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**En-bloc versus conventional
transurethral resection
of bladder tumors:
results from a single center
randomized controlled trial**

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Abstract

Background

Transurethral resection of bladder tumor (TURBT) represents a crucial step in the clinical care pathway of non-muscle-invasive bladder cancer. Despite its critical role, conventional TURBT (cTURBT) may lead to suboptimal pathological characterization, unreliable staging of the disease, incomplete tumor resection and increased local recurrence risk due to the limitations of the surgical technique.

En-bloc resection of bladder tumor (ERBT) was introduced with several supposed advantages over cTURBT, including a reduced risk of tumor cell scattering, a more precise and controlled resection, a better detrusor muscle sampling and the retrieval of a more informative pathological specimen.

In the last decades many studies suggested some advantages of ERBT over cTURBT, but a metaanalysis failed to demonstrate a substantial advantage and underscored the need for high-quality evidence to define the role of ERBT.

Materials and Methods

We designed a prospective randomized controlled trial comparing cTURBT to ERBT using different energy sources (monopolar, bipolar, thulium laser). We enrolled patients with a diagnosis or suspicion of bladder cancer, with a maximum of three 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, while secondary endpoints included various surgical, pathological and oncological outcomes, including T1 substaging feasibility.

Results

A total of 300 consecutive patients met the inclusion criteria and were enrolled in the study between April 2018 and June 2021. The two groups did not differ both in term of intra-operative and post-operative outcomes. We reported similar median operative time, with comparable irrigation and catheterization time. ERBT was converted to cTURBT in 6 cases (4.3%).

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 ($p=0.5$). Bladder wall perforation and obturator nerve stimulation rates did not differ between the two groups, with comparable rates of adjuvant intravesical treatment administration.

Similar rates of detrusor muscle presence (92.8% vs 93.2%, $p=0.9$) were found in the ERBT and cTURBT groups, but T1 substaging feasibility rate was significantly superior for ERBT (100% vs 84.2%, $p=0.02$). 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.

Conclusions

In a high-volume center, ERBT showed comparable rates of detrusor muscle sampling in comparison with cTURBT, while it provided an advantage in terms of T1 substaging feasibility. Our study confirmed the safety and feasibility of ERBT, with similar surgical and short-term oncological outcomes.

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Introduction to 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.

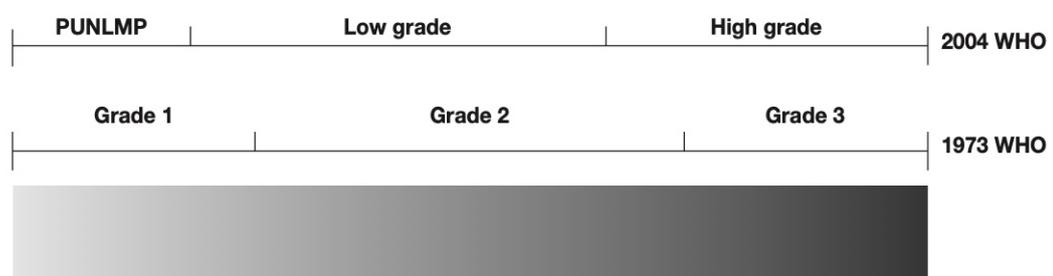


Fig. 1 - BC grading according to the WHO 1973 and 2004/2016 classifications.

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 <i>in situ</i> : '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 haematuria 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 standardised 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 cystoscopic 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 *Lichtleiter* (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].

