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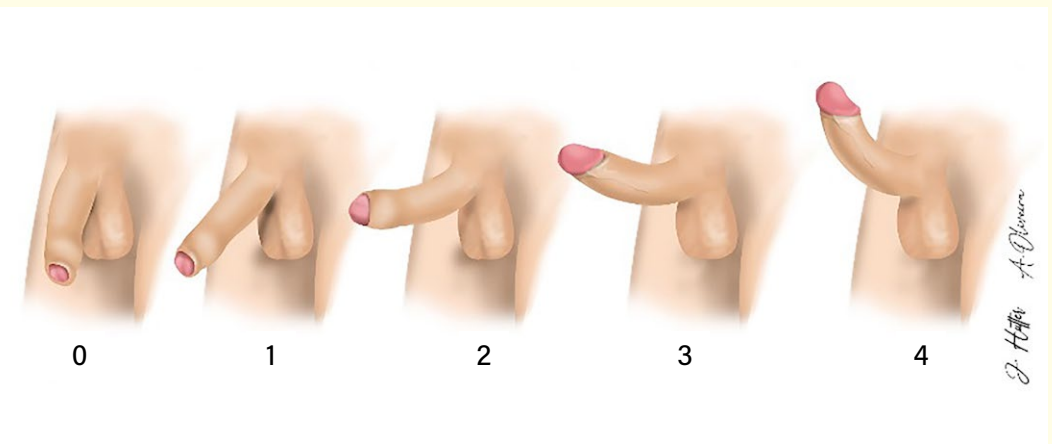

The figure shows the Visual Erection Hardness Score (V-EHS). This score is derived from the original Erection Hardness Score (5) but some modifications are incorporated: 1) The patient does not subjectively score; 2) It presents a new image, facilitating the perception and differentiation between the stages; 3) The scale itself, as we see above, is differentiated according to the axial resistance that the penis supports, which is functionally and directly related to the penetrative capacity and 4) It allows standardizing the erection test and the time of the re-dose (which should be done if a consistently hard erection (>3) is not obtained). In the figure we can observe: 0: Penis does not enlarge; 1: Penis is larger but not hard; 2: The penis is hard, but not hard enough to resist an axial force - it bends under a manual pulling force = not consistently hard erection; 3: Penis is hard, not completely hard, but resists an axial force - does not bends under a manual pulling force = consistently hard erection; 4: Penis is completely hard and fully rigid. (*e20249927*)

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EDITORIAL
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Vol. 51 (2): e20250201, March - April, 2025
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The New Visual Erection Hardness Score is the Topic Highligheted in this Issue of International Brazilian Journal of Urology

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The March-April 2024 number of Int Braz J Urol is the thirty-thirdunder my supervision. In this number the Int Braz J Urol presents original contributions with a lot of interesting papers in different fields: Bladder Cancer, Bladder dysfunction in Children, Renal cell Carcinoma, Intra-renal surgery, Cistoscopy, Prostate Biopsy, Gender affirming surgery, urogenital tuberculosis and erectile dysfuncion. The papers came from many different countries such as Brazil, USA, Italy, Turkey, Egypt, Serbia and China, and as usual the editor´s comment highlights some of them. The editor in chief would like to highlight some papers in this number, specially the papers about the new visual erection hardness score:

Dr. Figueiredo and collegues from Brazil, presented in e20240590 (1) a nice review about urogenital tuberculosis (UGT) and concluded that the diagnosis of UGT depends on a high degree of suspicion based on non-specific symptoms and radiological findings. Urinary bacteriological tests have low sensitivity, but even in the absence of diagnostic confirmation, treatment can be carried out through a combination of drugs for a period of six months. In the presence of ureteral stenosis or contracted bladder, complex but well stablished reconstruction procedures are necessary.

Dr. Lopes and collegues from Brazil performed in e20240490 (2) a nice systematic review about pelvic lymph node dissection before versus after radical cystectomy and concluded that the timing of the lymphadenectomy was not associated with a significant reduction in total operative time, pelvic lymph node dissection (PLND) time, number of LN dissected, and estimated blood loss.

