.012)	0.609	0.005 (– 0.005 to 0.014)	0.322
Gender				
Male	Ref		Ref	
Female	0.242 (– 0.019 to 0.504)	0.069	0.255 (0.001–0.513)	0.050
History of BC				
Yes	Ref		Ref	
No	0.143 (– 0.070 to 0.355)	0.187	0.103 (– 0.107–0.313)	0.336
Tumor diameter				
< 1 cm	Ref		–	–
> 1 cm	0.050 (– 0.155–0.255)	0.633		
Tumor location				
Trigone/posterior	Ref		Ref	
Lateral walls	0.185 (0.032–0.339)	0.018	0.188 (0.026–0.339)	0.015
Anterior/dome/neck				
Tumor number				
Single	Ref		–	–
Multiple	0.056 (– 0.175–0.287)	0.634		
Technique of resection				
cTURBT	Ref		–	–
ERBT	0.043 (– 0.167 to 0.253)	0.686		
Obturator nerve reflex				
Absent	Ref		Ref	
Present	0.518 (0.165–0.871)	0.004	0.503 (0.148–0.857)	0.006
Surgeon				
Urologist	Ref		–	–
Resident	0.108 (– 0.100 to 0.317)	0.308		

BC Bladder cancer, *cTURBT* conventional transurethral resection of bladder tumor, *ERBT* En bloc resection of bladder tumor

Post-operative variables distributed by DEEP grades are reported in Table 11. The rate of post-operative intravesical mitomycin administration was lower in high-grade perforations ($p < 0.001$), while the rate of complications ($p = 0.019$) and major complications ($p < 0.001$), length of irrigation ($p < 0.001$), length of catheterization ($p = 0.017$), and hospitalization time ($p = 0.002$) were higher compared to grade 0–1 perforation. In UVA, DEEP grade was significantly associated with the absence of post-operative intravesical instillation (OR = 5.579; $p < 0.001$), major complications (OR = 2.105; $p = 0.035$), length of irrigation (OR = 0.316; $p < 0.001$) and hospitalization time (OR = 0.385; $p < 0.001$). In MVA, DEEP scale remained an independent predictor of major complication [OR = 2.221 (1.098–4.495); $p = 0.026$], adjusted for age and surgeon experience (Supplementary table 1–5). DEEP scale [OR = 9.387 (2.434–36.20); $p = 0.001$] and female gender [OR = 6.727 (1.029–44.001); $p = 0.047$] were associated with no post-operative intravesical instillation in MVA adjusted for age, technique, and surgeon experience (Tables 12-16). DEEP scale [B. coeff 0.299 (0.166–0.441); $p < 0.001$] and age [B. coeff 0.019 (0.008–0.029); $p = 0.001$] independently predicted length of irrigation in MVA adjusted for surgical duration. DEEP scale [B. coeff 0.315 (0.111–0.519); $p = 0.003$], duration of surgery [B. coeff 0.013 (0.001–0.024); $p = 0.036$], and age [B. coeff 0.035 (0.020–0.050); $p < 0.001$] were independent predictors for hospital stay in MVA adjusted for history of BC and tumor size. The length of catheterization was not associated DEEP scale ($p = 0.11$).

Tab.11 - Chi-Square/ANOVA analysis and univariate logistic/linear regression analysis of the association between the DEEP scale and post- operative variables

	Perforation grade					Univariate analysis	
	0 (*n* = 146)	1 (*n* = 56)	2 (*n* = 41)	3 (*n* = 5)	*P*	OR or B coeff. (95% CI)	*P*
Detrusor muscle, *n* (%)							
Presence	136 (93.2)	53 (94.6)	40 (97.6)	5 (100)	0.683	Ref	0.238
Absence	10 (6.8)	3 (5.4)	1 (2.4)	0 (0)		0.611 (0.270–1.384)	
Tx, *n* (%)							
Yes	6 (4.1)	3 (5.4)	0 (0)	0 (0)	0.511	Ref	
No	140 (95.9)	53 (94.6)	41 (100)	5 (100)		1.720 (0.605–4.891)	0.309
Artifacts, *n* (%)							
Yes	131 (89.7)	53 (94.6)	40 (97.6)	5 (100)	0.281	Ref	
No	15 (10.3)	3 (5.4)	1 (2.4)	0 (0)		0.931 (0.296–2.928)	0.902
Mitomycin administration, *n* (%)							
Yes	71 (97.3)	24 (92.3)	7 (70)	0 (0)	< 0.001	Ref	
No	2 (2.7)	2 (7.7)	3 (30)	3 (100)		5.579 (2.359–13.191)	< 0.001
Complications (any grade), *n* (%)							
Yes	115 (78.8)	11 (19.6)	9 (22)	4 (20)	0.019	Ref	
No	31 (21.2)	45 (80.4)	32 (78)	1 (80)		1.258 (0.889–1.779)	0.105
Complications (CD > 2), *n* (%)							
Yes	4 (2.7)	1 (1.8)	2 (4.9)	3 (40)	< 0.001	Ref	
No	142 (97.3)	55 (98.2)	39 (95.1)	2 (60)		2.105 (1.054–4.203)	0.035
Hemoglobin drop, g/L	8.1 (11.5)	9.6 (9.2)	10.1 (9.9)	3.5 (8.0)	0.513	0.580 (– 1.192–2.351)	0.520
Median (IQR) length of irrigation, days	0.5 (0.5–1)	1 (0.5–1)	1 (0.5–1)	1 (0.5–2)	< 0.001	0.316 (0.173–0.459)	< 0.001
Median (IQR) length of catheterization, days	2 (1–2)	2 (1–2)	2 (2–4)	5 (5–7)	0.017	0.350 (– 0.002–0.703)	0.051
Median (IQR) length of stay, days	2 (1–2)	2 (1–3)	2 (2–3)	2 (2–5)	0.002	0.385 (0.171–0.597)	< 0.001

CD Clavien–Dindo

Tab.12 - Multivariate logistic regression analysis: detection of the factors predicting major complications (Clavien-Dindo Classification >2).

	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	11.695 (0.743-1.043)	0.059	1.071 (0.996-1.151)	0.062
Gender	1.199 (0.241-5.961)	0.825	-	-
History of bladder cancer	0.810 (0.212-3.095)	0.758	-	-
Tumor size	1.772 (0.155-6.900)	0.409	-	-
Tumor location	1.026 (-0.678-1.553)	0.904	-	-
Technique (cTURBT vs ERBT)	1.567 (0.383-6.414)	0.532	-	-
Obturator nerve reflex	0.811 (0.097-6.788)	0.847	-	-
DEEP scale	2.105 (1.054-4.203)	0.035	2.221 (1.098-4.495)	0.026
Duration of surgery	1.019 (0.82-1.058)	0.311	-	-
Surgeon (SU vs. Resident)	0.516 (0.220-1.214)	0.130	0.413 (0.164-1.044)	0.065

Tab.13 - Multivariate Logistic Regression Analysis: Predictive Factors of Postoperative Administration of Intravesical Chemotherapy

	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.052 (0.988-1.120)	0.155	1.103 (0.994-1.224)	0.064
Gender	4.100 (1.082-15.541)	0.038	6.727 (1.029-44.001)	0.047
History of bladder cancer	0.487 (0.127-1.866)	0.294	-	-
Tumor size	0.855 (0.233-3.133)	0.831	-	-
Tumor location	1.246 (0.823-1.885)	0.298	-	-
Technique (cTURBT vs ERBT)	0.379 (0.101-1.432)	0.153	0.141 (0.017-1.151)	0.067
Obturator nerve reflex	0.533 (0.101-2.812)	0.459	-	
DEEP scale	5.579 (2.359-13.191)	<0.001	9.387 (2.434-36.200)	0.001
Duration of surgery	1.004 (0.964-1.046)	0.832	-	-
Surgeon (SU vs. Resident)	2.398 (0.778-7.393)	0.128	1.681 (0.425-6.650)	0.459

Tab.14 - Multivariate Linear Regression Analysis: Detection of the Factors Predicting Length of Postoperative Irrigation

	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	0.019 (0.009-0.030)	<0.001	0.019 (0.008-0.029)	0.001
Gender	-0.083 (-0.395-0.229)	0.601	-	-
History of bladder cancer	0.100 (-0.152-0.352)	0.437	-	-
Tumor size	0.091 (-0.152-0.334)	0.462	-	-
Tumor location	0.044 (-0.034-0.121)	0.268	-	-
Technique (cTURBT vs ERBT)	-0.126 (-0.374-0.123)	0.320	-	-
Obturator nerve reflex	0.161 (-0.264-0.586)	0.456	-	-
DEEP scale	0.316 (-.173-0.459)	<0.001	0.299 (0.166-0.441)	<0.001
Duration of surgery	0.007 (-0.001-0.015)	0.076	0.003 (-0.005-0.011)	0.478
Surgeon (SU vs. Resident)	0.042 (-0.121-0.205)	0.614	-	-

Tab.15 - Multivariate Linear Regression Analysis: Detection of the Factors Predicting Length of Stay

	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	0.037 (0.022-0.052)	<0.001	0.035 (0.020-0.050)	<0.001
Gender	0.641 (-0.572 -0.338)	0.614	-	-
History of bladder cancer	0.314 (-0.051-0.680)	0.092	0.253 (-0.121-0.627)	0.183
Tumor size	0.257 (-0.096-0.610)	0.153	-0.015 (-0.387-0.356)	0.935
Tumor location	0.014 (-0.099-0.127)	0.809	-	-
Technique (cTURBT vs ERBT)	-0.219 (-0.580-0.143)	0.234	-	-
Obturator nerve reflex	0.237 (-0.382 -0.857)	0.451	-	-
DEEP scale	0.385 (0.177-0.597)	<0.001	0.315 (0.111-0.519)	0.003
Duration of surgery	0.020 (0.009 -0.032)	0.001	0.013 (0.001-0.024)	0.036
Surgeon (SU vs. Resident)	-0.082 (-0.302-0.156)	0.499	-	-

Tab.16 - Multivariate Linear Regression Analysis: Detection of the Factors Predicting Length of Catheterization

	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	0.051 (0.025-0.076)	<0.001	0.046 (-3.249-1.033)	<0.001
Gender	-0.154 (-0.899 -0.561)	0.684	-	-
History of bladder cancer	0.240 (-0.361-0.841)	0.433	-	-
Tumor size	0.744 (0.171-1.317)	0.011	0.564 (0.021-0.071)	0.058
Tumor location	-0.084 (-0.268-0.101)	0.372	-	-
Technique (cTURBT vs ERBT)	-0.579 (-1.169 -0.010)	0.054	-0.669 (-0.020-1.147)	0.021
Obturator nerve reflex	0.591 (-0.421-1.603)	0.251	-	-
DEEP scale	0.350 (-0.002-0.703)	0.051	0.249 (-0.063-0.621)	0.110
Duration of surgery	0.025 (0.006-0.044)	0.010	0.015 (-0.005-0.038)	0.132
Surgeon (SU vs. Resident)	-0.222 (-0.778-0.167)	0.262	-	-

Discussion

The randomized-controlled trial (Study 2) provides the highest level of evidence comparing the role of ERBT and cTURBT on an operative, pathological, and short-term oncological outcomes exploring all kind of energies available for both techniques.

The current literature shows controversial results from comparative RCTs on ERBT. This may depend on the study design heterogeneity, since the majority of the RCTs compared the two techniques employing two different kind of energies (i.e., laser ERBT versus electric TURBT) and different endpoints were assessed [101]. As reported by Teoh et al. in the international consensus statement the current quality of evidence prevents to draw solid conclusions [67].

The presence of DM has been considered the marker of a high-quality resection as it allows the pathologist to evaluate the extension of the disease and the urologist to give indications [110] [59] [65]. Our study demonstrated that ERBT was non-inferior to cTURBT in the rate of DM (94% and 95% for cTURBT and ERBT, respectively p=0.84) and Tx (3% and 4% for cTURBT and ERBT, respectively p=0.85) at final histology. Therefore, ERBT guarantees a resection quality comparable to that of cTURBT, proven the latter is performed according to the best surgical practice [65]. This finding is somehow surprising, as the improvement of resection quality has been considered the most important advantage of ERBT [76]. In fact, retrospective studies show an absence of DM in the specimen in up to 51% of cTURBT [110] [111] [112].

Hashem et al. reported a DM rate of 62% in cTURBTs versus 98% in laser ERBT [113] showing a statistically significant difference between the two groups ($p<0.001$); accordingly, Cheng et al. reported that the rate of DM was 97.1% and 80% with green-light laser ERBT and cTURBT ($p=0.04$), respectively [114]. In contrast, many other studies reported a DM rate that was not different between ERBT and cTURBT ($p>0.05$) [115] [97] [116].

Moreover, T1 substaging was possible in all cases of ERBT while the rate of T1 substaging feasibility was significantly lower in cTURBT group (80%; $p=0.02$). Just one previous study investigates the rate of T1 substaging feasibility that provided similar results (68.2% and 18.4% for laser ERBT vs cTURBT; $p>0.001$). However, the definition of T1 BC was not clear, as the rate of T1 tumors was 95.5% in ERBT and 93.9% in cTURBT groups, with a rate of DM absence that was 2% and 38%, respectively ($p>0.001$). Thus, a significant percentage of T1 BC was actually Tx. Nonetheless, these findings underline a higher accuracy of ERBT in T1 substaging, which is currently recommended by EAU Guidelines [27] [117] [28].

The advantage of ERBT over cTURBT in terms of operative outcomes is debated. Resection time has been shown longer for cTURBT in two studies ranging from 13-19 minutes versus 10-13 minutes for ERBT ($p<0.05$). Conversely, other two RCT showed an operative time significantly shorter for cTURBT ranging from 22-30 min versus 35-37 for ERBT ($p<0.05$) [114] [116]. Catheterization time results were more uniform showing significantly longer times for cTURBT [113] [114] [115] [97] [116] [118]. Similarly, hospitalization time was reported significantly shorter for ERBT in three RCT [97] [116] [118] and comparable ones reported in two study [113] [114]. Despite these results, similar perforation rates were reported in these RCTs. In our study, no statistical difference was found between ERBT and cTURBT in operative time, the rate of adjuvant instillation, catheterization time and hospital stay. These findings represent the logical consequence of the comparable rate of perforation and post-operative complications between the groups. Regarding the oncological outcomes, both disease persistence at 3 months and recurrence-free survival with a median follow-up of 12 months were comparable. This result is in line with the current literature [67]. Some limitations have to be acknowledged. This is a single-center study from an academic Hospital. Our center is highly experienced in NMIBC treatment and, thus, these results may potentially not reflect the current treatment outcomes. However, the heterogeneity of the operators, comprehending supervised residents as well, permits to generalize the current results and to underline that a high rate of DM should be considered standard, regardless of the surgeon and/or the technique of resection [119] [120]. Other limitations were the lack of specific analysis of the tumor margins, the short follow-up that does not permit to draw solid conclusion on the oncological outcomes; a long-term follow-up is foreseen to evaluate the definitive oncological results. Finally, this technique has been tested only on patients with a limited number of lesions and dimensions. Nonetheless, our results demonstrated why

ERBT should be considered a standard surgery worth employing. The ERBT technique preserves tumor integrity providing a high-quality specimen that increases pathological substaging accuracy without significant drawbacks compared to cTURBT.

Moreover, we reported the first evidence analyzing and comparing the different energies available to achieve ERBT in a RCT (Study 3). We found that both electrocautery and laser energies are suitable for an apparently satisfactory staging rate resulting in low rates of DM absence regardless of the energy employed and a comparable rate of artifacts in the specimens. Our results are in line with the previously reported rate of detrusor muscle presence in ERBT specimens, ranging from 87-98%, 40-100%, and 51-100% for laser [113] [115] [118], monopolar [121] [122], and bipolar [97] [123] [124] electrocautery energies, respectively. Given the number of patients included, the prospective, randomized design, and the head-to-head comparison of each energy used for ERBT, our study provides the best available evidence of what can be expected from each energy source to achieve detrusor muscle presence during ERBT.

The energy source to be used to perform ERBT may vary depending on the location of the lesion. For the lateral wall, we found a higher rate of ONR using monopolar or bipolar energies compared to a laser source. Therefore, l-ERBT seems to potentially be the best option to ensure a safer procedure.

Bipolar resection has been suggested to reduce the risk of perforation compared monopolar energy with rates of 21.5 % vs 6.1%, respectively ($p=0.039$) [125]. The hypothesis is founded on the decreased elicitation of ONR by using bipolar energy.