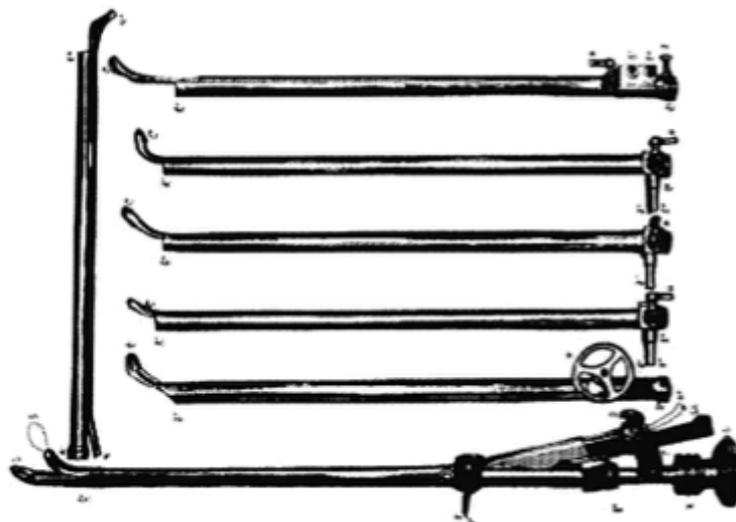


Fig. 3 - Operating cystoscope, developed by M. Nitze in 1891–1894.

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 growths behave 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 of 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].

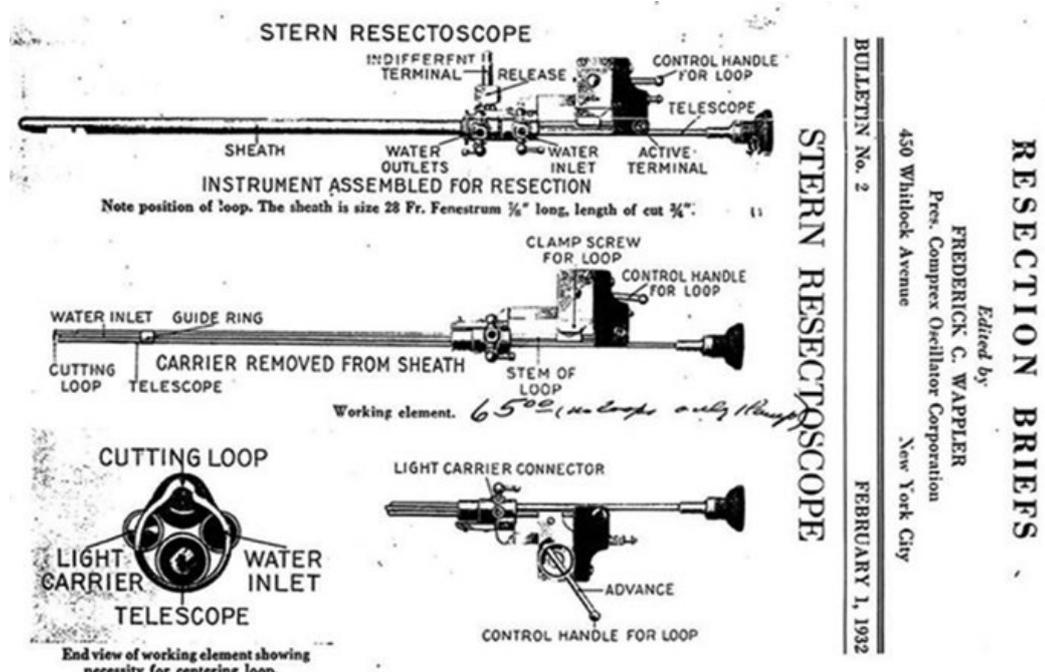


Fig. 4 - The first resectoscope, developed by Maximilian Stern, 1926

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 dual-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.