Dr. Alam from the group of Dr. Arthur Burnett from USA, presented in e20240332 (3) presented a important study about important systematic review about the penile prosthesis (PP) placement with concomitant non-reconstructive urologic procedures and concluded that patients undergoing PP implantation with a concomitant non- reconstructive urologic procedure, had no increased risk of complications or device infections when compared to patients undergoing first-time PP placement only. While further investigation is needed, our findings challenge the traditional dogma that secondary urologic procedures should be avoided at the time of PP implantation.

Dr. Mansour and collegues from Egypt and USA showing in e20244425 (4) a nice, randomized trial about the efficacy and safety of mirabegron compared to solifenacin in treatment of non-neurogenic overactive bladder in children and concluded that Mirabegron is more effective with fewer treatment-related adverse effects compared to solifenacin in children with OAB refractory to behavioral therapy and other anticholinergic medications. Mirabegron treatment improves

daytime symptoms and nocturnal enuresis with less risk of constipation. It may be considered as a first-line pharmacotherapy for select patients with non-neurogenic OAB.

The group of Dr. Ho from Serbia and USA performed in e20240427 (5) an interesting study about testicular implant complications after Transmasculine Gender Affirming Surgery and concluded that complications after testicular implants in transgender men are not uncommon events. The present paper suggests that implant size is not a significant predictor of complications requiring prosthetic removal.

Dr. Carbonara and collegues from Italy and USA performed in e20240565 (6) a nice study about Percutaneous cryotherapy (CRYO) and radiofrequency ablation (RFA) of renal masses: multicenter comparative analysis with minimum 3-year follow-up and concluded that CRYO and RFA are both valid minimally invasive options for the treatment of small renal tumors. They are particularly suitable for patients who are not good surgical candidate as they offer very low risk of major procedure-related complications. For the right indication, they both offer favorable mid to long term oncologic outcomes.

Dr. Zhou and collegues from China performed in e20240630 (7) a very nice study about Biplanar or Monoplanar Prostate Biopsy: Should Transrectal and Transperineal Approaches Be Combined for Prostate Cancer Detection ? and concluded that biplanar stereotactic biopsy was superior to monoplanar biopsy in detecting anterior csPCa. Both methods demonstrated no significant differences in overall PCa detection rates and safety.

Dr. Westin and Collegues from Urogenital Research Unit – Brazil performed in e20249923 (8) an interesting study about bladder mucosa harvested with holmium laser for treatment of urethral strictures: does the graft have its tissue integrity preserved? and concluded that the graft harvested from the bladder uroepithelium using Ho-YAG has its histological integrity preserved, which makes this technique a viable option for reconstructive surgery. However, more studies are needed to establish its long- term efficacy and safety of this new technique.

Dr. Schuh and collegues performed in e20249927 (9) the cover paper of this edition: a nice study about shock wave therapy (LI-ESWT) in the treatment of erection dysfunction: how to define clinical outcomes? a comparison between penile doppler ultrasound and a new visual erection hardness score (v-ehs) during a blinded, sham-controlled trial and concluded that LI-ESWT has proven effective in the treatment of moderate vasculogenic erectile dysfunction, with optimal results at 6 months. The new V-EHS offers a simple, reliable and reproducible assessment of erectile function.

The Editor-in-chief expects everyone to enjoy reading.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Urogenital Tuberculosis: A Narrative Review and recommendations for diagnosis and treatment

André Avarese Figueiredo [1], José Carlos Truzzi [2], Augusto Azevedo Barreto [1], Eduardo Carvalho Siqueira [3], Marcos Lucon [4], Marcos Broglio [5], Karin Marise Jaeger Anzolch [6], Antônio Peixoto de Lucena Cunha [7], Bruno Vilalva Mestrinho [8], Leandro Koifman [9], José de Bessa Júnior [10], Luciano Alves Favorito [11]

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ABSTRACT

Purpose: to review the more relevant aspects of urogenital tuberculosis (UGT) and make recommendations about the diagnosis and treatment.

Materials and Methods: a literature review was conducted in the Pubmed, Embase and Scielo databases in search of studies on UGT in the past 60 years. A narrative review was performed concerning six topics of UGT diagnosis and treatment. Recommendations were made supported on degrees of evidence according to the modified GRADE system.