However, this advantage is debated with RCT reporting the lack of this superiority (p=1) [126]. Our study is the first comparing bipolar and monopolar energies in the ERBT setting. The results show no significant difference in terms of either bladder perforation or post-operative outcomes.

Major importance should also be given to the rate of conversion to cTURBT. Out of 6 conversions, in 5 cases BC was found on the anterior wall and dome and in one case it was in the proximity of the meatus. In 22.7% of lesions of the anterior wall, conversion was necessary as no adequate visibility could be reached to perform ERBT. This limitation of laser should be kept in mind when planning the surgical approach as, in these cases, electrical energies (either monopolar or bipolar) should be preferred to avoid the increased potential risk of changing instruments and the subsequent waste of surgical material. The study by Kramer et al. compared the rate of conversion between different energies and found a higher rate of conversion to cTURBT compared to our study (19.9% vs. 4.3%) and almost all cases of conversion occurred in case of electrical energy employment [87]. As stated by the authors the change to cTURBT was influenced by an easier switch in case of employment of electrical energy as it does not require a change of the instrumentation. Most importantly, we believe that the location of the lesion is the main factor influencing the feasibility of ERBT rather than the kind of energy employed.

Finally, despite the shorter mean time of catheterization when monopolar is employed in case of posterior wall or trigone lesions was a statistically significant, the comparable length of irrigation and hospital stay make this difference less clinically relevant.

This study is not devoid of limitations. The numerosity of the population was calculated for the comparison between cTURBT versus ERBT and it was not focused on this sub-analysis that may result in underpowered analysis, thus these results should be confirmed by a tailored study design. Moreover, despite these were not the objective of this study, is the lack of comparison with cTURBT and of the oncological outcome that could give further information on energy employment indications. The results underline that there is no difference in the employment of monopolar, bipolar or laser energies in terms of diagnosis and staging when performing ERBT. The coexistence of different energy sources allows to provide indication to decide the surgical strategy and define what and where to employ different techniques ensuring safer, high quality, and cost-effective procedures.

Finally, we developed a novel classification of bladder perforation during TURBT, reporting the predictors of DEEP perforation and the implication of this classification in the postoperative course (Study 4). The rate of extraperitoneal (grade 2) and intraperitoneal (grade 3) perforations were 16.5% and 2.0%, respectively. These findings are in line with previous published data from our Institution where extraperitoneal perforation represented up to 83% of all BP. However, the perforation rate was lower than in the current study (1.3% vs 18.5%) [127]. This result may be influenced by several factors. It is acknowledged that the intraoperative complications are underreported due to lack of proper definition and, possibly, to a certain fear of consequential lawsuit [84]. The prospective fashion of this study increases the completeness of data recording in comparison to retrospective reports. Finally, the primary endpoint of this randomized-controlled trial was the presence of detrusor muscle, which may have led the surgeons to provide a muscle sampling higher than in routinary practice. The location of the bladder tumor was independent predictor of BP, as for the obturator nerve reflex. These results are expected, since it is technically easier to perform a trigone/posterior bladder wall resection and the obturator nerve reflex determines a leg adduction that may result in uncontrolled bladder resections. The female gender was an independent predictor of bladder perforation. This may reflect the bladder wall thickness of female patients, which is usually thinner than the male bladder wall due to the absence of bladder outlet obstruction.

The use of DEEP scale may be beneficial as high-grade perforations have proven to impact the clinical and surgical outcomes. In particular, the administration of immediate intravesical chemotherapy depended on the grade of DEEP. This is a crucial point, since it has been demonstrated that in low-risk bladder cancers, the postoperative instillation of chemotherapeutic agents decreases bladder cancer recurrence. Comploj et al. reported that the BP influences the natural history of superficial bladder cancer, resulting in a higher rate of bladder recurrence with no impact on overall and cancer-specific survival [128]. The authors postulated that the recurrence could depend on two factors: tumor seeding or implantation and inadequate initial tumor resection due to BP [128]. It should also be acknowledged the risk of intraperitoneal seeding, which occurrence may be considered anecdotical [129] [130] [131].

Furthermore, the rate of major postoperative complication, the irrigation time and the hospital stay were related to DEEP. Thus, the systematic use of DEEP scale might help to direct the postoperative management of the patients, adapting the postoperative strategies to the depth of endoscopic perforation.

The study is not devoid of limitations. First, we could not separate the patients treated with en-bloc and conventional TURBT due to paucity of high-grade perforations. However, the DEEP scale was designed to report the depth of endoscopic perforation independently from the type of resection or the energy source used. Therefore, the use of this classification should apply to any kind of TURBT. Second, as our study was not designed a priori to assess the reproducibility of the scale, future studies are warranted to assess inter- and intra-observer agreement. Third, this a result of a single center randomized trial. The DEEP scale should be validated for external clinical implementation. However, the present study demonstrated that this classification provides a standardized tool to classify the most important intraoperative complication of TURBT, that affects the clinical postoperative course. Its use could be implemented in daily practice.

Conclusions

This is the largest randomized-controlled trial on en-bloc resection of bladder tumors and the first comparing the different energy sources available to perform ERBT. ERBT is non-inferior to cTURBT in the staging of BC. The rate of T1 substaging feasibility was significantly higher in the ERBT group. The intraoperative and postoperative outcomes were comparable between the groups. With a median follow-up of 15 months, oncological outcomes were comparable.

Moreover, no difference was found in staging and diagnosis of BC as all energies ensure a high-quality specimen. Laser energy might be beneficial in lateral wall lesions to avoid ONR. Since there is an increased risk of ERBT conversion to cTURBT for lesions of the anterior wall, electrocautery might be preferred over laser to avoid waste of material. The energy source to be used during ERBT should be tailored to the lesion location to provide safest and highest quality procedure.

Finally, the DEEP scale provides a standardized tool to classify the most important intraoperative complication of TURBT, that affects clinical postoperative course. Female gender, tumor located in anterior wall/neck or dome, and obturator nerve reflex are independent predictors of intra/extraperitoneal perforation. The DEEP scale is an independent predictor of postoperative clinical course, such as post-operative intravesical instillation, the risk of major complication, the irrigation time and hospital stay.

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Abbreviations

BC	Bladder cancer
CI	Confidence interval
CIS	Carcinoma *in situ*
CT	Computed tomography
cTURBT	Conventional TURBT
cTURBT-b	cTURBT - bipolar energy
cTURBT-m	cTURBT - monopolar energy
EAU	European Association of Urology
ERBT	*En-bloc* resection of bladder tumor
ERBT-b	ERBT - bipolar energy
ERBT-m	ERBT - monopolar energy
ERBT-tl	ERBT - thulium laser energy
HG	High-grade
HR	Hazard ratio
IQR	Interquartile range
ISUP	International Society of Urological Pathology
LG	Low-grade
MIBC	Muscle-invasive bladder cancer
MRI	Magnetic resonance imaging
NMIBC	Non-muscle-invasive bladder cancer
PUNLMP	Papillary urothelial neoplasm of low malignant potential
RCT	Randomized controlled trial

TNM	Tumor Node Metastasis classification
TURBT	Transurethral resection of bladder tumor
US	Ultrasound
UTUC	Upper tract urothelial cancer
UUT	Upper urinary tract
WHO	World Health Organization

Anexos

Study 1

REVIEW

En bloc resection of bladder tumors: indications, techniques, and future directions

Angelo Territo, Giulio Bevilacqua, Iacopo Meneghetti, Asier Mercadé, and Alberto Breda

Purpose of review
En bloc resection of bladder tumor (ERBT) is an innovative new surgical technique, the use of which is becoming increasingly widespread. In this review, we analyze the recent literature and explore new developments, which may impact the future role of en bloc bladder surgery.

Recent findings
ERBT increases the frequency with which detrusor muscle is present in the specimen (to 95%) and offers a significant improvement in the quality of the resection specimen, thereby helping with T1 substaging. Furthermore, the laser treatment reduces the rate of obturator nerve-related bladder perforation.

Summary
ERBT represents a considerable advancement in the surgical management of nonmuscle-invasive bladder cancer. It delivers excellent oncological results and is a well tolerated procedure.

Video
In the accompanying video, we shortly report the different modalities and energy sources used for bladder cancer resection. The three strategies are currently employed at the Fundació Puigvert (Barcelona).

Video abstract:
http://links.lww.com/COU/A18

Keywords
bladder tumor, en bloc resection, lasers

INTRODUCTION

Bladder cancer is the second most frequent urological malignancy and the ninth most common cancer worldwide [1]. About 80% of newly diagnosed cases are nonmuscle invasive bladder cancer (NMIBC). Approximately 60% of patients with NMIBC who undergo transurethral resection of bladder tumor (TURBT) will experience intravesical recurrence, and approximately 20% will experience progression to muscle-invasive disease [2]. Due to the high recurrence rate, patients with NMIBC require frequent endoscopic follow-up and often need reintervention [3]. Although the rate of progression of NIMBC is relatively low, some authors [4] believe that the cellular dispersion and the large number of exfoliated cells during a conventional procedure can lead to metastases because of diffusion through the bloodstream and subsequent reimplantation. In 2000, Ukai *et al.* [5] developed a new TURBT method using a short curved needle electrode to improve the quality of histological diagnosis, with removal of not only the tumor but also the surrounding material in one piece.

The quality of the TURBT influences the prognosis. A second resection (re-TURBT) has been demonstrated to improve the recurrence-free survival, progression-free survival, and overall survival only in patients without muscle in the specimen from the initial resection: the absence of detrusor muscle in the specimen is associated with a high risk of residual disease and early recurrence [6]. Accordingly, the presence of detrusor muscle in the specimen is considered a criterion for resection quality. In this

Fundació Puigvert, Autonomous University of Barcelona, Barcelona, Spain

Correspondence to Alberto Breda, Fundació Puigvert, Autonomous University of Barcelona, Barcelona, Spain. E-mail: albbred@hotmail.com

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KEY POINTS

- The goal of an en bloc resection is to resect the tumor mass, ensuring the presence of detrusor muscle in the specimen, with tumor-free resection margins and without cutting into the neoplastic mass.
- ERBT is performed for lesions up to 3 cm of size, in order to avoid its later fragmentation during specimen retrieval.
- ERBT is usually performed using monopolar or bipolar current, thulium-YAG or holmium-YAG laser; however, other emerging resection techniques use KTP laser and water jet as energy sources.
- ERBT technique results in a noticeable improvement in the quality of collected samples facilitating the accurate identification of the T1 substaging.
- Improvements in length of hospital stay, postoperative irrigation time, catheterization time, hemoglobin loss, obturator reflex, and overall complication rate have been reported with ERBT.

context, the development of a new strategy to obtain the best possible specimens is crucial. Recent findings show that en bloc resection of bladder tumor (ERBT) increases the frequency with which detrusor muscle is present in the specimen (to 95%) [7▪,8▪]. Technological improvements, including new energy sources and other methods, are playing a key role in improving this rate.

The aim of this review is to analyze the recent literature (from the past 2 years) on ERBT, focusing on the indications, the different operative techniques, and future directions.

MATERIALS AND METHODS

A MEDLINE search for studies published in the last 2 years (2018 and 2019) was performed using the keywords 'en bloc resection of bladder tumor', 'conventional transurethral resection of bladder tumor', 'nonmuscle-invasive bladder cancer', and 'lasers in urologic surgery'. The following studies were considered for inclusion in this review: prospective and randomized studies, retrospective well designed studies, systematic reviews, and meta-analyses in the English language. Abstracts, technical notes, case reports, series shorter than 10 cases, comprehensive reviews, and articles written in languages other than English were not considered valuable for the review. The reference lists of the eligible articles were reviewed by two authors. PRISMA criteria used for this article are shown in Fig. 1.

RESULTS

Indications

TURBT using white light cystoscopy (WLC) continues to represent the gold standard treatment for primary NMIBC according to the 2019 EAU Guidelines. The goal is complete resection of the lesion, which is essential to a good prognosis, and this may be achieved by either a fractionated resection or an en bloc resection [9]. The goal of an en bloc resection is to resect the tumor mass, ensuring the presence of detrusor muscle in the specimen, with tumor-free resection margins and without cutting into the neoplastic mass: this facilitates the reading by the pathologist and reduces the risk of seeding and reimplantation of neoplastic cells.

According to the literature, ERBT is performed for lesions up to 3 cm of size [10], in order to avoid its later fragmentation during specimen retrieval, and without omitting the 'one piece concept' [11].

The localization of the lesion can also represent a limit to the indications for the en bloc technique. Same authors emphasized as the tumor location at the anterior and/or posterior bladder wall may potentially result in the risk of peritoneal damage [12,13]. On the other hand, in different bladder areas (i.e. bladder dome) the en bloc resection can be demanding from a technical point of view [14].

Tumor visualization and detection

An optimal view of a neoplastic lesion is essential for correct diagnosis and treatment. WLC is currently the gold standard for the treatment of bladder tumors; nevertheless, additional tumor visualization methods can improve the recognition of small lesions and flat lesions as carcinoma *in situ*.

Photodynamic diagnosis (PDD) is a technique that aims to improve the endoscopic recognition of a tumor based on the intravesical instillation of 5-aminolevulinic acid or hexaminolevulinic acid. These products are metabolized into protoporphyrin IX, which gives the neoplastic cells a red fluorescent appearance when excited by violet light. PDD appears to increase the tumor detection rate and to decrease the residual tumor rate [15] and is the most widespread additional tumor visualization method to be used [16].

Narrow-band imaging (NBI) technology uses wavelengths that are strongly absorbed by hemoglobin so that it enhances the surface capillary visualization and the contrast between normal urothelium and hypervascular cancer tissue. Unlike PDD, which increases the cost of the procedure, NBI slightly increases the duration of the procedure but the costs

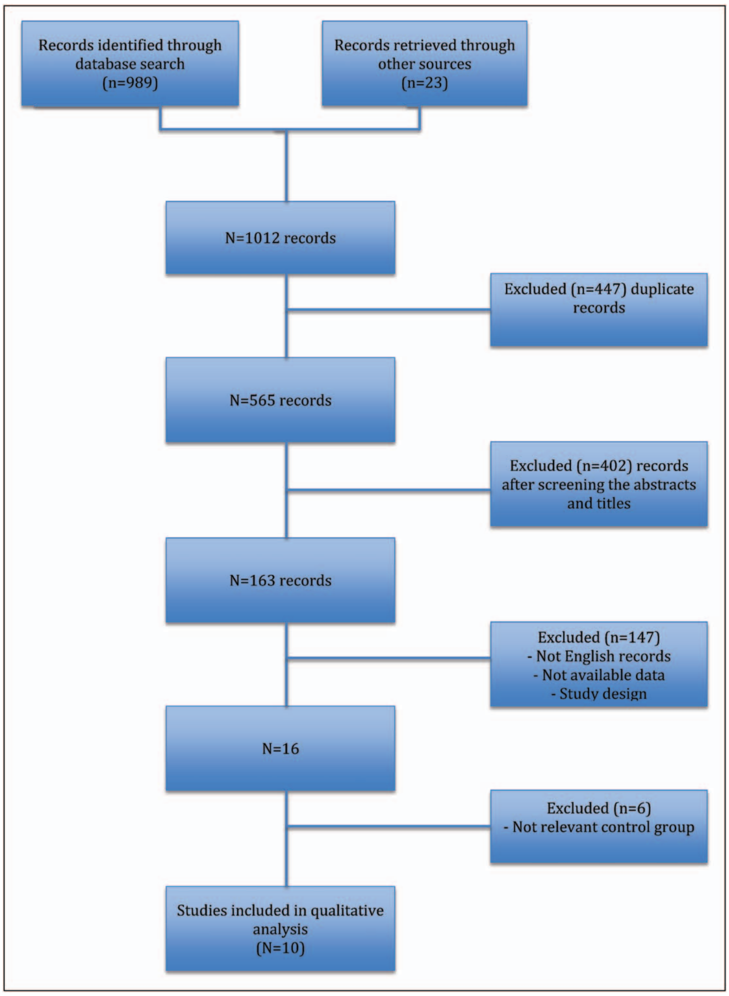

FIGURE 1. PRISMA flowchart for the selection of studies. It summarizes the research method used for this manuscript.

are comparable with those of WLC. Some studies have claimed that NBI improves the tumor detection rate [17] and that there is a reduction in recurrence risk if NBI is used during TURBT [18].