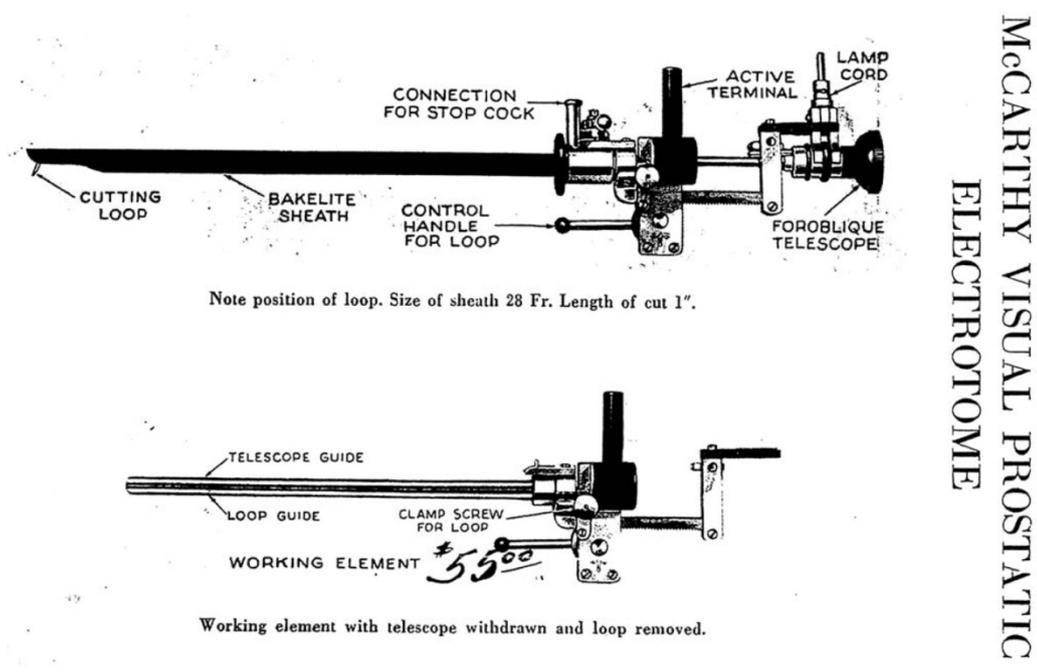


Fig. 5 - The Stern-McCarthy resectoscope, 1931

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 modification 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 areas within the reach of the resectoscope itself. Furthermore, he shortened the opening in the sheath for the cutting element, in order 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 configuration 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 has to 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.