Results: UGT suspicion occurs in persistent hematuria or pollakiuria with sterile pyuria; stenosis and/or thickening of the urinary tract; or chronic prostatitis or epididymitis. Urinary bacteriological tests have low sensitivity, and a negative test does not rule out UGT diagnosis. In ureteral stenosis, a double-J catheter or nephrostomy should be used early (up to 1 month) during pharmacological treatment and in single less than 2 cm stenosis endoscopic treatment may be attempted. Bladder augmentation with ileum, sigmoid or ileocecal segments should be performed when the contracted bladder capacity is less than 100 mL. Spontaneous voiding occurs in most patients after bladder augmentation.

Conclusion: The diagnosis of UGT depends on a high degree of suspicion based on non-specific symptoms and radiological findings. Urinary bacteriological tests have low sensitivity, but even in the absence of diagnostic confirmation, treatment can be carried out through a combination of drugs for a period of six months. In the presence of ureteral stenosis or contracted bladder, complex but well stablished reconstruction procedures are necessary.

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INTRODUCTION

Tuberculosis is a transmissible disease that ranks among the top 10 leading causes of death worldwide and, with the exception of coronavirus disease 2019 (COVID-19), is the leading cause of death due to a single infectious agent. Brazil was one of 30 countries comprising 87% of new tuberculosis cases in 2022 (1). Extrapulmonary forms of tuberculosis account for 16% of tuberculosis cases (2), with urogenital tuberculosis (UGT) being the second most common presentation in some regions, ranking behind only the lymphatic disease type (3). UGT, like all forms of extrapulmonary tuberculosis, has common features, such as nontransmissibility and difficulty in diagnosis, owing to the nonspecificity of symptoms, the elimination of few bacilli in urine and difficult access for biopsy of the affected organs.

UGT can affect all urogenital organs and always occurs secondary to the hematogenous spread of pulmonary tuberculosis. Initially, the bacillus colonizes the kidney parenchymal region bilaterally; this step is followed by the development of granulomas in the region near the kidney glomeruli, in the loop of Henle, in the medullary region, close to the renal papilla. The initial lesions are bilateral and consist of granulomas without caseous necrosis or nodule formation and, therefore, without kidney radiological changes (4). These granulomas may remain latent throughout life; however, the disease may be reactivated mainly in medullary granulomas due to less vascularization and a greater chance of ischemia in this kidney area. Moreover, caseous necrosis, ulceration and erosion of the renal papillae to the urinary tract may occur, accompanied by bacilluria and descending dissemination of the infection. Thus, changes in the renal papilla characterize the initial radiological signs of renal tuberculosis (5). The disease spreads to the urinary system with the development of granulomas in the renal pelvis and ureter, causing thickening and obstruction, eventually reaching the bladder (6). The two narrowest sites of the urinary tract are the most commonly affected in the urinary system: the pyeloureteral junction and the ureterovesical junction (5).

The sequential evolution of urinary tuberculosis, from this reactivation of tuberculosis in the kidney to severe forms of the disease, has been well established in publications since the early 21th century (7 ,8). An in-depth analysis of UGT case series revealed that the evolution of urinary tuberculosis follows a constant and progressive pattern: reactivation of tuberculosis occurs in one kidney (primary kidney), with the onset of clinically and radiologically detectable unilateral renal tuberculosis. As tuberculosis progresses through the urinary tract, the renal pelvis, ipsilateral ureter and bladder become involved. Most commonly, there is stenosis of the urinary tract with the possibility of loss of renal function due to obstruction, and the bladder may gradually contract; such contraction manifests as a low capacity and compliance bladder and causes vesicoureteral reflux to the contralateral kidney, which is secondarily affected. Thus, the primary kidney loses function because of the urinary tract obstruction caused by tuberculosis, and the secondary kidney may lose function owing to vesicoureteral reflux.