Confocal laser endomicroscopy (CLE) is an emergent in-vivo high-resolution optical imaging technique that uses a fluorescein dye that may enable real-time differentiation between high-grade and low-grade urothelial cancer. Liem *et al.* [19] used CLE to better characterize bladder lesions in 73 patients and found agreement between CLE imaging and histopathological results in 76 and 70% of low-grade and high-grade urothelial cancers, respectively. CLE could be used to identify, in the en bloc resection, the presence or absence of lesion-free margins and could serve as the basis for the decision on whether to extend the resection margins within the same operative session, but to date this technique has not been used routinely in clinical practice.

Technique of resection and energy sources

Regardless of the technique used in the en bloc resection, a circumferential incision is made with a safety margin of a few millimeters from the tissue that is macroscopically evaluated as a tumor with the aim of avoiding positive margins. The resection then proceeds deep into the muscular layers until progressive detachment of the lesion is achieved and until it floats in the bladder lumen. Subsequently, the tissue is recovered to be sent for analysis.

TURBT was traditionally performed with monopolar energy, which determines the passage of the energy itself between the resectoscope and the grounding pad applied to the patient's body. Subsequently, the use of bipolar energy was introduced for this type of procedure. The use of bipolar energy should theoretically reduce the risk of excitation of the obturator nerve, and therefore, reduce both the risk of bladder perforation, even if the literature data on these two points are conflicting [8▪,20,21]. In recent years, laser energies, including holmium, thulium, and KTP, have entered the arsenal for the execution of bladder resection procedures [22] (Fig. 2).

En bloc resection using monopolar or bipolar current, thulium-YAG, or holmium-YAG laser is feasible in selected exophytic tumors [23]. Other emerging resection techniques use KTP laser and water jet as energy sources.

Energy sources

Zhang *et al.* [21] evaluated the safety and efficacy of the bipolar button electrode for ERBT of NMIBC. In their study of 82 patients, the authors concluded that this technique guarantees accurate resection of the tumor, reduces postoperative irrigation and the period of catetherization, shortens postoperative hospital stay, is associated with a trifling number of intraoperative and postoperative complications, and provides good oncological outcomes. To overcome the limitation that performing a procedure with a new technique requires a learning curve, Teoh *et al.* [24] conceived a porcine training model for performance of transurethral piecemeal and en bloc resection as an easy-to-build and low-cost model for training purposes worldwide.

In 2018 Bălan *et al.* [8▪] conducted a clinical comparison to evaluate whether bipolar ERBT or standard monopolar TURBT is the best way to treat medium-sized superficial papillary bladder tumors. The patients treated with en bloc bipolar resection showed a lower frequency of obturator nerve reflex, a reduction in the average operating time, catheterization time, a decrease in hemoglobin levels, and a minor hospital stay. Furthermore, the authors emphasized that the specimens obtained from patients treated with en bloc resection had a well represented muscular layer with minimal cauterization artifacts, making evaluation of the tumor depth easier for the pathologists (Table 1).

Cheng *et al.* [25▪] compared the submucosal en bloc resection technique with the hybrid knife for treatment of NMIBC with conventional TURBT. The former technique uses a multifunctional probe that combines a water jet system and electrosurgical technology, allowing injection of solution into the submucosa to create a fluid cushion so as to facilitate en bloc resection with a single instrument. For the hybrid knife technology, the authors reported a longer average operating time for tumors greater than 3 cm diameter. Postoperative irrigation time, catheter indwelling time, and hospital stay were shorter in the hybrid knife group. The overall complication rate of TURBT was much higher than that of endoscopic submucosal dissection. Preoperative and postoperative changes in hemoglobin showed no significant

FIGURE 2. En bloc resection technique using monopolar energy (a), bipolar energy (b), and laser thulium energy (c). Shown is the en bloc resection technique for bladder cancer at Fundació Puigvert employing three different modalities: monopolar, bipolar, and Tm:YAG laser energy.

Table 1. Comparison between conventional TURBT and different en bloc resection techniques

	Bipolar	Laser (thulium)	KTP	Water jet	EMR with en bloc
Bălan *et al.*	↓ Obturator nerve reflex ↓ Average operating time ↓ Decrease in haemoglobin ↓ Catheterization time ↓ Duration of hospital stay ↑ Representation of muscular layer in the specimen ↓ Cauterization artifacts ↓ Recurrence rate				
Cheng *et al.*				↑ Operating time in tumors more than 3 cm ↓ Postoperative irrigation time ↓ Catheter indwelling time ↓ Duration of hospital stay ↓ Overall complication rate ↓ Recurrence rate	
Hayashida *et al.*					↑ Possibility of evaluating the presence or not of invasive disease in the specimen
Liang *et al.*			↑ Identification of muscularis mucosae		
Li *et al.* (compared with plasmakinetic transurethral resection)		↓ Operating time ↓ Hospitalization time ↓ Postoperative irrigation time ↓ Catheterization time ↑ Representation of muscular layer in the specimen			

EMR, endoscopic mucosal resection; KTP, potassium titanyl phosphate.

differences between the two groups. Compared with conventional TURBT, application of the hybrid knife led to a decrease in complications and the rate of recurrence and offered a safer and more effective approach for NMIBC.

In their study, Hayashida *et al.* [26▪] used a combined technique consisting of transurethral endoscopic mucosal resection using a polypectomy snare (EMR) and en bloc resection in 39 patients with tumors at least 1.5 cm in diameter and compared the results with those in a group of patients with the same characteristics who were treated with conventional TURBT. They found no difference between the two techniques in terms of operative time, incidence of severe complications, blood transfusion, risk of recurrence, urinary catheterization, or recurrence rate. Nevertheless, the pathologists were able to assert the presence or absence of invasive disease in all specimens from patients who underwent en bloc surgery, with a statistically significant difference compared with the other group.

Histological findings

The latest findings considered in our review suggest that, although further studies are needed, the en bloc resection technique can offer significant advantages. First of all, from an anatomopathologic point of view, the technique results in a noticeable improvement in the quality of collected samples in terms of representation of muscle layers, with a reduction in cauterization artefacts [8▪,26▪,27].

Furthermore, the possibility of obtaining a good sample of the underlying layers of the mucosa could lead to different therapeutic decisions compared with samples of more superficial layers [28▪▪,29,30▪▪].

Kardoust Parizi *et al.* [29] confirmed that T1 substaging, according to the relationship between muscularis mucosae and tumor, is of prognostic value as it is associated with prognostic outcomes of bladder cancer.

In 2019, Liang *et al.* [30■■] suggested that, although further confirmation needs to be obtained in larger studies, ERBT using KTP green-light laser improves the identification of muscularis mucosae in the specimen, which may facilitate accurate identification of the T1 substage.

Many concerns are related to the oncologocial outcomes. Particularly, some authors [8■,25■] have also found a reduction in the recurrence rate in patients treated with en bloc resection compared with patients who underwent conventional resection.

Surgical outcomes

The reviewed studies not only indicate that ERBT improves the histological sample but also contain interesting results on the surgical outcomes of ERBT compared with the conventional procedure. As regards operating times, some authors have reported a reduction [7■,8■] whereas others have reported an increase for larger lesions [25■]. Improvements in length of hospital stay, postoperative irrigation time, catheterization time, hemoglobin loss, obturator reflex, and overall complication rate have been reported with en bloc resection [7■,8■,25■].

In a retrospective comparison of thulium laser en bloc resection and plasmakinetic transurethral resection, no difference in complications or recurrence-free rates were noted [7■], but the authors did report shorter operative, hospitalization, postoperative irrigation, and catheterization times in those patients who underwent thulium laser en bloc resection.

Hurle *et al.* [31■] evaluated the role of en bloc resection in patients who had previously undergone en bloc resection for high-risk NIMBC and concluded that ERBT appears to be a feasible, well tolerated, and effective procedure with a low rate of complications.

CONCLUSION

En bloc resection is widely considered an ideal alternative to traditional TURBT in selected cases. The evidence that ERBT enhances the percentage of specimens with detrusor muscle is noteworthy. Most studies in recent years [7■,8■,25■] have confirmed an improvement in surgical outcomes that could translate into lower overall costs for a single procedure. In view of the results in respect of oncological outcomes and safety, ERBT appears to represent a considerable advancement in the surgical management of NMIBC. The prognostic role of pathological features, such as a subclassification of the T1 stage, could be reconsidered, thanks to the improvement in the quality of the samples and the ability to improve the identification of muscularis mucosae through ERBT.

To date, the reviewed studies compared classic endoscopic resection and en bloc procedures using different types of energy. It would be interesting, in the future, to evaluate which is the optimal energy source by comparing different energies for ERBT.

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Conflicts of interest

There are no conflicts of interest.

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The re-en bloc resection technique has demonstrated to be very effective after an initial en bloc dissection in terms of low complication rate. Furthermore, it may possibly improve the oncological outcomes.

Study 2

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European Association of Urology

En Bloc Versus Conventional Transurethral Resection of Bladder Tumors: A Single-center Prospective Randomized Noninferiority Trial

Andrea Gallioli [a,†], *Pietro Diana* [a,b,†,*], *Matteo Fontana* [a], *Angelo Territo* [a], *Óscar Rodriguez-Faba* [a], *Josep Maria Gaya* [a], *Francesco Sanguedolce* [a], *Jordi Huguet* [a], *Asier Mercade* [a], *Alberto Piana* [a], *Julia Aumatell* [a], *Alejandra Bravo-Balado* [a], *Ferran Algaba* [c], *Joan Palou* [a,d], *Alberto Breda* [a,d]

[a] Department of Urology, Fundació Puigvert, Autonomous University of Barcelona, Barcelona, Spain; [b] Department of Urology, Humanitas Research Hospital IRCCS, Rozzano, Italy; [c] Department of Pathology, Fundació Puigvert, Autonomous University of Barcelona, Barcelona, Spain; [d] Department of Surgery, Autonomous University of Barcelona, Barcelona, Spain

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Abstract

Background: It has been proposed that en bloc resection of bladder tumor (ERBT) improves the quality of tumor resection. A recent international collaborative consensus statement on ERBT underlined the lack of high-quality prospective studies precluding the achievement of solid conclusion on ERBT.
Objective: To compare conventional transurethral resection of bladder tumor (cTURBT) and ERBT.
Design, setting, and participants: This study (NCT04712201) was a prospective, randomized, noninferiority trial enrolling patients diagnosed with bladder cancer (BC) undergoing endoscopic intervention. Inclusion criteria were: tumor size ≤3 cm, three or fewer lesions, and no sign of muscle invasion and/or ureteral involvement. For a noninferiority rate in BC staging of 5% (α risk 2.5%; β risk 20%), a total of 300 subjects were randomized to ERBT treatment at a 1:1.5 allocation ratio.
Intervention: TURBT and ERBT.
Outcome measurements and statistical analysis: The primary outcome was the presence of detrusor muscle at final histology. Secondary outcomes include BC staging, T1 substaging, artifacts, complications, the rate of adjuvant treatment, and oncological outcomes.
Results and limitations: From April 2018 to June 2021, 300 patients met the inclusion criteria. Of these, 248 (83%) underwent the assigned intervention: 108 patients (44%) underwent cTURBT and 140 (57%) underwent ERBT. The rate of detrusor muscle presence for ERBT was noninferior to that for TURBT (94% vs 95%; $p = 0.8$). T1 substaging was feasible in 80% of cTURBT cases versus 100% of ERBT cases ($p = 0.02$). Complication rates, rates of postoperative adjuvant treatment, catheterization time, and hospital stay were comparable between the two groups ($p > 0.05$). The recurrence rate at median follow-up of 15 mo (interquartile range 7–28) was 18% for cTURBT versus 13% for ERBT ($p = 0.16$). Limitations include the single high-volume institution and the short-term follow-up.
Conclusions: Our study has the highest level of evidence for comparison of ERBT versus TURBT. ERBT was noninferior to TURBT for BC staging. The rate of T1 substaging feasibility was significantly higher with ERBT.

† These authors contributed equally to this work.
* Corresponding author. Department of Urology, Fundació Puigvert, Autonomous University of Barcelona, Cartagena 340–350, 08025 Barcelona, Spain. Tel. +39 39 27104765.
E-mail address: pietros.diana@gmail.com (P. Diana).

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Patient summary: We compared two techniques for removing tumors from the bladder. The en bloc technique removes the tumor in one piece and is not inferior to the conventional method in terms of the quality of the surgical resection and cancer staging assessment.

1. Introduction

Transurethral resection of bladder tumor (TURBT) is the gold standard for the diagnosis and local staging of bladder cancer (BC) [1]. Although it is considered a basic urological procedure, TURBT is a crucial step in the management of non–muscle-invasive BC (NMIBC); it defines the patient's risk class and prognosis, from which indications for adjuvant intravesical therapies and follow-up schedules can be drawn. Conventional TURBT (cTURBT) involves a piece-by-piece resection of the tumor using monopolar or bipolar energy. This procedure violates one of the key principles of oncological surgery, the preservation of tumor integrity, raising some concerns regarding the risk of tumor cell scattering and seeding and thus local recurrence. Moreover, although the presence of detrusor muscle (DM) in the histopathological specimen is crucial to ensure correct staging and it is considered a surrogate for resection quality, DM can be missed in up to 30–35% of cTURBT procedures [2,3]. In addition, the pathologist may be unable to provide reliable information about disease staging and T1 substaging because of a fragmented, non-orientable specimen [4]. En bloc resection of bladder tumor (ERBT) was introduced in an attempt to improve cTURBT outcomes [5-7]. In ERBT, the bladder tumor is resected as a single piece comprising both its exophytic and endophytic parts, which reduces tumor cell dispersion, allows precise resection, facilitates DM sampling in proximity to the tumor base, and yields a more informative pathological specimen. Several retrospective studies have suggested multiple advantages for ERBT over cTURBT, although these were not confirmed in a subsequent randomized controlled trial (RCT) [3,7-12]. In 2020, an international collaborative consensus statement confirmed the feasibility of ERBT without providing solid conclusions regarding its indications and advantages, as the high-quality data required for robust recommendations are limited [7]. Thus, the consensus underlines the need for a high-quality prospective RCT.

The aim of our study was to provide the highest level of evidence for comparison of cTURBT versus ERBT by analyzing surgical, pathological, and oncological outcomes for these two techniques, using all the energy sources available.

2. Patients and methods

2.1. Study design and endpoints

This was a single-center, prospective, randomized, controlled, noninferiority trial analyzing patients undergoing ERBT or cTURBT for BC. All the patients were prospectively enrolled and randomized to receive one of the following treatments: ERBT using monopolar (m-ERBT), bipolar (b-ERBT), or thulium laser (l-ERBT) energy; or cTURBT using monopolar (m-cTURBT) or bipolar (b-cTURBT) energy. The primary endpoint of the study was DM presence in the pathological specimen. Secondary endpoints included: staging of BC, evaluated according to the American Joint Committee on Cancer/Union for International Cancer Control TNM system and the World Health Organization classification [13]; the feasibility of T1 subclassification (T1a/b/c) according to the depth of invasion in the muscularis mucosae-vascular plexus [4]; the rate of artifacts in the pathological specimen; the rate of treatment with a single instillation of mitomycin/epirubicin postoperatively according to the European Association of Urology (EAU) guidelines [1]; operative and postoperative variables (operative time, irrigation and catheterization time, hospital length of stay, hemoglobin decrease, and postoperative complications scored according to the Clavien-Dindo classification [14]); and early oncological outcomes (3-mo recurrence rate, recurrence-free survival, overall survival). The study was carried out according to the principles of the Declaration of Helsinki and was approved by the institutional review board (2017/09c). The study is registered on ClinicalTrials.gov as NCT04712201. All participants were adequately informed and provided written consent.

2.2. Study population

The target population included patients undergoing TURBT for the diagnosis and treatment of BC according to the EAU guidelines on NMIBC [1]. Preoperative evaluation included recording of anthropometric variables, comorbidities, and history of NMIBC; bladder ultrasound and/or flexible cystoscopy; and urine cytology. An abdominal computed tomography scan was performed in cases with suspicion of muscle-invasive bladder cancer (MIBC) or upper urinary tract involvement. We included patients affected by primary or recurrent BC, located anywhere in the bladder, with a maximum of three separated lesions and/or a maximum size of 3 cm for each lesion. Patients were excluded from the study if there was preoperative evidence of MIBC, ureteral involvement, and/or nodal/metastatic extension of the disease.