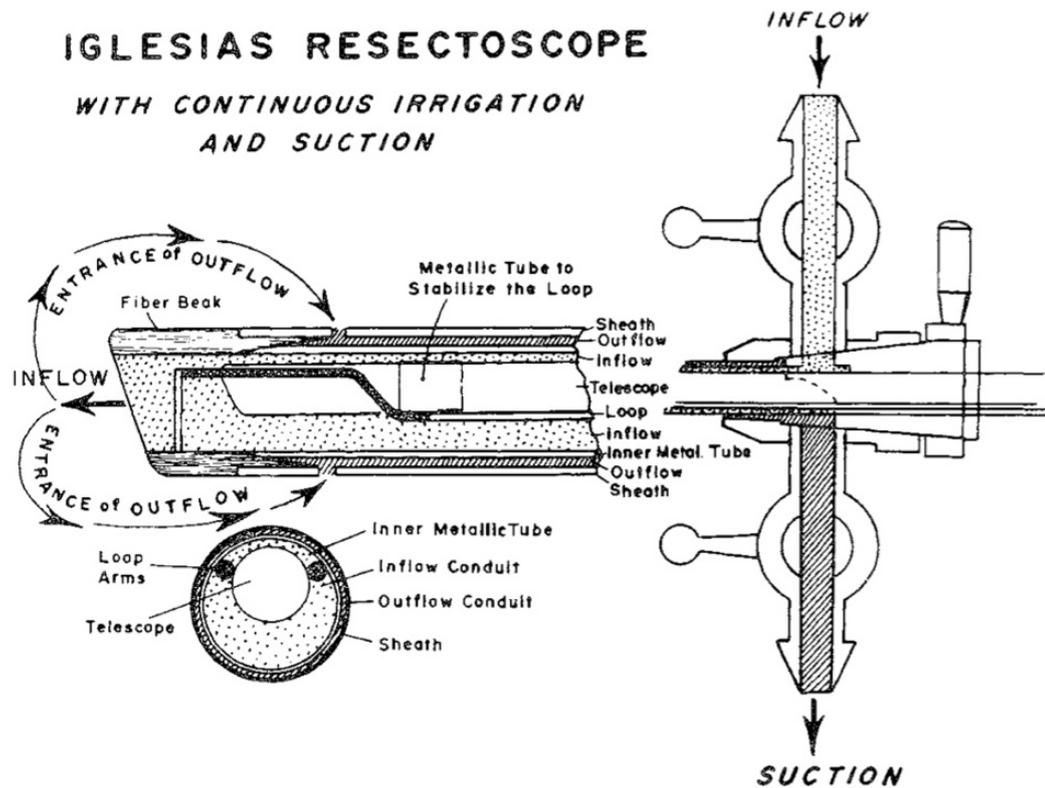


FIG. 1

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 a 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 meta-analysis 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

Pedunculated 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].

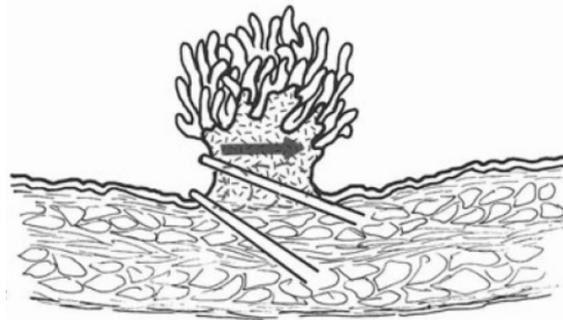


Fig. 7 - Stalk resection. W. Mauermayer, 1983.

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 of 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].

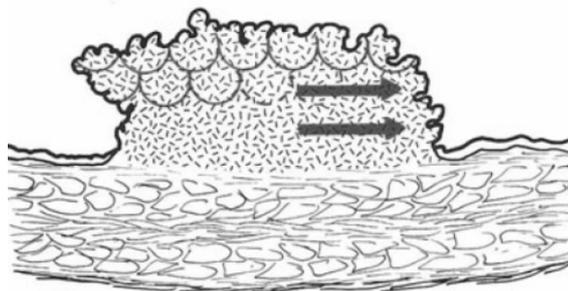


Fig. 8 - Parallel resection. W. Mauermayer, 1983.

Vertical resection

Vertical resection consists in resecting progressively deeper layers of a segment of a voluminous bladder mass, in order 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].

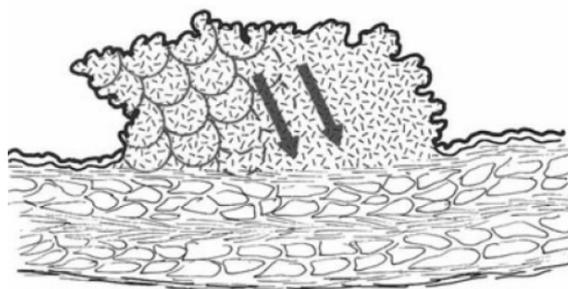


Fig. 9 - Vertical resection. W. Mauermayer, 1983.

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 anecdotal.

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, in order 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 receive 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 *muscularis 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.