Male genital tuberculosis in some cases may be associated with renal tuberculosis. The prostate, according to autopsy studies (9), is the first organ of the male genital tract to be affected by hematogenous or urinary dissemination. Through the canalicular route, there is secondary involvement of the seminal vesicles, vas deferens and epididymis. In genital tuberculosis, the prostate is the most affected organ, but in most cases, prostate tuberculosis is asymptomatic. In contrast, epididymitis is the most frequent clinical manifestation, and tuberculosis of the epididymis can also occur alone via direct hematogenous dissemination (3). Male genital tuberculosis can manifest as six clinical syndromes: asymptomatic (simulating prostate cancer with PSA elevation and prostatic nodules); prostatic obstruction; chronic prostatitis; recurrent acute prostatitis; and prostatic abscess and chronic epididymitis, which may be unilateral or bilateral, with or without a cutaneous fistula (10).

Despite being a disease well known by urologists, UGT is still characterized by nonspecific

symptoms, a lack of physician familiarity with its more specific clinical and radiological presentations, a low sensitivity of bacteriological tests and, consequently, a late diagnosis. Therefore, destruction of the urogenital tract may occur, with the appearance of renal exclusion, contracted bladder, renal failure and epididymal or prostate abscesses requiring complex reconstructive surgery.

In this review we will describe the more relevant aspects of urogenital tuberculosis and show some recommendations about the diagnosis and treatment of UGT.

MATERIAL AND METHODS

In this study we carried out a review about urogenital tuberculosis. We analyzed papers published in the past 60 years in the databases of Pubmed, Embase and Scielo, found by using the key expressions: "Tuberculosis"; "Urogenital Tuberculosis"; "Tuberculosis treatment"; "Tuberculosis surgery"; "Prostate tuberculosis"; "Kidney Tuberculosis" and "Radiology". In this review we found several papers in these databases, and included only papers in English, and excluded case reports, editorials and opinions of specialists. Six topics of UGT diagnosis and treatment were elaborated by the Consultation Group of the Division of Infections from the Brazilian Society of Urology. From these topics, recommendations were made based on the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) system, according to guidance from the Ministry of Health. In the GRADE system, the level of evidence is classified as high, moderate, low or very low, and the strength of the recommendation is classified as strong or weak (11). After the recommendation, the following information is given (GRADE: level of evidence, strength of recommendation).

RESULTS

1 - Clinical and radiological presentation.

Suspicion of UGT is based on the clinical/radiological situation at presentation. The three main symptoms of UGT are hematuria (35.6%), low back pain (34.4%) and pollakiuria (50.5%) (12). However, most patients present radiological kidney findings suggestive of UGT. In a review of almost 9,000 patients from 33 case series, in only 15% of the cases, there were no radiological changes in the kidneys (12). In another study evaluating the clinical/radiological presentation of 80 patients with UGT, it was observed that, in only 7.5% of the patients, no or minimal damage to the kidneys was observed, and in these patients, the only symptom present was hematuria. All the other patients presented with radiological changes (13). Male genital tuberculosis may be present without urinary tuberculosis and has specific clinical symptoms, mainly chronic prostate and epidydimal infections. Thus, the suspicion of a UGT should be based on three situations:

1. Clinical presentation: Persistent (more than three months) macroscopic hematuria or pollakiuria with sterile pyuria with no relevant findings in a urinary tract radiological investigation.
2. Radiological presentation: Regardless of the symptoms, the presence of the following radiological findings on computed tomography (CT) or magnetic resonance imaging (MRI) (14):

Stenosis and/or thickening of the urinary tract with corresponding hydronephrosis, usually unilateral (bilateral stenosis is extremely rare).

Stenosis may be intrarenal (infundibular), in the renal pelvis or ureter. Furthermore, the stenotic sites may be single or multiple, with hydronephrosis and corresponding total or partial loss of renal function. The evolution of the UGT may or may not be associated with a contracted bladder and contralateral hydronephrosis due to reflux.

3. Clinical presentation of the male genital tract:
   a. Chronic prostatitis (pelvic pain or dysuria for more than 3 months, associated with lower urinary tract symptoms [LUTS]. The symptoms may be persistent or intermittent.)

b. Chronic epididymitis (unilateral or bilateral pain and thickening of the epididymis for more than 3 months) with or without cutaneous fistulization.