The sample size was calculated using the primary outcome of the rate of DM presence in the specimen as a surrogate for resection quality. Previous studies have shown that approximately 90% of specimens were suitable for correct staging using conventional approaches [15,16]. For this noninferiority clinical trial we estimated that 95% of specimens would have DM presence and a minimum noninferiority margin of 5% for ERBT in comparison to cTURBT. Accepting a one-sided α risk of 2.5%, a β risk of 20%, and an anticipated dropout rate of 12%, a minimum of 120

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patients per group for randomization (107 after dropouts) was foreseen for an adequately powered analysis. Two energy types were used in the cTURBT group (m-cTURBT and b-cTURBT) and three in the ERBT group (m-ERBT, b-ERBT, and l-ERBT). Thus, patients were allocated to the ERBT or cTURBT group in a 3:2 ratio using computer-generated randomization tables during operating room planning on the day before surgery. Thus, 180 patients were randomized to the ERBT group (60 patients each in the m-ERBT, b-ERBT, and l-ERBT subgroups) and 120 to the cTURBT control group (60 patients each in the m-cTURBT and b-cTURBT subgroups). The study was suspended between March and September 2020 because of the COVID-19 pandemic, when no patients were considered for eligibility.

2.3. *Surgical procedure and follow-up*

Every procedure was performed by the uro-oncology team of Fundació Puigvert, which consists of seven senior urologists (>5 yr of experience), four junior urologists (<5 yr of experience), and 3rd-5th-year residents supervised by at least one urologist from the team. The patient was positioned in a standard lithotomy position under spinal or general anesthesia. A 28 Ch resectoscope (Karl Storz, Tuttlingen, Germany) was used with saline or glycine solution as the distension medium. m-cTURBT and b-cTURBT were performed using standard loop monopolar and bipolar electrodes. A Collins knife was used for m-ERBT and rectangular bipolar loop (Karl Storz) electrodes for b-ERBT. l-ERBT was performed using of a 550-μm fiber connected to a thulium laser generator (Revolix Duo; LisaLaser, Katlenburg-Lindau, Germany) set to 10–20 W of power. At the start of the procedure, the bladder was carefully inspected to verify the inclusion or exclusion status of the patient. For cases not meeting the inclusion criteria, dropout status was recorded and the patient was excluded from the per-protocol analysis.

ERBT, regardless of the energy used, involved a circular incision around the tumor base, cutting through macroscopically healthy mucosa with a safety margin of 5–10 mm and bluntly dissecting the tumor from the bladder wall at the desired depth.

The specimen was extracted by grabbing it with the electrode or using a glass Toomey evacuator; subsequent processing for pathological evaluation was according to a standard internal protocol. All samples were examined by an expert uropathologist (F.A.). For T1 tumors, T1 substaging (T1a/b/c [4]) was performed if feasible. The presence of artifacts was recorded and graded as focal or extensive. Perforation was defined as a resection depth reaching the perivesical fat and beyond. A 20–22 Ch three-way bladder catheter was inserted at the end of the procedure, and continuous bladder irrigation was started. An early one-shot instillation of 40 mg of mitomycin C or 50 mg of epirubicin was administered according to current guidelines for primary tumors or recurrent tumors detected more than 1 yr after the previous TURBT (2006 European Organisation for Research and Treatment of Cancer recurrence score <5) [17]. In cases of perforation or bleeding, no single instillation was performed. Patient care was in accordance with the postoperative and follow-up protocols of our institution, which are in line with the current EAU NMIBC guidelines [1].

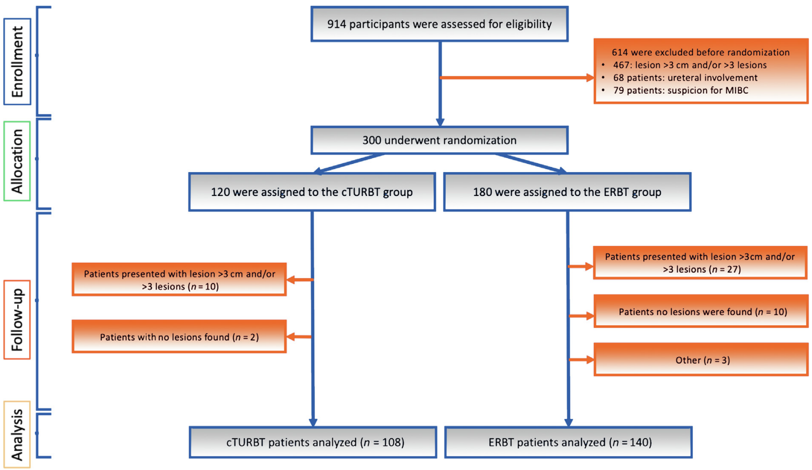

Fig. 1 – CONSORT flowchart showing the assessment, inclusion/exclusion, and randomization of patients in the study. cTURBT = conventional transurethral resection of bladder tumor; ERBT = en bloc resection of bladder tumor; MIBC = muscle-invasive bladder cancer.

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Table 1 – Population demographics by technique (ERBT vs cTURBT)

	cTURBT	ERBT	*p* value*
Patients, *n* (%)	108 (44)	140 (56)	
Males, *n* (%)	91 (84)	109 (78)	0.2
Median age, yr (interquartile range)	73 (65–79)	72 (61–80)	0.7
Median hemoglobin, g/l (interquartile range)	142.5 (129–154)	144 (135–154)	0.6
Tobacco use, *n* (%)			0.8
Active smoker	33 (30.5)	49 (35)	
Former smoker	33 (30.5)	40 (29)	
Nonsmoker	42 (39)	51 (36)	
Hypertension, *n* (%)	63 (58)	76 (54)	0.5
Diabetes, *n* (%)	28 (26)	34 (24)	0.8
History of myocardial infarction, *n* (%)	12 (11)	20 (14)	0.5
History of stroke, *n* (%)	6 (5.6)	5 (3.6)	0.5
Anticoagulant therapy, *n* (%)	14 (13)	17 (12)	0.9
Antiplatelet therapy, *n* (%)	19 (18)	25 (18)	1
Positive urine culture before surgery, *n* (%)	5 (4.6)	5 (3.6)	0.7
Radiation-induced cystitis, *n* (%)	4 (3.7)	1 (0.7)	0.1
History of bladder cancer, *n* (%)	48 (44)	50 (36)	0.2
Low-grade bladder cancer	28 (26)	31 (22)	0.5
High-grade bladder cancer	21 (19)	24 (17)	0.6
Preoperative urine cytology, *n* (%)			0.9
Positive	18 (17)	20 (14)	
Negative	84 (78)	109 (78)	
Suspicious	4 (4)	8 (6)	
Not performed	2 (1)	3 (2)	

cTURBT = conventional transurethral resection of bladder tumor; ERBT = en bloc resection of bladder tumor.
* χ^2 and Mann-Whitney tests were performed for comparison of cTURBT versus ERBT.

2.4. *Statistical analysis*

A descriptive statistical analysis of all data was performed. Analysis for quantitative variables included measures of central tendency and measures of dispersion and position. Differences between study groups in baseline variables were analyzed using a χ^2 test for categorical or nominal variables (or Fisher's test) and a *t* test (U Mann-Whitney U test) for continuous variables. Kaplan-Meier curves were generated to assess recurrence-free survival and overall survival. All the tests were conducted at a significance level of $p = 0.05$. Statistical analyses were performed using SPSS v.26 (IBM Corp., Armonk, NY, USA).

3. Results

We enrolled a total of 300 patients between April 2018 and June 2021 (Fig. 1). Fifty-two patients (17%) were excluded after randomization because they did not meet the inclusion criteria at the time of the surgical procedure, leaving 248 patients for the analysis, 140 in the ERBT group and 108 in the cTURBT group. Population characteristics are summarized in Table 1. There were no significant differences between the two study groups (all $p > 0.05$).

3.1. *Intraoperative and postoperative outcomes*

Intraoperative and postoperative data are shown in Table 2. In the ERBT group, the specimen was extracted inside the resectoscope in 127/140 cases (91%). The median irrigation

Table 2 – Intraoperative and postoperative outcomes by technique (ERBT vs cTURBT) and energy source (monopolar vs bipolar vs laser)

Parameter	cTURBT			ERBT				*p* value*
	Total	Monopolar	Bipolar	Total	Monopolar	Bipolar	Thulium laser	
Patients, *n* (%)	108 (44)	57 (23)	51 (21)	140 (56)	49 (20)	45 (18)	46 (18)	
Surgeon, *n* (%)								0.1
Senior urologist	16 (15)	11 (19)	5 (10)	30 (21)	4 (8)	12 (27)	14 (30)	
Junior urologist	31 (29)	17 (30)	17 (33)	52 (37)	25 (51)	14 (31)	15 (33)	
Resident	61 (56)	29 (51)	29 (57)	58 (42)	20 (41)	19 (42)	17 (37)	
Median surgery time, min (IQR)	30 (20–35)	30 (20–40)	30 (20–30)	30 (20–40)	30 (20–40)	30 (20–40)	30 (20–45)	0.1
Conversion to cTURBT, *n* (%)	–	–	–	6 (4.3)	2 (4.1)	2 (4.4)	2 (4.3)	–
Obturator nerve reflex, *n* (%)	7 (6.5)	3 (5.3)	4 (7.8)	15 (11)	5 (10)	10 (22)	0 (0)	0.3
Perforation, *n* (%)	18 (17)	8 (14)	10 (20)	28 (20)	7 (14)	13 (29)	8 (17)	0.9
Specimen extraction, *n* (%)	–	–	–					–
cTURBT				6 (5)	2 (4)	2 (4)	2 (4.5)	
Inside resectoscope				127 (91)	45 (92)	40 (89)	42 (91)	
With resectoscope				5 (4)	0 (0)	3 (7)	2 (4.5)	
Lesion splitting				2 (1)	2 (4)	0 (0)	0 (0)	
Early CTx installation, *n* (%)								
Planned	43 (40)	21 (37)	22 (43)	69 (49)	26 (53)	22 (49)	21 (46)	0.1
Performed	37 (86)	20 (95)	17 (77)	65 (94)	26 (100)	20 (91)	19 (86)	0.1
Complications, *n* (%)								0.5
No complications	82 (76)	43 (75)	39 (77)	111 (79)	43 (88)	23 (73)	35 (76)	
Clavien-Dindo 1–2	23 (21)	12 (21)	11 (22)	23 (16)	5 (10)	8 (18)	10 (22)	
Clavien-Dindo 3	3 (3)	2 (4)	1 (1)	6 (5)	1 (2)	4 (9)	1 (2)	
Blood transfusion, *n* (%)	2 (1.9)	1 (1.8)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0.2
Median irrigation time, d (IQR)	0.5 (0.5–1)	1 (0.5–1)	0.5 (0.5–1)	0.5 (0.5–1)	0.5 (0.5–1)	0.5 (0.5–1)	0.5 (0.5–1)	0.1
Median vesical catheter time, d (IQR)	2 (2–3)	2 (2–3)	2 (1–3)	2 (1–3)	2 (1–2)	2 (1–2)	2 (2–3)	0.2
Median hospitalization, d (IQR)	2 (2–2)	2 (2–2.5)	2 (1–2)	2 (1.3–2)	2 (1–2)	2 (1–2)	2 (2–2)	0.6
Median postoperative Hb, g/l (IQR)	137 (120–147)	135 (119–146)	138 (121–149)	137 (123–144)	137 (125–137)	139 (122–148)	132 (119–144)	0.9

cTURBT = conventional transurethral resection of bladder tumor; ERBT = en bloc resection of bladder tumor; IQR = interquartile range; CTx = chemotherapy; Hb = hemoglobin.
* χ^2 and Mann-Whitney tests were performed for comparison of cTURBT versus ERBT.

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and catheterization times were 0.5 d (interquartile range [IQR] 0.5-1) and 2 d (IQR 1–3) days in the ERBT group versus 0.5 d (IQR 0.5–1) and 2 d (IQR 2–3) in the cTURBT group, respectively (all $p > 0.05$). The median hospitalization time was 2 d (IQR 1.3–2) in the ERBT group and 2 d (IQR 2–2) in the cTURBT group ($p = 0.6$). Adjuvant treatment was planned for 69/140 patients (49%) in the ERBT group and 43/108 (40%) in the cTURBT group ($p = 0.1$) and was actually performed in 65/69 (94%) and 37/43 (86%), respectively ($p = 0.1$). Six patients (4.3%) undergoing ERBT had a conversion to cTURBT. Five of these six patients had anterior wall lesions for which ERBT was not feasible and one patient had a lesion in close proximity to the meatus so the surgeon decided to perform cTURBT.

Complications were reported for 29/140 patients (21%) in the ERBT group and 26/108 (24%) in the cTURBT group ($p = 0.5$). Clavien-Dindo >2 complications occurred in 6/140 patients (5%) in the ERBT group and 3/108 (3%) in the cTURBT group ($p = 0.5$). Only two patients in the cTURBT group received a blood transfusion. Obturator nerve reflex was reported for 15 patients (11%) in the ERBT group and seven (6.5%) in the TURBT group ($p = 0.2$).

3.2. *Pathological outcomes*

Per-patient analysis for the ERBT and cTURBT groups revealed similar rates of DM presence (95% vs 94%; $p = 0.8$; difference 1.5%, 95% confidence interval [CI] −0.01% to 3%), Tx stage (4% vs 3%; $p = 0.8$), and artifacts (7.9% vs 7.4%; $p = 0.8$) between the groups (Table 3). T1 substaging feasibility rate was significantly superior in the ERBT group: all 40 pT1 cases could be subclassified, in comparison to 34/37 cases in the cTURBT group (100% vs 80%; $p = 0.02$). These findings were confirmed in per-lesion anal-

Table 3 – Per-patient analysis of pathological outcomes for endoscopic resection by technique (ERBT vs cTURBT) and energy source (monopolar vs bipolar vs and laser)

Parameter	cTURBT			ERBT				*p* value*
	Total	Monopolar	Bipolar	Total	Monopolar	Bipolar	Thulium laser	
Patients, *n* (%)	108 (44)	57 (23)	51 (21)	140 (56)	49 (20)	45 (18)	46 (18)	
Bladder SBx, *n* (%)	85 (78.7)	48 (84.2)	37 (72.6)	116 (82.9)	40 (81.6)	35 (77.8)	41 (89.1)	0.4
Positive bladder SBx, *n* (%)	16 (19)	11 (23)	5 (14)	22 (19)	7 (18)	6 (17)	9 (22)	1
Stage on BSM, *n* (%)								1
Tx	2 (13)	2 (18)	0 (0)	3 (13)	1 (14)	1 (17)	1 (11)	
Ta	1 (6)	0 (0)	1 (20)	1 (5)	1 (14)	0 (0)	0 (0)	
Carcinoma in situ	13 (81)	9 (82)	4 (80)	18 (82)	5 (72)	5 (83)	8 (89)	
Grade on BSM, *n* (%)								0.9
Low grade	2 (13)	1 (9)	1 (20)	2 (9)	1 (14)	1 (17)	0 (0)	
High grade	1 (6)	1 (9)	0 (0)	1 (5)	1 (14)	0 (0)	0 (0)	
Carcinoma in situ	13 (81)	9 (81)	4 (80)	18 (81)	5 (72)	5 (83)	8 (89)	
Unspecified	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)	1 (11)	
Artifacts, *n* (%)	8 (7.4)	3 (5.3)	5 (9.8)	11 (7.9)	2 (4.1)	6 (13)	3 (6.5)	0.8
Detrusor muscle, *n* (%)								0.8
Yes	101 (94)	52 (96)	49 (96)	133 (95)	47 (96)	42 (93)	44 (96)	
No	7 (6)	5 (4)	2 (4)	7 (5)	2 (4)	3 (7)	2 (4)	
Tumor stage, *n* (%)								0.9
Tx	3 (3)	1 (2)	2 (4)	6 (4)	2 (4)	1 (2)	3 (7)	
Tis	2 (2)	2 (4)	0 (0)	2 (2)	0 (0)	2 (4)	0 (0)	
Ta	76 (70)	39 (68)	37 (72)	90 (64)	32 (65)	29 (65)	29 (63)	
T1	15 (14)	9 (16)	6 (12)	25 (18)	9 (19)	8 (18)	8 (17)	
T2	5 (5)	3 (5)	2 (4)	6 (4)	3 (6)	0 (0)	3 (6.5)	
T0/benign/other	7 (6)	3 (5)	4 (8)	11 (8)	3 (6)	5 (11)	3 (6.5)	
T1 substage feasibility, *n* (%)								**0.02**
Yes	12 (80)	7 (78)	5 (83)	25 (100)	9 (100)	8 (100)	8 (100)	
No	3 (20)	2 (22)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	
T1 substage, *n* (%)								0.1
1a	9 (60)	5 (56)	4 (66)	20 (80)	9 (100)	6 (75)	5 (62)	
1b	1 (7)	1 (11)	0 (0)	5 (20)	0 (0)	2 (25)	3 (38)	
1c	2 (13)	1 (11)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	
Not feasible	3 (20)	2 (22)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	
Tumor grade, *n* (%)								0.9
Low grade	56 (52)	30 (53)	26 (51)	70 (50)	26 (53)	20 (44)	24 (52)	
High grade	41 (38)	20 (35)	21 (41)	55 (39)	20 (41)	16 (36)	19 (41)	
Carcinoma in situ[a]	4 (4)	4 (7)	0 (0)	4 (3)	0 (0)	4 (9)	0 (0)	
T0/benign/other	7 (6)	3 (5)	4 (8)	11 (8)	3 (6)	5 (11)	3 (7)	
Risk category, *n* (%)[a]								0.4
Low	12 (11)	8 (14)	4 (8)	11 (8)	3 (6)	3 (7)	5 (11)	
Intermediate	42 (39)	19 (33)	23 (45)	71 (51)	15 (31)	18 (40)	14 (30)	
High	47 (44)	27 (48)	20 (39)	47 (33)	28 (57)	19 (42)	24 (52)	
T0/benign/other	7 (6)	3 (5)	4 (8)	11 (8)	3 (6)	5 (11)	3 (7)	

cTURBT = conventional transurethral resection of bladder tumor; ERBT = en bloc resection of bladder tumor; SBx = systematic biopsy; BSM = bladder systematic mapping.