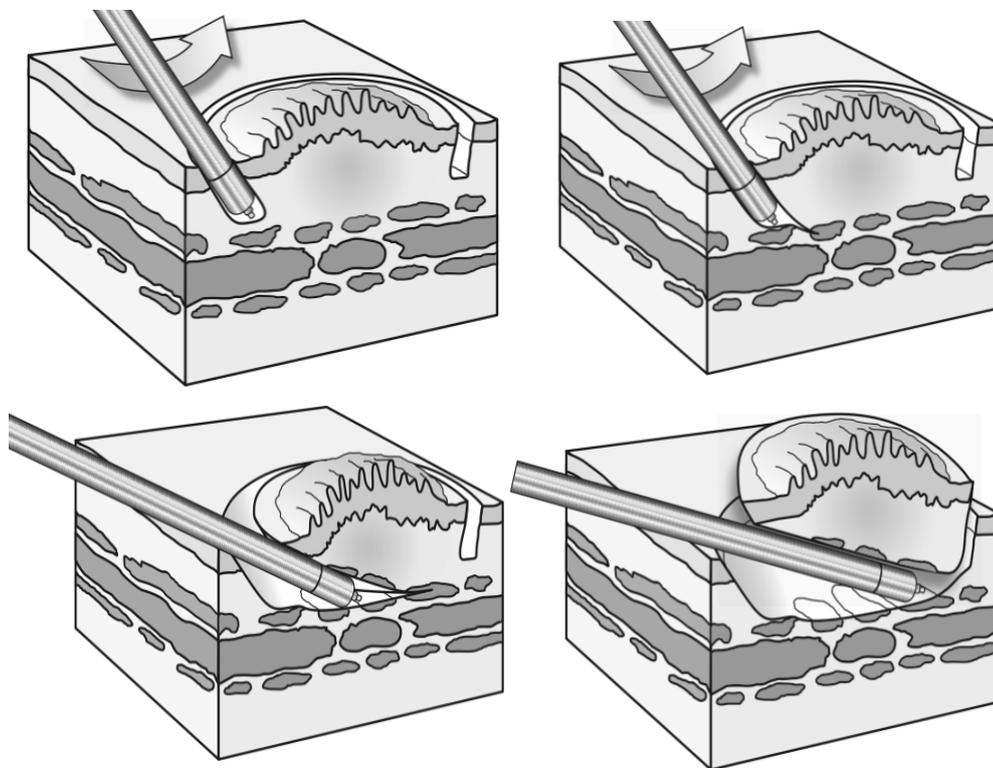


Fig. 10 - The en-bloc resection concept. Kramer, 2014

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 hydrodissection. A clear advantage of one energy source over the others has not been demonstrated, 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 hydrodissection, it implies a higher risk of residual disease and understaging due to its nature [78].

Outcomes

A recent systematic review and meta-analysis 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, $I^2 = 86%$, $p = 0.002$; very low certainty evidence), and a shorter irrigation time than TURBT (mean difference -7.24 h, 95% CI -9.29 to -5.20 , $I^2 = 85%$, $p < 0.001$; 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 , $I^2 = 97%$, $p = 0.06$; 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, $I^2 = 79%$, $p = 0.08$; 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 an 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.

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 considered as a surrogate criterion of the resection quality and is required in all resection specimens except in Ta G1/LG tumors [18], it can be absent in a noteworthy proportion of the cTURBT specimens [79].

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 80s [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 ERBT over cTURBT [76]. Recently, an International Collaborative Consensus Statement on ERBT including a meta-analysis 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 metaanalysis 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

Study 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 [80]. 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 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% [79] and 97% of the cases [81]. 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.

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.

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 $p=0.05$.

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. 11*). 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 underwent ERBT because of surgeon's preference.

Population characteristics are summarized in Table 1. The two population did not differ in a statistically significant way in all the analyzed variables.