Recommendations:

1. UTG should be suspected in the following situations:
2. Persistent (more than three months) macroscopic hematuria or pollakiuria with sterile pyuria (GRADE: moderate, strong)
3. Stenosis and/or thickening of the urinary tract with corresponding hydronephrosis, usually unilateral on CT or MRI (GRADE: moderate, strong)
4. Chronic prostatitis or chronic epididymitis (GRADE: moderate, strong)

2 - Bacteriological investigation through urine culture and nucleic acid amplification (NAA) tests.

When UGT is suspected, bacteriological investigations in the urine are performed by specific culture for *Mycobacterium tuberculosis* or by identification of DNA fragments via nucleic acid amplification (NAA) techniques. The most studied NAA technique is the commercially available Xpert MTB/RIF, which also identifies resistance to rifampicin. Urine culture is considered the gold standard for diagnosis, but it takes six to eight weeks to obtain results, whereas it takes 24 to 48 hours to obtain results with NAA techniques. Both methods have high specificity. However, there is great uncertainty regarding the sensitivity values (3), and the high prevalence of false negatives makes diagnosis difficult; this situation is responsible for delays in treatment initiation. In addition, low-sensitivity diagnostic tests are unfeasible as the gold standard; therefore, other diagnostic strategies are needed.

The precise determination of the sensitivity and specificity of urine culture and NAA techniques requires studies that evaluate these tests in comparison with broader diagnostic strategies, a composite reference standard, including four different criteria of UGT diagnosis: 1) positive urine culture; 2) histological diagnosis; 3) radiological diagnosis; and 4) positive response to pharmacological treatment. There are four studies in the literature in which urine culture and NAA techniques were evaluated in relation to at least three of the four diagnostic criteria (15–18). The data from this analysis are described in Table-1. The total sensitivity of the culture was 40.1%, ranging from 24.0% to 56.4%. The total sensitivity of Xpert (NAA test) was 60.7%, ranging from 41.3% to 88.0%. When the two tests were used together, the total sensitivity was 63.1%, which was slightly greater than that of Xpert alone. The specificity of culture was 100% in all the studies, as it was the gold standard diagnostic method, and that of Xpert was 99.4%.

In the 2021 Guideline, the World Health Organization recommended that in patients with signs and symptoms of extrapulmonary tuberculosis (including UGT), Xpert MTB/RIF should be the initial diagnostic test performed (19).

Recommendations:

1. The investigation of UGT in suspected cases should be performed initially and preferably with the Xpert MTB/RIF test in urine (GRADE: moderate, strong).
2. Urine culture for *Mycobacterium tuberculosis* must be performed in at least three samples on different days and must be performed together with the Xpert MTB test, since culture alone has a sensitivity of only 40%, and both tests have a sensitivity of 63% (GRADE: moderate, strong).
3. A diagnosis of active UGT is made on the basis of a positive urine culture or Xpert MTB result, as both tests have a specificity of almost 100% (GRADE: moderate, strong).
4. Negative results for culture or Xpert MTB in urine do not rule out the diagnosis of UGT, as these methods have low sensitivity. This situation implies that there is a need for other criteria for the diagnosis of UGT (GRADE: moderate, strong).

3 - Clinical, laboratory and radiological criteria for UGT diagnosis in negative bacteriological investigation cases.

Table 1 - The table shows the data description of four articles analyzed in this review (15-18) with analysis of the sensitivity and specificity of urine culture and GeneXpert MTB in relation to a composite reference standard.

Author	Pang, et al. (2017) (15)	Samuel, et al. (2018) (16)	Chen, et al. (2019) (17)	Liu, et al. (2021) (18)	Total
N	163	100	302	112	677
TB cases	81	55	150	83	369
No TB cases	82	45	152	29	308
Culture medium	LJ	MGIT 960	MGIT 960	LJ + MGIT 960	
CRS					
Bacteriological	X	X	X	X	
Histology	X	X	X	X	
Radiological		X	X	X	
Pharmacological response	X		X	X	
SENSITIVITY					
Culture	45.7%	56.4%	24.0%	53.0%	40.1%
GeneXpert MTB	63.0%	69.1%	41.3%	88.0%	60.7%
Both	65.4%	72.7%	42.67%	91.6%	63.1%
SPECIFICITY					
Culture	100%	100%	100%	100%	100%
GeneXpert MTB	98.8%	100%	100%	96.6%	99.4%

N = number of patients; TB = tuberculosis; LJ = Lowenstein–Jensen solid medium; MGIT 960 = liquid culture systems BACTEC MGIT 960; CRS = composite reference standard.