* χ^2 and Mann-Whitney tests were performed for comparison of cTURBT versus ERBT.

[a] Patients were stratified according to the risk categories in the 2018 European Association of Urology guidelines.

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Table 4 – Per-lesion analysis of pathological outcomes after endoscopic resection by technique (ERBT vs cTURBT) and energy source (monopolar vs bipolar vs laser)

Parameter	cTURBT			ERBT				*p* value*
	Total	Monopolar	Bipolar	Total	Monopolar	Bipolar	Thulium laser	
Lesions, *n* (%)	147 (43)	76 (22)	71 (21)	194 (57)	61 (18)	73 (21)	60 (18)	
Tumor dimension, *n* (%)								0.07
<10 mm	84 (57)	46 (61)	38 (54)	92 (47)	33 (54)	32 (44)	27 (45)	
10–30 mm	63 (43)	30 (39)	33 (46)	102 (53)	28 (26)	41 (56)	33 (55)	
Tumor location, *n* (%)								0.7
Trigone	24 (16)	16 (21)	8 (11)	24 (12)	7 (11)	12 (16)	5 (8)	
Posterior wall	26 (18)	10 (13)	16 (23)	29 (15)	12 (20)	8 (11)	9 (16)	
Right wall	27 (19)	15 (19)	12 (17)	51 (26)	14 (23)	19 (26)	18 (30)	
Left wall	43 (29)	19 (25)	24 (33)	56 (29)	17 (28)	20 (27)	19 (32)	
Anterior wall	8 (5)	6 (8)	2 (3)	11 (6)	5 (8)	4 (6)	2 (3)	
Dome	10 (7)	5 (7)	5 (7)	12 (6)	3 (5)	4 (6)	5 (8)	
Bladder neck	9 (6)	5 (7)	4 (6)	11 (6)	3 (5)	6 (8)	2 (3)	
Tumor location, *n* (%)								0.7
Trigone	24 (16)	16 (21)	8 (11)	24 (12)	7 (11)	12 (17)	5 (8)	
Posterior wall	26 (18)	10 (13)	16 (22)	29 (15)	12 (20)	8 (11)	9 (15)	
Lateral walls	70 (48)	34 (45)	36 (51)	107 (55)	31 (51)	39 (53)	37 (62)	
Anterior wall/dome	18 (12)	11 (14)	7 (10)	23 (12)	8 (13)	8 (11)	7 (12)	
Bladder neck	9 (6)	5 (7)	4 (6)	11 (6)	3 (5)	6 (8)	2 (3)	
Artifacts, *n* (%)								0.2
Absent	135 (92)	71 (93)	64 (90)	180 (93)	58 (95)	66 (90)	56 (94)	
Present	3 (2)	2 (3)	1 (1)	8 (4)	3 (5)	3 (4)	2 (3)	
Extensive	9 (6)	3 (4)	6 (9)	6 (3)	0 (0)	4 (6)	2 (3)	
DM presence, *n* (%)	137 (93.2)	69 (90.8)	68 (95.8)	180 (92.8)	58 (95.1)	65 (89)	57 (95)	0.9
Tumor stage, *n* (%)								0.8
Tx	6 (4)	3 (4)	3 (4)	12 (6)	3 (5)	5 (7)	4 (7)	
Carcinoma in situ	3 (2)	3 (4)	0 (0)	4 (2)	0 (0)	4 (5)	0 (0)	
Ta	101 (69)	50 (66)	51 (72)	124 (64)	38 (62)	47 (64)	39 (65)	
T1	19 (13)	11 (14)	8 (11)	30 (16)	11 (18)	10 (14)	9 (15)	
T2	7 (5)	3 (4)	4 (6)	7 (3)	4 (7)	0 (0)	3 (5)	
T0/Benign/other	11 (7)	6 (8)	5 (7)	17 (9)	5 (8)	7 (10)	5 (8)	
T1 substage feasibility, *n* (%)								**0.03**
Yes	15 (84)	9 (82)	6 (86)	30 (100)	11 (100)	10 (100)	9 (100)	
No	3 (16)	2 (18)	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	
T1 substage, *n* (%)	18	11	7	30	11	10	9	0.2
1a	10 (55)	5 (46)	5 (72)	23 (77)	11 (100)	7 (70)	5 (56)	
1b	3 (17)	3 (27)	0 (0)	7 (23)	0 (0)	3 (30)	4 (44)	
1c	2 (11)	1 (9)	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	
Not feasible	3 (17)	2 (18)	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	
Tumor grade, *n* (%)								0.9
Low grade	75 (51)	39 (51)	36 (51)	94 (49)	32 (53)	34 (46)	28 (47)	
High grade	56 (38)	26 (34)	30 (42)	76 (39)	24 (39)	26 (36)	26 (43)	
Carcinoma in situ	5 (3)	5 (7)	0 (0)	6 (3)	0 (0)	6 (8)	0 (0)	
T0/benign/other	11 (8)	6 (8)	5 (7)	18 (9)	5 (8)	7 (10)	6 (10)	

cTURBT = conventional transurethral resection of bladder tumor; ERBT = en bloc resection of bladder tumor; DM = detrusor muscle.
* χ^2 and Mann-Whitney tests were performed for comparison of cTURBT versus ERBT.

ysis, which showed a statistically significant difference in T1 substaging feasibility in favor of ERBT (100% vs 84%; p = 0.03). Similar results were achieved in the per-lesion analysis, as shown in Table 4. Out of 248 patients, eight (3.2%) underwent second-look TURB: 1/5 patients in the ERBT group had residual tumor (T1a + carcinoma in situ), while 1/3 patient in the cTURBT group had residual tumor (T1b) and one patient was lost to follow-up.

3.3. *Oncological outcomes*

Median follow-up was 15 mo (IQR 7–28). The risk of death was similar for the cTURBT and ERBT groups (hazard ratio [HR] 1.43, 95% CI 0.41–4.95; p = 0.6), as was the risk of recurrence (HR 1.53, 95% CI 0.80–2.91; p = 0.2). Kaplan-Meier analysis revealed that recurrence-free survival was similar between the groups (p = 0.2); the survival curves are shown in Figure 2.

4. Discussion

This study provides the highest level of evidence for comparison of ERBT and cTURBT regarding operative, pathological, and short-term oncological outcomes and exploring all energy types available for the two techniques.

The literature contains controversial results from comparative RCTs on ERBT. This may reflect the heterogeneity study design, since the majority of the RCTs compared the two techniques using two different types of energy (laser ERBT versus electric TURBT) and different endpoints were assessed [18]. As reported by Teoh et al [7] in the international consensus statement, the current quality of evidence does not allow solid conclusions to be drawn.

The presence of DM has been considered a marker of a high-quality resection as it allows the pathologist to evaluate the extent of the disease and the urologist to give indications [2,3,19]. Our study demonstrated that ERBT was noninferior

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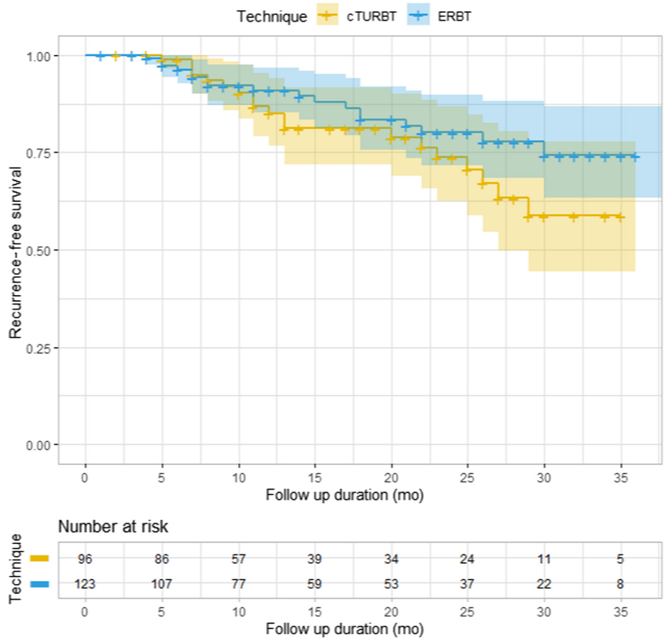

Fig. 2 – Kaplan-Meier analysis of recurrence-free survival. There was no statistically significant difference in survival rates between the cTURBT and ERBT groups (p = 0.2). cTURBT = conventional transurethral resection of bladder tumor; ERBT = en bloc resection of bladder tumor.

to cTURBT in terms of rates of DM presence (94% for cTURBT and 95% for ERBT; p = 0.84) and Tx stage (3% for cTURBT and 4% for ERBT; p = 0.85) at final histology. Therefore, ERBT guarantees a resection quality comparable to that with cTURBT, provided the latter is performed according to the best surgical practice [19]. This finding is somewhat surprising, as an improvement in resection quality has been considered the most important advantage of ERBT [6]. In fact, retrospective studies show an absence of DM in the specimen in up to 51% of cTURBT procedures [3,8,9].

Hashem et al [10] reported a DM rate of 62% with cTURBT versus 98% with laser ERBT, with a statistically significant difference between the groups (p < 0.001). Similarly, Cheng et al [20] reported that the rate of DM presence was 97.1% with green-light laser ERBT and 80% with cTURBT (p = 0.04). By contrast, other studies reported a DM rate that did not significantly differ between ERBT and cTURBT (p > 0.05) [11,12,21].

T1 substaging was possible in all ERBT cases, while the rate of T1 substaging feasibility was significantly lower in our cTURBT group (80%; p = 0.02). Just one previous study investigated the rate of T1 substaging feasibility and also found a significant difference (68.2% for laser ERBT vs 18.4% for cTURBT; p < 0.001) [10]. However, the definition of T1 BC was not clear, as the rate of T1 tumors was 95.5% in the ERBT and 93.9% in the cTURBT group, with DM absence rates of 2% and 38%, respectively (p < 0.001) [10]. Thus, a significant percentage of the T1 BC cases were actually Tx. Nonetheless, these findings underline the higher accuracy of ERBT for T1 substaging, which is currently recommended by the EAU guidelines [4,22,23].

The advantage of ERBT over cTURBT in terms of operative outcomes is debated. Resection time was longer for cTURBT in two studies, ranging from 13 to 19 min in comparison to 10–13 min for ERBT (p < 0.05). Conversely, two other RCTs found a significantly shorter operative time for cTURBT (22–30 min) than for ERBT (35–37 min; p < 0.05) [12,20]. Results for catheterization time were more uniform, with significantly longer times for cTURBT [10-12,20,21,24]. Hospitalization time was significantly shorter for ERBT in three RCTs [11,12,24] and comparable in two studies [10,20]. Despite these results, similar perforation rates were reported in these RCTs. In our study, there was no significant difference between ERBT and cTURBT in operative time, the rate of adjuvant instillation, catheterization time, or hospital stay. These findings represent the logical consequence of comparable rates of perforation and postoperative complications between the groups. Regarding

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oncological outcomes, both disease persistence at 3 mo and recurrence-free survival at median follow-up of 12 mo were comparable between the groups. These results are in line with the literature [7].

Our study is not devoid of limitations. This was a single-center study in an academic hospital. Our center is highly experienced in NMIBC treatment and thus the results may potentially not reflect current treatment outcomes. However, the heterogeneity of the operators, including supervised residents, means that the current results are generalizable and underline that a high rate of DM presence should be considered standard, regardless of the surgeon or resection technique [25,26]. Other limitations are the lack of specific analysis of tumor margins and the short follow-up, which precludes solid conclusions regarding oncological outcomes; long-term follow-up is foreseen to evaluate the definitive oncological results. Finally, we only tested EBRT in patients with a limited number of lesions that were ≤3 cm. Therefore, in translating these results to our daily practice, ERBT is only indicated for the clinical scenario considered in our study. Nonetheless, our results demonstrate why ERBT should be considered a standard surgery worth employing. The ERBT technique preserves tumor integrity, providing a high-quality specimen that increases pathological substaging accuracy without significant drawbacks in comparison to cTURBT. Further subanalysis will provide new insights regarding the different energy sources for ERBT.

5. Conclusions

This is the largest RCT of ERBT and demonstrates that ERBT is noninferior to cTURBT in the staging of BC. The rate of T1 substaging feasibility was significantly higher in the ERBT group. The intraoperative and postoperative outcomes were comparable between the groups. With median follow-up of 15 mo, oncological outcomes were comparable.

Author contributions: Pietro Diana had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Breda, Palou, Gallioli.
Acquisition of data: Diana, Fontana, Piana, Algaba.
Analysis and interpretation of data: Diana, Gallioli, Gaya.
Drafting of the manuscript: Diana, Gallioli, Territo.
Critical revision of the manuscript for important intellectual content: Breda, Palou, Sanguedolce.
Statistical analysis: Diana, Gallioli, Rodriguez-Faba.
Obtaining funding: Breda.
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Supervision: Breda, Huguet.
Other: None.

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Study 3

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TOPIC PAPER

Energy source comparison in en-bloc resection of bladder tumors: subanalysis of a single-center prospective randomized study

Pietro Diana[1,2] · Andrea Gallioli[1] · Matteo Fontana[1] · Angelo Territo[1] · Alejandra Bravo[1] · Alberto Piana[1] · Michael Baboudjian[1,3,4] · Pavel Gavrilov[1] · Óscar Rodriguez-Faba[1] · Josep Maria Gaya[1] · Ferran Algaba[5] · Joan Palou[1] · Alberto Breda[1]

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Abstract

Purpose Different energy sources are employed to perform en-bloc transurethral resection of bladder tumor (ERBT). No study compared different energy sources in ERBT. The aim is to compare the different ERBT sources in terms of pathological, surgical and postoperative outcomes.

Methods This is a sub-analysis of a prospective randomized trial enrolling patients submitted to ERBT vs conventional TURBT from 03/2018 to 06/2021 (NCT04712201). 180 patients enrolled in ERBT group were randomized 1:1:1 to receive monopolar (m-ERBT), bipolar (b-ERBT) or thulium laser (l-ERBT). Endpoints were the comparison between energies in term of pathological analysis, intra, and post-operative outcomes.

Results 49 (35%) m-ERBT, 45 (32.1%) b-ERBT, and 46 (32.9%) l-ERBT were included in final analysis. The rate of detrusor muscle (DM) presence was comparable between the energies used ($p = 0.796$) or the location of the lesion ($p = 0.662$). Five (10.2%), 10 (22.2%) and 0 cases of obturator nerve reflex (ONR) were recorded in m-ERBT, b-ERBT and I-ERBT groups, respectively ($p = 0.001$). Conversion to conventional TURBT was higher for lesions located in the anterior wall/dome/neck ($p < 0.001$), irrespective from the energy used. The presence of artifact in the pathological specimen was higher for lesions at the posterior wall ($p = 0.03$) and trigone ($p = 0.03$).

Conclusions In our study, no difference in staging feasibility among energies was found. Laser energy might be beneficial in lateral wall lesions to avoid ONR. Since there is an increased risk of ERBT conversion to conventional TURBT for lesions of the anterior wall, electrocautery might be preferred over laser to avoid waste of material.