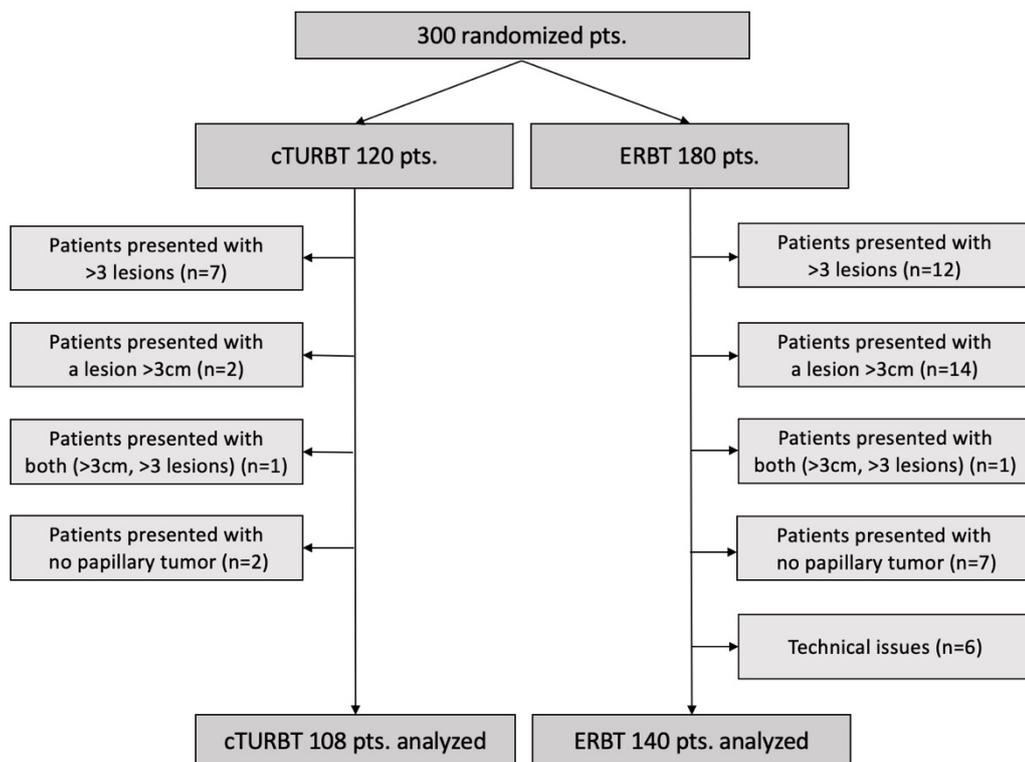


Fig. 11 - Patients flowchart

Tab. 1 - 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 (%)				
Yes	32 (12.9)	12 (11.1)	20 (14.3)	0.460
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)	0.859
Negative	193 (77.8)	84 (77.8)	109 (77.8)	
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 2.

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. 2 - 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)	0.905
Grade 1	56 (22.6)	26 (24.1)	30 (21.4)	
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)	0.715
Clavien 1	13 (5.2)	7 (6.5)	6 (4.3)	
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. 3 - 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)	

Oncological 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.