Due to the low sensitivity of bacteriological tests (culture and NAA techniques), there is a need for clinical, laboratory and radiological criteria for UGT diagnosis in negative bacteriological investigation cases, which would allow pharmacological treatment to be initiated. Currently, there are no accepted diagnostic criteria for UGT; therefore, the initiation of treatment is based on experience and common sense. The lack of standardized diagnostic criteria leads to great variability in the diagnosis of UGT. The authors of this review decided, out of necessity, to propose provisional diagnostic criteria until studies could validate them.

1. Definitive diagnosis:
   a. Positive result of culture or NAA test for Mycobacterium tuberculosis in urine; sperm; renal, prostatic or epididymal abscess; or renal, bladder, prostate or epididymal biopsy sample.
   b. Presence of a granuloma, with or without caseous necrosis, in a biopsy sample of an organ/tissue of the urogenital tract.

2. Probable diagnosis:

Evidence of previous tuberculosis, namely, a history or radiological signs of pulmonary or extrapulmonary tuberculosis, a positive interferon gamma release assay (IGRA) result, or a positive purified protein derivative (PPD) test (reaction greater than 5 mm), associated with the following:

a. Persistent macroscopic hematuria (more than 3 months) without radiological changes in the urinary tract on CT or MRI.
b. Thickening and/or stenosis of the urinary tract with or without a nonfunctioning kidney for no apparent reason.
c. Contracted bladder: Bladder capacity less than 100 mL and radiological observance of a small bladder that has thickened walls without diverticula and is associated with at least one kidney with hydronephrosis owing to thickening and/or stenosis of the urinary tract.
d. Chronic epididymitis (more than 3 months) without improvement with the use of conventional antibiotic therapy with or without epididymal-cutaneous fistula.
e. Chronic prostatitis (more than 3 months) without improvement with the use of conventional antibiotic therapy.

3. Possible diagnosis:

The same findings as for the probable diagnosis, but with no evidence of previous tuberculosis.

Pharmacological treatment should be initiated for patients with a definitive or probable diagnosis, whereas for patients with a possible diagnosis, pharmacological treatment should be initiated after consensus between the medical team and the patient, with an explanation of the risks and benefits.

Recommendations:

Currently, without specific criteria validated in the literature, in the absence of bacteriological or histological confirmation, the initiation of treatment for UGT should be based on the presence of suggestive clinical situations or radiological findings (GRADE: very low, weak).

4 - Pharmacologically treatment.

The tuberculosis treatment regimen should be administered according to the recommendations of the World Health Organization and comprises two phases: intensive (or attack) and maintenance (20). The aim of the intensive phase is to rapidly reduce the bacillary population and eliminate bacilli with natural resistance to any of the drugs. The aim of the maintenance phase is to eliminate latent or persistent bacilli and reduce the possibility of disease recurrence. In Brazil, the basic regimen for tuberculosis treatment consists of four drugs in the intensive phase (rifampicin, isoniazid, pyrazinamide and ethambutol), which lasts 2 months, and two drugs (rifampicin and isoniazid, which have greater bactericidal power) in the maintenance phase, which lasts 4 months (20). The main concern during treatment is the hepatic toxicity of the drugs.

Liver disease should be managed with caution, and the use of alternative drugs may be necessary. Patients who drink alcohol should be instructed to discontinue alcohol intake because of the risk of drug-induced hepatitis. At the beginning of treatment, the following tests should be performed: blood glucose and liver and kidney function tests. During treatment, these tests should be repeated at the clinician's discretion.

Recommendations (20):

The treatment of UGT comprises two phases (Table-2): an intensive (or attack) phase with rifampicin, isoniazid, pyrazinamide and ethambutol that lasts for two months and a maintenance phase with rifampicin and isoniazid that lasts for months (GRADE: high, strong).