Keywords Urothelial cancer · Endoscopy · Resection · Diagnosis · Treatment · Energy · Energies

Pietro Diana and Andrea Gallioli equally contributed to the manuscript.

✉ Pietro Diana
pietros.diana@gmail.com

1 Fundació Puigvert, Department of Urology, Autonomous University of Barcelona, Cartagena 340-350, 08025 Barcelona, Spain

2 Department of Urology, Humanitas Research Hospital-IRCCS, Rozzano, Italy

3 Department of Urology, APHM, North Academic Hospital, Marseille, France

4 Department of Urology, La Croix du Sud Hôpital, Quint Fonsegrives, France

5 Fundació Puigvert, Department of Pathology, Autonomous University of Barcelona, Barcelona, Spain

Abbreviations

BC	Bladder cancer
EAU	European association of urology
ERBT	En-bloc resection of bladder tumor
b-ERBT	ERBT-bipolar energy
m-ERBT	ERBT-monopolar energy
l-ERBT	ERBT-thulium laser energy
cTURBT	Conventional transurethral resection of bladder tumor
MIBC	Muscle-invasive bladder cancer
NMIBC	Non-muscle invasive bladder cancer
TURBT	Transurethral resection of bladder tumor
UUT	Upper urinary tract

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Introduction

Conventional transurethral resection of bladder tumor (cTURBT) is the standard treatment for non-muscle-invasive bladder cancer (NMIBC) [1]. Optimal staging at tumor resection is a crucial step in the management of BC, as it provides valuable information and prognostic elements that help guide further treatment decisions. Detrusor muscle presence/absence appears to be a surrogate marker of resection quality by independently predicting early bladder recurrence [2]. However, absence of detrusor muscle has been reported up to 40% using the cTURBT technique [3]. To overcome this and other drawbacks, en-bloc resection of bladder tumor (ERBT) has been introduced by Kawada et al. two decades ago [4]. Thus, ERBT is employed to improve the quality of pathological analysis, obtaining a more informative specimen, to preserve tumor integrity avoiding tumor cell dispersion and improve oncological outcomes [5, 6].

To date, different energy sources (monopolar, bipolar, laser, and hybridknife) have been introduced in performing ERBT [6]. In this scenario, multiple studies have compared the different energy sources used without providing clear conclusions due to heterogeneity in study design and ERBT energy sources [7]. In addition, high-quality data from head-to-head randomized controlled trials (RCTs) are still lacking. To address this question, we designed the a RCT comparing cTURBT versus ERBT employing all available energies to perform a sub-analysis comparing the different ERBT sources (monopolar, bipolar and laser) in terms of operative and postoperative outcomes and to provide guidance based on lesion location and energy source.

Materials and methods

Study design and population

This is a subanalysis of a single-center prospective, randomized, controlled, non-inferiority trial analyzing patients subjected to ERBT versus cTURBT for bladder cancer (BC). Only patients treated with ERBT were included for the purpose of this study. Eligible patients were aged ≥ 18 years, had primary or recurrent BC with a maximum of 3 concomitant lesions and a maximum of 3 cm of diameter. Patients with suspicion of MIBC or ureteral involvement were excluded from the randomization. Patients randomly allocated to ERBT were further randomized depending on energy source: monopolar (m-ERBT), bipolar (b-ERBT-b) or thulium laser (l-ERBT) energy in a 1:1:1 manner using computer-generated randomization tables. In particular, 180 patients were randomized to the ERBT test group (60 patients each for the m-ERBT, b-ERBT, and l-ERBT subgroups). Re-evaluation was ultimately performed before the endoscopic procedure and in case inclusion criteria were not met (e.g. increase in tumor size and/or number or absence of tumor) the patient was excluded and recorded as drop-out. The study was suspended between March 2020 and September 2020 due to Sars-COV2 pandemic and in this period of time, no patient was considered for eligibility. This study was carried out according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board (2017/09c). The study was registered on ClinicalTrials.gov (NCT04712201). All participants were adequately informed and provided a written consent.

Pre-operative evaluation, surgical procedure, and histopathological analysis

Pre-operative evaluation included patients' anthropometric variables, comorbidities, history of NMIBC, bladder ultrasound and/or flexible cystoscopy, and urine cytology. An abdominal computed tomography (CT) scan was performed in case of suspicion of muscle-invasive bladder cancer (MIBC) or upper urinary tract (UUT) involvement. The resections were performed by 7 senior urologists (> 5 year of experience), 4 junior urologists (< 5 year of experience), and by 3rd–5th residents supervised by at least one urologist of the team. Surgical procedures were performed with the patient in the standard lithotomy position under spinal or general anesthesia. Resectoscope of 26Ch. (*Karl Storz*, Tuttlingen, Germany) were employed and saline (b-ERBT and l-ERBT) or glycine (m-ERBT) solutions as bladder distension mediums depending on energy source. After initial intra-operative cystoscopy, the lesion was identified and described according to number of lesions, dimension, and position (trigon, posterior wall, lateral walls, anterior wall, dome, and bladder neck). Collins loop and rectangular (*Karl Storz*, Tuttlingen, Germany) loop were employed when m-ERBT and b-ERBT were performed, respectively (Fig. 1) using Karl Storz UH 400 surgical generator. l-ERBT was carried out with the employment of a 550 μm fiber connected to a thulium laser generator (Revolix Duo, *LisaLaser*, Katlenburg-Lindau, Germany) set to 10–20 W power. ERBT, regardless of the energy employed, was performed as a circular incision around the tumor base, cutting through macroscopically healthy mucosa with a safety margin of 5–10 mm and bluntly dissecting the tumor from the bladder wall at the desired depth. The specimen was extracted by grabbing it with the electrode or using a glass Toomey evacuator, and it was subsequently processed for pathological evaluation according to a standard internal protocol. In cases in which the specimen was too large to pass through the

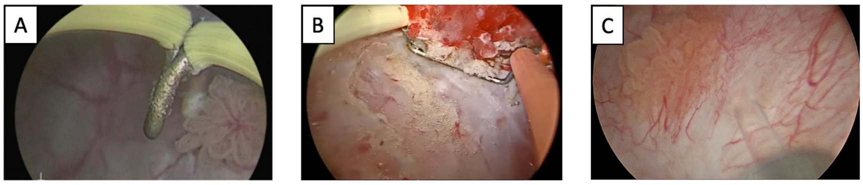

Fig. 1 Collins monopolar knife (**A**), rectangular bipolar loop-*Karl Storz*, Tuttlingen, Germany (**B**) and 550 µm Thulium: YAG laser fiber (**C**)

resectoscope, the lesion was subsequently cut in two or three pieces for extraction. Perforation was defined as a resection depth reaching the perivesical fat and beyond. A 20–22 Ch three-way bladder catheter was inserted at the end of the procedure, and continuous bladder irrigation was started. Early one-shot instillation of 40 mg mitomycin C or 50 mg epirubicin was administered according to current guidelines, recording if the instillation was indicated but not given due to bladder wall perforation or excessive bleeding. Patients followed the postoperative care and follow-up protocols of our institution in line with current EAU NMIBC guidelines [1]. Finally, a dedicated uropathologist (F.A.) blinded to the type of energy used analyzed all specimens for staging. BC staging of the lesion was classified according to the American Joint Committee on Cancer/Union for International Cancer Control TNM system and the World Health Organization classification [8]. In case of a T1 tumor, T1 substaging was performed if feasible according to the T1a, T1b, and T1c substaging system depending on the depth of invasion of the muscularis mucosae–vascular plexus [9].

Endpoints

Primary endpoint of the subanalysis was the comparison between energies in term of pathological analysis (detrusor muscle (DM) presence, staging feasibility, and presence of artifacts). Secondary endpoints were intra-operative (obturator nerve reflex (ONR), hemoglobin (Hb) drop, and bladder wall perforation) and post-operative (the rate of post-operative intravesical instillation feasibility after BC resection in patients meant to receive it according to the European Association of Urology (EAU) guidelines [1], irrigation and catheterization time, hospital stay, and post-operative complications scored according to the Clavien-Dindo classification [10]) outcomes.

Statistical analysis

Data were complemented by descriptive statistical analysis. Categorical variables were reported as frequencies and percentages (%), and continuous variables as means and standard deviations (SD). Differences between study groups in baseline variables were analyzed with ANOVA for continuous variables or chi-squared test for categorical ones. All the tests were conducted at a significance level $p = 0.05$. Statistical analyses were performed using SPSS v.26 (IBM Corp., Armonk, NY).

Results

A total of 180 participants were enrolled between April 2018 and June 2021. Fourty (22.2%) patients were subsequently excluded because they did not meet inclusion criteria. One hundred and forty patients were included in the final analysis: 49 (35%) m-ERBT, 45 (32.1%) b-ERBT, and 46 (32.9%) l-ERBT. One-hundred nine (77.9%) patients were male and mean age was 71 years (± 11.8). Each energy group were similar in terms of patient (Supplementary Table 1) and tumor (Supplementary Table 2) characteristics, except for the baseline number of tumor which was higher in the l-ERBT patients (1.62 ± 0.59) than patients who underwent m-ERBT (1.24 ± 0.48) and b-ERBT (1.3 ± 0.78; $p = 0.009$). Pathological tumor staging was as follow: 11 T0 (7.8%), 6 Tx (4.3%), 2 CIS (1.4%), 90 Ta (64.3%), 20 T1a (14.3%), 5 T1b (3.6%), 6 T2 (4.3%) tumors.

Tables 1, 2 show the intra- and post-operative outcomes by either energy source employed (m-ERBT, b-ERBT, and l-ERBT) or by bladder walls (group 1: trigone and the posterior wall; group 2: right and left lateral walls; and group 3: anterior wall, dome, and bladder neck), respectively. In total, DM was present in 133 pathological specimens (95%). The rate of DM presence was comparable between the energies used ($p = 0.796$) or the location of the lesion ($p = 0.662$). The rate of DM presence was similar between residents and attendings (96.4 vs. 94% $p = 0.702$). While no case of ONR occurred in the I-ERBT group, five (10.2%) and ten (22.2%) cases were recorded in the m-ERBT and b-ERBT patients, respectively ($p = 0.001$). The overall length of postoperative catheterization was 2.4 days (± 1.8) and was significantly shorter in the m-ERBT group ($p = 0.034$). As shown in Table 2, conversion from EBRT

Table 1 Intra-operative and post-operative outcome divided by energy source (monopolar, bipolar, and laser) and ANOVA or Fisher exact test analysis of the overall distribution between the three groups and pair comparisons

Energy employed	Overall	Monopolar	Bipolar	Thulium laser	ANOVA or fisher exact test (*p* value)	Monopolar vs bipolar	Monopolar vs thulium laser	Bipolar vs thulium laser
Number of patients, *n* (%)	140	49 (35)	45 (32.1)	46 (32.9)	–	–	–	–
Lesion location, *n* (%)					0.505	–	–	–
Posterior/trigone	39 (27.9)	15 (30.6)	15 (33.3)	9 (19.6)				
Lateral walls	79 (56.4)	25 (51)	25 (55.6)	29 (63)				
Anterior/dome/neck	22 (15.7)	9 (18.4)	5 (11.1)	8 (17.4)				
Surgery duration, mean (SD)	33.4 (17.5)	31.8 (16.9)	34.7 (17.6)	33.8 (18.3)	0.72	–	–	–
Conversion to cTURBT, *n* (%)	6 (4.3)	2 (4.1)	2 (4.4)	2 (4.3)	1	–	–	–
Obturator nerve reflex, *n* (%)	**15 (10.7)**	**5 (10.2)**	**10 (22.2)**	**0 (0)**	**0.001**	0.159	**0.056**	**< 0.001**
Perforation, *n* (%)	28 (20)	7 (14.3)	13 (28.9)	8 (17.4)	0.193	0.129	0.781	0.221
Planned early CT instillation, *n* (%)	69 (49.3)	26 (53.1)	22 (48.9)	21 (45.7)	0.633	–	–	–
Performed early CT instillation of planned, n (%)	65 (94.2)	26 (100)	20 (90.9)	19 (86.4)	0.494	–	–	–
Complications, *n* (%)					–	–	–	–
No complications	111 (79.3)	43 (87.8)	23 (73.3)	35 (76.1)				
Clavien-dindo 1–2	23 (16.4)	5 (10.2)	8 (17.8)	10 (21.7)				
Clavien-dindo 3	6 (4.3)	1 (2)	4 (8.9)	1 (2.2)				
Overall complications, *n* (%)	29 (20.7)	6 (12.2)	12 (26.7)	11 (23.9)	0.172	0.114	0.182	0.812
Major complications, *n* (%)	6 (4.3)	1 (2)	4 (8.9)	1 (2.2)	0.282	–	–	–
Artifacts	11 (7.9)	2 (4.1)	6 (13.3)	3 (6.5)	0.253	–	–	–
Detrusor muscle					0.796	–	–	–
Yes	133 (95)	47 (95.9)	42 (93.3)	44 (95.7)				
No	7 (5)	2 (4.1)	3 (6.7)	2 (4.3)				
T1 substage feasibility					1	–	–	–
Yes	25 (100)	9 (100)	8 (100)	8 (100)				
No	0 (0)	0 (0)	0 (0)	0 (0)				
Length of irrigation, mean (SD)	0.9 (0.9)	0.9 (0.9)	1 (0.9)	0.9 (0.8)	0.692	–	–	–
Length of catheterization days, mean (SD)	**2.4 (1.8)**	**1.9 (1.3)**	**2.5 (1.8)**	**2.8 (2.1)**	**0.034**	0.162	**0.033**	0.779
Length of stay, mean (SD)	2.1 (1.2)	2.1 (1.4)	2.4 (1.3)	2.1 (0.9)	0.525	–	–	–
Post-op hemoglobin, mean (SD)	9 (9.4)	6.8 (8.8)	9.7 (9.8)	10.7 (9.3)	0.167	0.374	0.166	0.891

cTURBT conventional transurethral resection of bladder tumor, *SD* standard deviation, *CT* chemotherapy, *ANOVA* analysis of variance

to cTURBT was found to be higher for lesions located in the anterior wall, dome or bladder neck, reaching 22.7% (5/22; $p < 0.001$). The presence of artifact in the pathological specimen ($p = 0.030$) was higher for lesions located to the posterior wall and trigone (17.9%; 7/39, $p = 0.03$). Overall complication rate and major complication rate was 12.2/2%, 26.7/8.9%, and 23.9/2.2% for m-ERBT, b-ERBT, and l-ERBT, respectively. Subgroup analysis comparing the energy used per bladder wall is provided in supplementary Tables 3, 4. In case of anterior wall lesions, the rate of conversion from ERBT to cTURBT was significantly higher for both monopolar ($p = 0.031$) and laser energy ($p = 0.027$); the occurrence of ONR, recorded only in the lateral walls, was significantly higher when we used monopolar and bipolar electrocautery energies ($p = 0.016$ and $p < 0.001$, respectively).