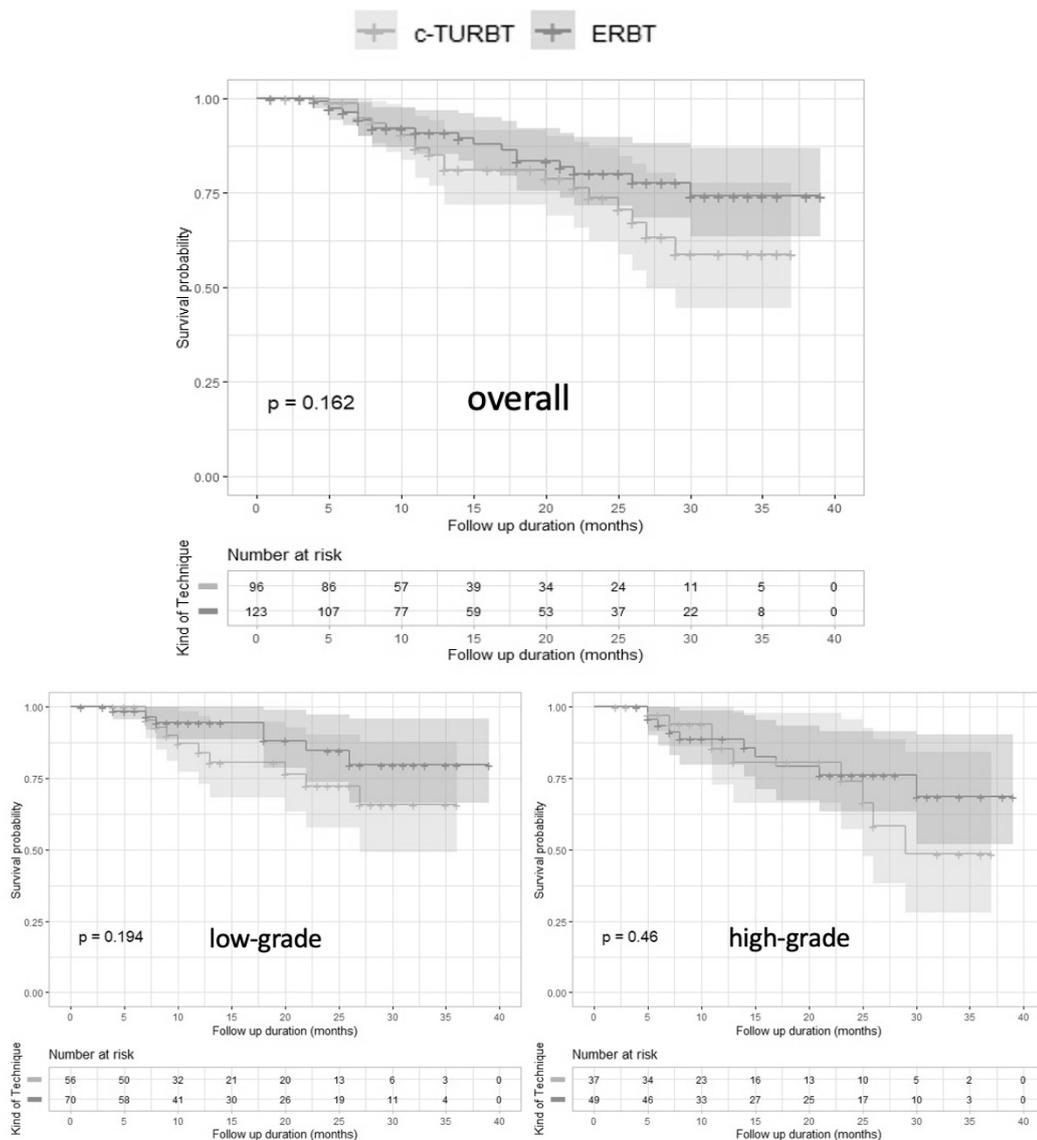


Fig. 12 - Kaplan-Meier estimates for RFS

Discussion

This randomized controlled study directly compares cTURBT and ERBT, providing us with high level of evidence results to help clarify the role of ERBT in the management of NMIBC. We showed that the two approaches are comparable in term of surgical, pathological and early oncological outcomes, but that ERBT is superior to cTURBT regarding T1 substaging feasibility.

The rate of detrusor muscle sampling in the pathological specimen was similar and very high in the two groups, being 96.1% in ERBT and 93.5% in cTURBT ($p=0.836$). Our findings agree with the metanalysis from Teoh et al. [67], suggesting that ERBT has no real advantage over cTURBT regarding detrusor sampling. However, when discussing this result, we have to consider that the reported range of detrusor muscle presence in the resected specimens of cTURBT may vary very widely according to the expertise of centers and operators [79], while it appears to be more consistent in the ERBT arms, as showed in some RCTs (62-93.7% for cTURBT vs 87.9-98% for ERBT). According to this finding, we may affirm that even though ERBT is not superior to cTURBT in detrusor sampling in experienced hand, it may be more reliable in a real-world settings in which the detrusor muscle may be missed more frequently with cTURBT [79].

Moreover, we demonstrated an higher T1 substaging feasibility rate in the ERBT group in both the per-patient and per-lesion analysis, suggesting that, even though we reported a similar rate of coagulation artifacts in both arms, ERBT may provide more high-quality, informative specimens, especially when it comes to a technically difficult evaluation such as the T1 substaging, in which the quality of the resected specimen is of utmost importance [27, 28].