5 - Reconstructive surgery in stenosis of the urinary tract.

Tuberculosis causes stenosis of the entire urinary tract and may be intrarenal (infundibular or renal pelvis) or ureteral, single or multiple; the most frequent site is the distal ureter. Urinary tract stenosis is the main cause of loss of renal function in patients with tuberculosis and almost always occurs unilaterally (3). In two retrospective case series of renal tuberculosis, the following factors were associated with a greater chance of preserving renal function at the initial diagnosis: distal ureteral stenosis,

Table 2 - The tuberculosis treatment regimen according to the recommendations of the World Health Organization (20).

Scheme	Weight range	Unit/dose	Duration
RHZE 150/75/400/275 mg	20 to 35 kg	2 tablets	2 months (intensive phase)
	36 to 50 kg	3 tablets	
	51 to 70 kg	4 tablets	
	Above 70 kg	5 tablets	
HR 300/150 mg or 150/75 mg	20 to 35 kg	1 tablet 300/150 mg or 2 tablets 150/75 mg	4 months (maintenance phase)
	36 to 50 kg	1 tablet 300/150 mg + 1 tablet 150/75 mg or 3 tablets 150/75 mg	
	51 to 70 kg	2 tablets 300/150 mg or 4 tablets 150/75 mg	
	Above 70 kg	2 tablets 300/150 mg + 1 tablet 150/75 mg or 5 tablets 150/75 mg	

R-rifampicin; H-isoniazid; Z-pyrazinamide; E-ethambutol

good cortical thickness and a glomerular filtration rate greater than 15 mL/min. (21, 22).

After the initiation of pharmacological treatment, ureteral obstruction may worsen with the loss of renal function due to fibrosis progression. In a retrospective study of 77 patients with ureteral stenosis, early placement (less than 1 month) of a double J catheter or nephrostomy reduced the chance of nephrectomy by 50% and may have led to the resolution of the stenosis in some cases (23). The definition of reconstructive surgery varies according to the segment and extent of the ureter involved, the ipsilateral renal function and the degree of bladder involvement. Definitive surgical treatment can be performed four to six weeks after pharmacological treatment is initiated (24).

For cases of stenosis smaller than two centimeters, in which it is possible to pass a guidewire, endoscopic treatment with balloon dilation and a ureteral incision can be attempted. Balloon dilation can be performed in a retrograde or anterograde manner, with a double J catheterization for 6 weeks. In 1982, Murphy et al. reported a success rate of 64%, with a mean of 4 dilations per patient (25). In 2005, Sinha et al. reported a 59% success rate at 12 months (26). Endoureterotomy is performed under direct vision with a cold knife, electrode or laser, and the incision should be made anteromedially in the distal ureter and posterolaterally in the proximal ureter until the periureteral fat is visualized (24).

In the event of endoscopic treatment failure or strictures greater than two centimeters, traditional open, laparoscopic or robotic reconstructive surgery should be performed (24). The techniques used are the same as those employed for other forms of ureteral stricture: short stricture, usually in the middle or upper ureter, primary anastomosis may be sufficient; upper ureteral stenosis can be surgically treated with ureteropyelostomy if there is short stenosis with the extrarenal pelvis; or with ureterocalicostomy when the renal pelvis is not greatly dilated but there is calyceal dilatation. When the distal ureter is affected, ureteral reimplantation can be performed, possibly with a psoas hitch or Boari flap (27, 28). In the middle segments, transuretero-anastomosis may be necessary, and if the stenosis is throughout the ureter, replacement by a segment of the ileum (ileal ureter) or autotransplantation may be necessary (24, 25). If joint bladder augmentation is needed, the ileocecal segment is preferred, with the cecum used for bladder augmentation and the ileum used for reconstruction of the ureter (8, 29).