Table 2 Intra-operative and post-operative outcome divided by bladder walls (posterior/trigone, lateral walls, and anterior/dome/neck) and ANOVA or Fisher exact test analysis of the overall distribution between the three groups and pair comparisons

Energy employed	Overall	Posterior/trigone (1)	Lateral walls (2)	Anterior/dome/neck (3)	ANOVA or fisher exact test (*p* value)	1 vs. 2	1 vs. 3	2 vs. 3
Number of patients, *n* (%)	140	39 (27.9)	79 (56.4)	22 (15.7)	–	–	–	–
Energy, *n* (%)					0.285	–	–	–
Monopolar	39 (27.9)	15 (38.5)	25 (31.6)	9 (40.9)				
Bipolar	79 (56.4)	15 (38.5)	25 (31.6)	5 (22.7)				
Thulium laser	22 (15.7)	9 (23)	29 (36.8)	8 (36.4)				
Surgery duration, mean (SD)	33.4 (17.5)	29.6 (16.8)	35.2 (16.4)	33.6 (21.9)	0.261	–	–	–
Conversion to cTURBT, *n* (%)	**6 (4.3)**	**1 (2.6)**	**0 (0)**	**5 (22.7)**	**< 0.001**	0.33	**0.019**	**< 0.001**
Obturator nerve reflex, *n* (%)	15 (10.7)	3 (7.7)	13 (16.5)	0 (0)	0.071	0.257	0.547	0.065
Perforation, *n* (%)	28 (20)	8 (20.5)	16 (20.3)	4 (18.2)	1	–	–	–
Planned early CT instillation, *n* (%)	69 (49.3)	16 (41)	42 (53.2)	11 (50)	0.461	–	–	–
Performed early CT instillation of planned, *n* (%)	65 (94.2)	15 (38.5)	40 (50.6)	10 (45.5)	0.787	–	–	–
Complications, *n* (%)					–	–	–	–
No complications	111 (79.3)	31 (79.5)	65 (82.3)	15 (68.2)				
Clavien-dindo 1–2	23 (16.4)	6 (15.4)	11 (13.9)	6 (27.3)				
Clavien-dindo 3	6 (4.3)	2 (5.1)	3 (3.8)	1 (4.5)				
Overall complications, *n* (%)	29 (20.7)	8 (20.5)	14 (17.7)	7 (31.8)	0.357	–	–	–
Major complications, *n* (%)	6 (4.3)	2 (5.1)	3 (3.8)	1 (4.5)	1	–	–	–
Artifacts	**11 (7.9)**	**7 (17.9)**	**3 (3.8)**	**1 (4.5)**	**0.03**	**0.014**	0.238	1
Detrusor muscle					0.662	–	–	–
Yes	133 (95)	36 (92.3)	76 (96.2)	21 (95.5)				
No	7 (5)	3 (7.7)	3 (3.8)	1 (4.5)				
T1 substage feasibility					1	–	–	–
Yes	25 (100)	6 (100)	18 (100)	2 (100)				
No	0 (0)	0 (0)	0 (0)	0 (0)				
Length of irrigation, mean (SD)	0.9 (0.9)	0.8 (0.6)	0.9 (0.9)	1.3 (1.2)	0.069	0.671	0.057	0.152
Length of catheterization days, mean (SD)	2.4 (1.8)	2.1 (1.4)	2.5 (1.8)	2.6 (2.3)	0.382	–	–	–
Length of stay, mean (SD)	2.1 (1.2)	1.9 (0.9)	2.3 (1.3)	2.4 (1.5)	0.275	–	–	–
Hemoglobin drop, mean (SD)	9 (9.4)	7.2 (6.7)	8.8 (9.2)	12.1 (12.4)	0.203	0.746	0.182	0.349

cTURBT conventional transurethral resection of bladder tumor, *SD* standard deviation, *CT* chemotherapy, *ANOVA* analysis of variance

Discussion

Presence of DM in the histopathological specimens after resection of BC is the most reliable indicator for an adequate and high-quality resection [11]. This concept is fundamental to decide the surgical strategy in the setting of BC as the lack of DM could bring to a suboptimal staging of BC and subsequent management and prognosis. ERBT has proven to be the a highly reliable method for obtaining DM in resected specimens [12, 13], but whether the different energy sources available are capable of providing the same results was an unresolved question until then. Here we report the first evidence analyzing and comparing the different energies available to achieve ERBT in a RCT. We found that both electrocautery and laser energies are suitable for an apparently satisfactory staging rate resulting in low rates of DM absence regardless of the energy employed and a comparable rate of artifacts in the specimens. Our results are in line with the previously reported rate of detrusor muscle presence in ERBT specimens, ranging from 87–98, 40–100, and 51–100% for laser [14–16], monopolar [17, 18], and bipolar [19–21] electrocautery energies, respectively. Given the number of patients included, the prospective, randomized design, and the head-to-head comparison of each energy used for ERBT, our study provides the best available evidence of what can be expected from each energy source to achieve detrusor muscle presence during ERBT.

The energy source to be used to perform ERBT may vary depending on the location of the lesion. For the lateral wall, we found a higher rate of ONR using monopolar or bipolar energies compared to a laser source. Therefore, l-ERBT seems to potentially be the best option to ensure a safer procedure.

Bipolar resection has been suggested to reduce the risk of perforation compared monopolar energy with rates of 21.5 vs 6.1%, respectively ($p = 0.039$) [22]. The hypothesis is founded on the decreased elicitation of ONR using bipolar energy. However, this advantage is debated with RCT reporting the lack of this superiority ($p = 1$) [23]. Our study is the first comparing bipolar and monopolar energies in the ERBT setting. The results show no significant difference in terms of either bladder perforation and post-operative.

Major importance should also be given to the rate of conversion to cTURBT. Out of 6 conversion, in 5 cases BC was found on the anterior wall and dome and in one case it was in the proximity of the meatus. In 22.7% of lesions of the anterior wall, conversion was necessary as no adequate visibility could be reached to perform ERBT. This limitation of laser should be kept in mind when planning the surgical approach as, in these cases, electrical energies (either monopolar or bipolar) should be preferred to avoid the increased potential risk of changing instruments and the subsequent waste of surgical material. The study by Kramer et al. compared the rate of conversion between different energies and found a higher rate of conversion to cTURBT compared to our study (19.9 vs. 4.3%) and almost all cases of conversion occurred in case of electrical energy employment [24]. As stated by the authors the change to cTURBT was influenced by an easier switch in case of employment of electrical energy as it does not require a change of the instrumentation. Most importantly, we believe that the location of the lesion is the main factor influencing the feasibility of ERBT rather than the kind of energy employed.

Finally, despite the shorter mean time of catheterization when monopolar is employed in case of posterior wall or trigone lesions was a statistically significant, the comparable length of irrigation and hospital stay make this difference less clinically relevant.

Our study is not devoid of limitations. First of all, this is a single-center study conducted in a high-volume center with expertise in performing EBRT which does not reflect low and medium volume centers performance. The numerosity of the population was calculated for the comparison between cTURBT versus ERBT and it was not focused on this sub-analysis that may result in underpowered analysis, thus these results should be confirmed by a tailored study design. Moreover, despite these were not the objective of this study, is the lack of comparison with cTURBT and of the oncological outcome that could give further information on energy employment indications. This study is first prospective randomized trial analyzing the energy sources available to perform ERBT. The results underline that there is no difference in the employment of monopolar, bipolar or laser energies in terms of diagnosis and staging when performing ERBT. The coexistence of different energy sources allows to provide indication to decide the surgical strategy and define what and where to employ different techniques ensuring safer, high quality, and cost-effective procedures.

Conclusion

This is the first prospective randomized trial comparing the different energy sources available to perform ERBT. In our study, no difference was found in staging and diagnosis of BC as all energies ensure a high-quality specimen. Laser energy might be beneficial in lateral wall lesions to avoid ONR. Since there is an increased risk of ERBT conversion to cTURBT for lesions of the anterior wall, electrocautery might be preferred over laser to avoid waste of material. The energy source to be used during ERBT should be tailored to the lesion location to provide safest and highest quality procedure.

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Author contributions PD: data collection, data analysis, manuscript writing. AG: protocol/project development, data analysis, manuscript writing. MF: data collection. AT: data collection, data analysis, manuscript editing. AB: data collection, manuscript writing. AP: data collection. MB: manuscript editing. PG: data collection. ÓR: data collection, data analysis. JG: data collection, data analysis. FA: data collection, data analysis. JP: project development. AB: protocol/project development, manuscript editing.

Declarations

Conflict of interest The authors report no conflict of interest.

Research involving human participants and/or animals This study respected the principles of the Declaration of Helsinki and was approved by the Institutional Review Board (2017/09c).

Informed consent All participants were adequately informed and provided a written consent.

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Study 4

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TOPIC PAPER

The DEpth of Endoscopic Perforation scale to assess intraoperative perforations during transurethral resection of bladder tumor: subgroup analysis of a randomized controlled trial

Alberto Breda[1,5] · Andrea Gallioli[1] · Pietro Diana[1,2] · Matteo Fontana[1] · Angelo Territo[1] · Josep Maria Gaya[1] · Óscar Rodriguez-Faba[1,5] · Jordi Huguet[1] · Alberto Piana[1] · Paolo Verri[1] · Michael Baboudjian[1,4] · Julia Aumatell[1] · Ferran Algaba[3] · Joan Palou[1,5]

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Abstract

Purpose Bladder perforation (BP) is the most important intraoperative adverse event of transurethral resection of bladder tumor (TURBT). It is frequently underreported despite its impact on the postoperative course. There is no standardized classification of BP. The study aims to develop a classification of the depth of endoscopic bladder perforation during TURBT.

Methods This is a sub-analysis of a prospective randomized trial enrolling 248 patients submitted to en-bloc vs conventional TURBT from 03/2018 to 06/2021. The DEpth of Endoscopic Perforation (DEEP) scale is as follows: "0" visible muscular layer with no perivesical fat; "1" visible muscle fibers with spotted perivesical fat; "2" exposition of perivesical fat; "3" intraperitoneal perforation. Logistic and linear regression models were used to investigate predictors of high-grade perforations (DEEP 2–3) and to assess whether the DEEP scale independently predicted patients' postoperative outcomes.

Results A total of 146/248 (58.9%), 56/248 (22.6%), 41/248 (16.5%), 5/248 (2.0%) patients presented DEEP grade 0, 1, 2, and 3, respectively. Female gender [*B* coeff. 0.255 (95% CI 0.001–0.513); $p=0.05$], tumor location [*B* coeff. 0.188 (0.026–0.339); $p=0.015$], and obturator-nerve reflex [*B* coeff. 0.503 (0.148–0.857); $p=0.006$] were independent predictors of DEEP. The scale predicted independently major complications [Odd Ratio (OR) 2.221 (1.098–4.495); $p=0.026$], no post-operative chemotherapy intravesical instillation [OR 9.387 (2.434–36.200); $p=0.001$], longer irrigation time [*B* coeff. 0.299 (0.166–0.441); $p<0.001$] and hospital stay [*B* coeff. 0.315 (0.111–0.519); $p=0.003$].

Conclusion The DEEP scale provides a visual tool for grading bladder perforation during TURBT, which can help physicians standardize complication reporting and plan postoperative management accordingly.

Keywords Urothelial cancer · Endoscopy · Resection · Diagnosis · Treatment

Abbreviations

BP	Bladder perforation
cTURBT	Conventional transurethral resection of bladder tumor
EAU	European Association of Urology
ERBT	En-bloc resection of bladder tumor
MVA	Multivariate regression analysis
NMIBC	Non-muscle invasive bladder cancer
TURBT	Transurethral resection of bladder tumor
UVA	Univariate regression analysis

Alberto Breda and Andrea Gallioli equally contributed to the manuscript.

✉ Alberto Breda
albbred@hotmail.com

1 Department of Urology, Fundació Puigvert, Barcelona, Spain

2 Department of Urology, Humanitas Research Hospital-IRCCS, Rozzano, Italy

3 Fundació Puigvert, Department of Pathology, Autonomous University of Barcelona, Barcelona, Spain

4 Department of Urology, North Hospital, APHM, Marseille, France

5 Present Address: Department of Surgery, Autonomous University of Barcelona, Barcelona, Spain

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Introduction

Transurethral resection of bladder tumor (TURBT) is employed for the diagnosis of bladder cancer (BC). In non-muscle invasive BC (NMIBC), TURBT and adjuvant intravesical instillation are considered the gold standard treatment [1, 2]. Despite TURBT is a very common surgery in urology, it is not devoid of complications. Bleeding and bladder perforation (BP) are typical complications [3]. Moreover, the absence of BP is considered a quality indicator of TURBT, on par with the presence of detrusor muscle in the specimen [4]. Although BP is considered uncommon, reaching a 2.5–5% risk during procedure [5], several studies showed a non-negligible underdiagnosis and underreporting rates leading to a real frequency ranging up to 58.3% [6]. The absence of standardized methods to report intraoperative adverse events has been recognized as a major issue by the European Association of Urology, which created an ad hoc Complication Guideline Panel to propose a dedicated classification [7]. This may help identifying proper measures of benchmarking, to compare surgeons, institutions and surgical techniques, to characterize surgical morbidity and report it accurately to patients [7]. Moreover, a universal standard reporting system of intraoperative adverse events is being developed through a Delphi Consensus (ICARUS project) [8]. In TURBT, the resection depth is the most conditioning factor, either intraoperatively or postoperatively. Depending on resection depth, the surgeon may decide to interrupt the procedure and/or to avoid immediate intravesical instillation of chemotherapy to limit drug extravasation [6].

Thus, a standardized classification of resection depth is necessary to identify the preoperative risk factors and analyze the post-operative consequences. The aim of this study is to provide a novel classification describing the depth of resection to provide a standard and reproducible tool to the urological community.

Materials and methods

Study population

The study was designed within a single-center randomized, controlled, non-inferiority trial comparing patients subjected to en-bloc versus conventional TURBT for BC (NCT04712201). Inclusion criteria comprehended patients affected by primary or recurrent BC, located anywhere in the bladder, with a maximum of 3 separated lesions and/or with a maximum size of 3 cm per each lesion. As part of the secondary endpoints of the study, an ad-hoc classification of BP was created and prospectively applied between April 2018 and June 2021. A total of 248 patients were included in the final analysis. The study was suspended between March 2020 and September 2020 due to SARS-CoV-2 pandemic and in this period of time no patient was considered for eligibility. This study respected the principles of the Declaration of Helsinki and was approved by the Institutional Review Board (2017/09c). All participants were adequately informed and provided a written consent.

Surgical procedure

The patient was placed in the standard lithotomy position under spinal or general anesthesia. Conventional TURBT was performed with standard monopolar and bipolar loops. En-bloc TURBT was carried out with monopolar Collins loop, bipolar rectangular loop (*Karl Storz*, Tuttlingen, Germany) or 550-µm fiber connected to a thulium laser generator (Revolix Duo, LisaLaser, Katlenburg-Lindau, Germany) set to 10–20 W power. En-bloc TURBT technique provided for a circular incision around the base of the lesion with a margin of 5–10 mm of healthy mucosa. The lesion was then bluntly dissected form the bladder wall at the desired depth. After specimen extraction either through the resectoscope or with a Toomey evacuator, a careful hemostasia of the resection bed was carried out. A 20–22 Ch three-way bladder catheter was inserted at the end of the procedure, and continuous bladder irrigation was started. In accordance with our institution's protocol, six additional biopsies were performed to detect subclinical carcinoma in situ in patients with primo-resection, recurrence with positive cytology and/or prior high-grade BC.

TURBTs were performed by experienced, dedicated, surgeons or resident under the direct supervision of a senior surgeon. When the procedure was performed by a resident, intraoperative assessment of resection depth and DEEP grade was performed and recorded by the senior surgeon. All tumor samples were examined by a dedicated uropathologist (F.A.). Early postoperative instillation of 40 mg mitomycin C or 50 mg epirubicin was administered according to current guidelines. The postoperative course and follow-up protocol were planned according to the institutional protocol. The complications were evaluated at 30 days according to Clavien–Dindo classification [9].

DEpth of Endoscopic Perforation (DEEP) scale

Four grades of vesical endoscopic perforation during TURBT were defined (Fig. 1). Grade 0 indicates that, after the resection, the vesical muscular layer is visible with no sign of perivesical fat. In grade 1, the vesical muscular layer is visible with some spots of perivesical fat. Grade 2

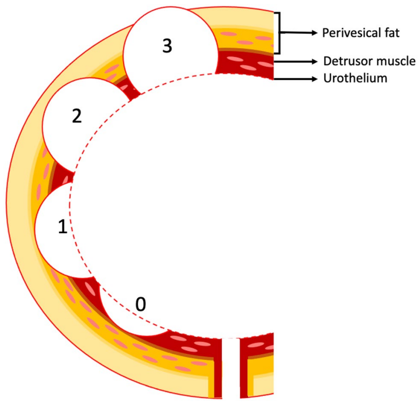

Fig. 1 Grades of DEEP scale: (0) vesical muscular layer is visible with no sign of perivesical fat, (1) the vesical muscular layer is visible with some spots of perivesical fat, (2) the muscular layer is completely resected with the exposition of the perivesical fat (extraperitoneal perforation) (3) muscular layer, perivesical fat and peritoneum are perforated (intraperitoneal perforation)

identifies those cases where the muscular layer was completely resected with the exposition of the perivesical fat (extraperitoneal perforation). Grade 3 indicates the resection of muscular layer, perivesical fat and peritoneum (intraperitoneal perforation). Grade 2 (extraperitoneal) and grade 3 (intraperitoneal) perforations were defined as high-grade complications as they could significantly affect the postoperative course of patients.