Our work confirms that ERBT is a surgical approach that is feasible for the treatment of up to three tumors with dimensions smaller than three centimeters, located anywhere in the bladder [67]. We reported six cases (4.3%) of conversion to cTURBT because of an inability to safely or completely resect the tumor with the *en-bloc* approach, with additional four cases that were randomized to the ERBT group and did not undergo the allocated treatment because the surgeon judged the technique unsuitable for the clinical case. Moreover, we reported that the ERBT specimen could be extracted inside the resectoscope sheath in over 90% of the cases, showing that surgical specimens can be safely extracted in the majority of cases, with the exception of large, bulky tumors with a predominantly solid component. As such, we believe that ERBT is not a universally feasible technique that can be employed in every patient, but our data suggest that in most cases its feasibility is not limited by factors related to the disease such as tumor location or architecture.

The currently available literature shows that cTURBT is characterized by a shorter operative time in comparison with ERBT [82, 83, 84, 85, 86, 87], with a mean difference of around ten minutes [67]. In contrast with this evidence, our data demonstrated that, in the hands of experienced surgeons, the employment of an ERBT technique did not mean a longer operative time. Even though ERBT is generally considered a more technically challenging technique, it allows the surgeon to avoid repeated cutting in the exophytic part of the tumor and to directly remove the tumor with its endophytic part, and our findings demonstrate that this approach ultimately compensates for the time spent planning the resection and carefully dissecting around the tumor base. Even though some

studies reported a shorter irrigation time for EBRT [83, 86], we recorded a similar irrigation time for both technique of around twelve hours. We confirmed the available evidence recording comparable catheterization time and hospital length of stay for the two groups [67].

Our results confirm that ERBT has a safety profile that is comparable to that of cTURBT, with no difference in the rates of Clavien I-III complications. Moreover, the use of the ERBT approach did not have any impact on the rate of administration of adjuvant one-shot intravesical chemotherapy. Most RCT reported an advantage in the rate of bladder perforation in favor of ERBT [86, 87, 88], but in these studies ERBT was performed with a laser energy, so that this advantage may be due to the use of lasers and not to a technical advantage. Our findings agree with the work of Gakis et al. [84] and seem to support this thesis, not recording any meaningful difference between ERBT and cTURBT, with similar obturator reflex stimulation rates in the two groups and no reported events in the ERBT-tl subgroup. As previously reported, the employment of laser energies has the advantage of completely avoiding this risk, and its use should be considered for the treatment of tumors located on the bladder lateral walls [83, 86, 87].

Finally, our early oncological outcomes described similar three-months and overall recurrence rates between the ERBT and cTURBT groups, in agreement with the evidence from current literature [67]. Even though these data are still immature to draw some conclusion, the comparable three-month recurrence rate suggests a similar efficacy in tumor eradication and control for the two different techniques.

To the best of our knowledge, this is the largest randomized trial ever performed on EBRT and the first including a wide variety of energy sources that were employed for both approaches (monopolar current, bipolar current and thulium laser energy). Even though this may be interpreted as a confounding factor, we believe that it may help us understand the outcomes of the surgical technique irrespective of the chosen energy used to dissect the tumor.

Conclusions

In a high-volume center, ERBT demonstrated comparable outcomes in terms of detrusor muscle sampling in comparison with cTURBT, while it provided an advantage in terms of T1 substaging feasibility. Our study confirmed the safety and feasibility of ERBT, with similar surgical and short-term oncological outcomes.

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Abbreviations

BC	Bladder cancer
CI	Confidence interval
CIS	Carcinoma <i>in situ</i>
CT	Computed tomography
cTURBT	Conventional TURBT
cTURBT-b	cTURBT - bipolar energy
cTURBT-m	cTURBT - monopolar energy
EAU	European Association of Urology
ERBT	<i>En-bloc</i> 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

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