Statistical analysis

Data were represented by descriptive statistical analysis. The quantitative variables were reported as median and interquartile range (IQR). The qualitative variables were described as absolute number and frequency. Differences between study groups in variables were analyzed with Chi-square test in categorical or nominal variables (or Fisher test) and with *T* Test in continuous variables. Variables with $p < 0.20$ in univariate analysis were included in multivariate logistic and linear regression (MVA) models to assess predictors of high-grade perforation according to the DEEP scale (Table 2) and predictors of major postoperative complications (Clavien–Dindo classification > 2) (Supplementary Table 1), administration of intravesical chemotherapy (Supplementary Table 2), postoperative irrigation time (Supplementary Table 3), length of stay (Supplementary Table 4), and catheterization time (Supplementary Table 5). All the tests were conducted at a significance level $p = 0.05$. Statistical analyses were performed using SPSS v.26 (IBM Corp., Armonk, NY).

Results

A total of 140 patients underwent en-bloc TURBT and 108 conventional TURBT. Population and operative characteristics are summarized in Table 1. After resection, 146/248 (58.9%), 56/248 (22.6%), 41/248 (16.5%), 5/248 (2.0%) patients presented a DEEP grade 0, 1, 2, and 3, respectively. All cases of intraperitoneal bladder perforation were treated conservatively with prolonged catheterization (5–7 days) and no surgical repair was ultimately required.

Preoperative predicting factors

Pre-operative variables distributed by DEEP grades are shown in Table 2. High-grade DEEP (grade 2–3) were more frequent in case of tumors located at the lateral walls (17.7% and 3.1% for grade 2 and 3, respectively) of the bladder and anterior wall/dome/neck (23.1% and 0% for grade 2 and 3, respectively) in respect to lesions found in the trigone and posterior walls (11.4% and 1.3% for grade 2 and 3, respectively).

A linear regression analysis was performed to investigate the pre- and intra-operative variables that could be correlated with higher grade of DEEP scale (Table 2). At MVA, female gender [*B* coeff. 0.255; 95% CI 0.001–0.513; $p = 0.05$], tumor location [*B* coeff. 0.188 (0.026–0.339); $p = 0.015$], and obturator nerve reflex [*B* coeff. 0.503(0.148–0.857); $p = 0.006$] were independent predictors of higher DEEP grades.

Post-operative variables

Post-operative variables distributed by DEEP grades are reported in Table 3. The rate of post-operative intravesical mitomycin administration was lower in high-grade perforations ($p < 0.001$), while the rate of complications ($p = 0.019$) and major complications ($p < 0.001$), length of irrigation ($p < 0.001$), length of catheterization ($p = 0.017$), and hospitalization time ($p = 0.002$) were higher compared to grade 0–1 perforations.

In UVA, DEEP grade was significantly associated with the absence of post-operative intravesical instillation (OR = 5.579; $p < 0.001$), major complications (OR = 2.105; $p = 0.035$), length of irrigation (OR = 0.316; $p < 0.001$) and hospitalization time (OR = 0.385; $p < 0.001$). In MVA, DEEP scale remained an independent predictor of major complication [OR = 2.221 (1.098–4.495); $p = 0.026$], adjusted for age and surgeon experience (Supplementary table 1–5). DEEP scale

Table 1 Demographic and operative characteristics of the total cohort of patients, stratified for DEEP grade and compared using Chi-square or Kruskal–Wallis test

Variable	Total cohort (*n* = 248)	DEEP grade 0 (*n* = 146)	DEEP grade 1 (*n* = 56)	DEEP grade 2 (*n* = 41)	DEEP grade 3 (*n* = 5)	*P*
Gender, *n* (%)						
Male	200 (80.6)	122 (83.6)	44 (78.6)	32 (78)	2 (40)	0.093
Female	48 (19.4)	24 (16.4)	12 (21.4)	9 (22)	3 (60)	
Median (IQR) age, *years*	72 (64–80)	73 (64–80)	69.5 (64–76)	72 (65–78)	82 (76–85)	0.33
Median (IQR) preoperative hemoglobin, *g/L*	143 (133–154)	144 (133–154)	143 (132–155)	144 (135–150)	141 (136–143)	0.68
Tobacco, *n* (%)						
Active smoker	82 (33.1)	47 (32.2)	18 (32.1)	17 (41.5)	0	0.8
Former smoker	73 (29.4)	45 (30.8)	18 (32.1)	8 (19.5)	2 (40)	
Non-smoker	93 (37.5)	54 (37)	20 (35.8)	16 (39)	3 (60)	
History of bladder cancer, *n* (%)						
Yes	98 (39.5)	64 (43.8)	19 (33.9)	12 (29.3)	3 (60)	0.21
No	150 (60.5)	82 (56.2)	37 (66.1)	29 (70.7)	2 (40)	
Surgeon, *n* (%)						
Senior urologist	134 (52)	84 (57.5)	26 (46.4)	22 (53.7)	2 (40)	0.7
Resident	114 (48)	62 (42.5)	30 (53.6)	19 (46.3)	3 (60)	
Median (IQR) surgery duration, min	30 (20–40)	27.5 (20–40)	30 (20–40)	35 (30–40)	40 (30–45)	0.013
Systematic random biopsies, *n* (%)						
Yes	195 (78.6)	119 (81.5)	39 (69.6)	34 (82.9)	3 (60)	0.18
No	53 (21.4)	27 (18.5)	17 (30.4)	7 (17.1)	2 (40)	
Tumor diameter, *n* (%)						
< 1 cm	118 (47.6)	70 (47.9)	28 (50)	19 (46.3)	1 (20)	0.88
≥ 1 cm	130 (52.4)	76 (52.1)	28 (50)	22 (53.7)	4 (80)	
Tumor location, *n* (%)						
Trigone/posterior	79 (31.9)	58 (39.7)	11 (19.6)	9 (22)	1 (20)	0.059
Lateral walls	130 (52.4)	68 (46.6)	35 (62.5)	23 (56)	4 (80)	
Anterior/dome /neck	39 (15.7)	20 (13.7)	10 (17.9)	9 (22)	0	
Tumor number, *n* (%)						0.94
Single	178 (71.8)	106 (72.6)	40 (71.4)	29 (70.7)	3 (60)	
Multiple	70 (28.2)	40 (27.4)	16 (28.6)	12 (29.3)	2 (40)	
Technique of resection, *n* (%)						
cTURBT	108 (43.5)	64 (43.8)	26 (46.4)	16 (39)	2 (40)	0.91
EBRT	140 (56.5)	82 (56.2)	30 (53.6)	25 (61)	3 (60)	
Surgeon, *n* (%)						
Urologist	134 (54)	84 (57.5)	26 (46.4)	22 (53.7)	2 (40)	0.49
Resident	114 (46)	62 (42.5)	30 (53.6)	19 (46.3)	3 (60)	
Obturator nerve reflex, *n* (%)						
Absent	226 (91.1)	138 (94.5)	49 (87.5)	35 (85.4)	3 (60)	0.017
Present	22 (8.9)	8 (5.5)	7 (12.5)	6 (14.6)	2 (40)	
No. of planned postoperative CT instillations, *n* (%)						
Yes	112 (45.2)	71 (48.6)	25 (44.6)	13 (31.7)	3 (60)	0.25
No	136 (54.8)	75 (51.4)	31 (55.4)	28 (68.3)	2 (40)	
No. of postoperative CT instillations performed, *n* (%)						
Yes	102 (91.1)	71 (97.3)	24 (92.3)	7 (70)	0	
No	10 (8.9)	2 (2.7)	2 (7.7)	3 (30)	3 (100)	< 0.001

IQR Interquartile Range, *cTURBT* Conventional TransUrethral Resection of Bladder Tumor, *ERBT* En bloc Resection of Bladder Tumor, *CT* chemotherapy, *CD* Clavien–Dindo

Table 2 Linear regression analysis: preoperative and intraoperative predictors of high-grade perforation according to the DEEP scale (2–3)

	Univariate analysis		Multivariate analysis	
	B coeff. (95% CI)	*P*	*B* coeff. (95% CI)	*P*
Age	0.002 (− 0.007 to 0.012)	0.609	0.005 (− 0.005 to 0.014)	0.322
Gender				
Male	Ref		Ref	
Female	0.242 (− 0.019 to 0.504)	0.069	0.255 (0.001–0.513)	0.050
History of BC				
Yes	Ref		Ref	
No	0.143 (− 0.070 to 0.355)	0.187	0.103 (− 0.107–0.313)	0.336
Tumor diameter				
< 1 cm	Ref		–	–
> 1 cm	0.050 (− 0.155–0.255)	0.633		
Tumor location				
Trigone/posterior	Ref		Ref	
Lateral walls	0.185 (0.032–0.339)	0.018	0.188 (0.026–0.339)	0.015
Anterior/dome/neck				
Tumor number				
Single	Ref		–	–
Multiple	0.056 (− 0.175–0.287)	0.634		
Technique of resection				
cTURBT	Ref		–	–
ERBT	0.043 (− 0.167 to 0.253)	0.686		
Obturator nerve reflex				
Absent	Ref		Ref	
Present	0.518 (0.165–0.871)	0.004	0.503 (0.148–0.857)	0.006
Surgeon				
Urologist	Ref		–	–
Resident	0.108 (− 0.100 to 0.317)	0.308		

BC Bladder cancer, *cTURBT* conventional transurethral resection of bladder tumor, *ERBT* En bloc resection of bladder tumor

[OR = 9.387 (2.434–36.20); $p = 0.001$] and female gender [OR = 6.727 (1.029–44.001); $p = 0.047$] were associated with no post-operative intravesical instillation in MVA adjusted for age, technique, and surgeon experience. DEEP scale [*B*. coeff 0.299 (0.166–0.441); $p < 0.001$] and age [*B*. coeff 0.019 (0.008–0.029); $p = 0.001$] independently predicted length of irrigation in MVA adjusted for surgical duration. DEEP scale [*B*. coeff 0.315 (0.111–0.519); $p = 0.003$], duration of surgery [*B*. coeff 0.013 (0.001–0.024); $p = 0.036$], and age [*B*. coeff 0.035 (0.020–0.050); $p < 0.001$] were independent predictors for hospital stay in MVA adjusted for history of BC and tumor size. The length of catheterization was not associated DEEP scale ($p = 0.11$).

Discussion

In this prospective study, we developed a novel classification of bladder perforation during TURBT, reporting the predictors of DEEP perforation and the implication of this classification in the postoperative course. The rate of extraperitoneal (grade 2) and intraperitoneal (grade 3) perforations were 16.5% and 2.0%, respectively. These findings are in line with previous published data from our Institution where extraperitoneal perforation represented up to 83% of all BP. However, the perforation rate was lower than in the current study (1.3% vs 18.5%)[10]. This result may be influenced by several factors. It is acknowledged that the intraoperative complications are underreported due to lack of proper definition and, possibly, to a certain fear of consequential lawsuit [8]. The prospective fashion of this study increases the completeness of data recording in comparison to retrospective reports. Finally, the primary endpoint of this randomized-controlled trial was the presence of detrusor muscle, which may have led the surgeons to provide a muscle sampling higher than in routinary practice. The location of the bladder tumor was independent predictor of BP, as for the obturator nerve reflex. These results are expected, since it is technically easier to perform a trigone/posterior bladder wall resection and the obturator nerve reflex determines a leg

Table 3 Chi-Square/ANOVA analysis and univariate logistic/linear regression analysis of the association between the DEEP scale and post-operative variables

	Perforation grade					Univariate analysis	
	0 (*n* = 146)	1 (*n* = 56)	2 (*n* = 41)	3 (*n* = 5)	*P*	OR or B coeff. (95% CI)	*P*
Detrusor muscle, *n* (%)							
Presence	136 (93.2)	53 (94.6)	40 (97.6)	5 (100)	0.683	Ref	0.238
Absence	10 (6.8)	3 (5.4)	1 (2.4)	0 (0)		0.611 (0.270–1.384)	
Tx, *n* (%)							
Yes	6 (4.1)	3 (5.4)	0 (0)	0 (0)	0.511	Ref	
No	140 (95.9)	53 (94.6)	41 (100)	5 (100)		1.720 (0.605–4.891)	0.309
Artifacts, *n* (%)							
Yes	131 (89.7)	53 (94.6)	40 (97.6)	5 (100)	0.281	Ref	
No	15 (10.3)	3 (5.4)	1 (2.4)	0 (0)		0.931 (0.296–2.928)	0.902
Mitomycin administration, *n* (%)							
Yes	71 (97.3)	24 (92.3)	7 (70)	0 (0)	< 0.001	Ref	
No	2 (2.7)	2 (7.7)	3 (30)	3 (100)		5.579 (2.359–13.191)	< 0.001
Complications (any grade), *n* (%)							
Yes	115 (78.8)	11 (19.6)	9 (22)	4 (20)	0.019	Ref	
No	31 (21.2)	45 (80.4)	32 (78)	1 (80)		1.258 (0.889–1.779)	0.105
Complications (CD > 2), *n* (%)							
Yes	4 (2.7)	1 (1.8)	2 (4.9)	3 (40)	< 0.001	Ref	
No	142 (97.3)	55 (98.2)	39 (95.1)	2 (60)		2.105 (1.054–4.203)	0.035
Hemoglobin drop, g/L	8.1 (11.5)	9.6 (9.2)	10.1 (9.9)	3.5 (8.0)	0.513	0.580 (− 1.192–2.351)	0.520
Median (IQR) length of irrigation, days	0.5 (0.5–1)	1 (0.5–1)	1 (0.5–1)	1 (0.5–2)	< 0.001	0.316 (0.173–0.459)	< 0.001
Median (IQR) length of catheterization, days	2 (1–2)	2 (1–2)	2 (2–4)	5 (5–7)	0.017	0.350 (− 0.002–0.703)	0.051
Median (IQR) length of stay, days	2 (1–2)	2 (1–3)	2 (2–3)	2 (2–5)	0.002	0.385 (0.171–0.597)	< 0.001

CD Clavien–Dindo

adduction that may result in uncontrolled bladder resections. The female gender was an independent predictor of bladder perforation. This may reflect the bladder wall thickness of female patients, which is usually thinner than the male bladder wall due to the absence of bladder outlet obstruction.

The use of DEEP scale may be beneficial as high-grade perforations have proven to impact the clinical and surgical outcomes. In particular, the administration of immediate intravesical chemotherapy depended on the grade of DEEP. This is a crucial point, since it has been demonstrated that in low-risk bladder cancers, the postoperative instillation of chemotherapeutic agents decreases bladder cancer recurrence. Comploj et al. reported that the BP influences the natural history of superficial bladder cancer, resulting in a higher rate of bladder recurrence with no impact on overall and cancer-specific survival [11]. The authors postulated that the recurrence could depend on two factors: tumor seeding or implantation and inadequate initial tumor resection due to BP [11]. It should also be acknowledged the risk of intraperitoneal seeding, which occurrence may be considered anecdotical [12–14].

Furthermore, the rate of major postoperative complication, the irrigation time and the hospital stay were related to DEEP. Thus, the systematic use of DEEP scale might help to direct the postoperative management of the patients, adapting the postoperative strategies to the depth of endoscopic perforation.

The study is not devoid of limitations. First, we could not separate the patients treated with en-bloc and conventional TURBT due to paucity of high-grade perforations. However, the DEEP scale was designed to report the depth of endoscopic perforation independently from the type of resection or the energy source used. Therefore, the use of this classification should apply to any kind of TURBT. Second, as our study was not designed a priori to assess the reproducibility of the scale, future studies are warranted to assess inter- and intra-observer agreement. Third, this a result of a single-center randomized trial. The DEEP scale should be externally validated before clinical implementation. However, the present study demonstrated that this classification provides a standardized tool to classify the most important intraoperative complication of TURBT, that affects the clinical postoperative course. Its use could be implemented in daily practice.

Conclusion

Female gender, tumor located in anterior wall/neck or dome, and obturator nerve reflex are independent predictors of intra/extraperitoneal perforation. The DEEP scale is an independent predictor of postoperative clinical course, such as post-operative intravesical instillation, the risk of major complication, the irrigation time and hospital stay. This scale provides a standardized tool to classify the most important intraoperative complication of TURBT, that affects clinical postoperative course.

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Author contributions AB: protocol/project development, manuscript editing. AG: protocol/project development, data analysis, manuscript writing. PD: data collection, data analysis, manuscript writing. MF: data collection. AT: data collection, data analysis, manuscript editing. JG: data collection, data analysis. ÓR-F: data collection, data analysis. JH: data collection. AP: data collection. PV: data collection, manuscript editing. MB: manuscript editing. JA: data collection, manuscript writing. FA: data collection, data analysis. JP: project development.

Declarations

Conflict of interest The authors report no conflict of interest.

Research involving human participants and/or animals This study respected the principles of the Declaration of Helsinki and was approved by the Institutional Review Board (2017/09c).

Informed consent All participants were adequately informed and provided a written consent.

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