Recommendations:

a. In the presence of ureteral stenosis due to tuberculosis, a double-J catheter or nephrostomy should be used early (up to 1 month), before the beginning of pharmacological treatment, in cases in which kidney function preservation is necessary (GRADE: moderate, strong).
b. For patients with a single stenotic site measuring less than 2 cm through which it is possible to pass a guidewire, endoscopic treatment with balloon dilation or endoureterotomy followed by the insertion of a double-J catheter for 6 weeks can be attempted (success rate of up to 60%) (GRADE: low, weak).
c. For cases of complex strictures (those with multiple strictures greater than 2 cm in size or the impossibility of passing through a guidewire) or failure of endoscopic treatment, traditional open, laparoscopic or robotic reconstructive surgery should be performed (GRADE: low, strong).

6 - Surgical treatment for contracted bladder.

Bladder tuberculosis is always secondary to renal tuberculosis that has spread through descending urinary dissemination of the infection. In more advanced bladder tuberculosis, the detrusor muscles are replaced by fibrotic tissue, resulting in a contracted bladder (8). Radiologically, there is diffuse bladder wall thickening without trabeculations or diverticula, and functionally, there is pollakiuria with a voiding interval of less than 1 hour and a bladder capacity of less than 100 mL. Commonly, UGT is associated with uni- or bilateral secondary vesicoureteral reflux (8).

Between 1969 and 2014, 11 case series of patients with contracted bladder due to tuberculosis were published (8, 30–39). Among the 316 patients, 64% were men, and their mean age was between 30 and 40 years. Bladder augmentation was performed for 90% of the patients, and cystectomy with an orthotopic neobladder was performed for 10%. Bladder augmentation was performed with the ileal segment for 35.4% of the patients, with detubularization of the ileum in all patients, except a few patients from two older series published in 1969 and 1970. The sigmoid was used for 38.9% of the patients, with detubularization in almost all patients, and the ileocecal segment was used for 25.8% of patients, but without detubularization, in its original configuration. In patients who underwent neobladder surgery, the Studer technique with the ileum was the most commonly employed (73.3%), but other segments were also used (sigmoid and ileocecum). The success criteria varied between case sets but were usually defined as voiding improvement with an increasing voiding interval and preservation of the upper urinary tract. Good voiding results were achieved for 80 to 100% of the patients. However, there were patients whose condition progressed to end-stage renal failure in some case series (8, 30, 35, 37, 39). Despite the improvement in voiding with good reservoir quality, there was progression of kidney injury regardless of the success of surgery and improvement of the bladder reservoir. The vast majority of patients spontaneously urinated without the need for self-catheterization after surgery, which initially occurred in 85.8% of the patients; however, this value reached 94.2% after new surgery for bladder outlet obstruction, such as transurethral resection of the prostate. In two case series (8, 33), data from the urodynamic evaluation after bladder augmentation were available. In cystometry, the presence of detrusor overactivity (or its equivalent in the augmented bladder, where the elevation of intravesical pressure can occur by contraction of the bladder or intestinal segment) occurred in 72% of the patients and was not associated with low capacity (8). Phasic contractions, apparently of the intestinal segment triggered by bladder filling, were observed. In the pressure–flow study, all patients urinated because of a voluntary increase in abdominal pressure (Valsalva maneuver), which, in some patients, may have occurred in association with increased bladder pressure owing to contraction of the augmented bladder. Worse results of bladder augmentation were associated with low reservoir capacity but not with increased bladder contraction (8).

The largest case series of patients with UGT was published in 1997 and was derived from experience in Moscow since 1960, with the description of 4298 patients and surgical treatment of 2364 (55%) patients (40). A contracted bladder was present in 454 patients. Owing to the lack of detailed case descriptions, these cases were not included in the present review. However, because of the magnitude of experience, conclusions regarding surgical treatment techniques for contracted bladders have become relevant. In almost all cases, the sigmoid was used (95.6%), with the justification that in ileal augmentation, there is greater postvoiding residue due to the lower contractility of the ileal segment than the sigmoid. The use of cystoprostatectomy and an orthotopic neobladder comprising an ileocecal segment with ureteral anastomosis to the terminal ileum, bladder augmentation with cecum and invagination of the appendix stump into the urethra was proposed in men with greater bladder and prostatic destruction by tuberculosis to avoid stenosis of the enterovesical anastomosis with a very contracted bladder and to allow the removal of all scar tissue. In men, the optimal choice between bladder augmentation versus cystoprostatectomy and orthotopic neobladder is not well established, but a neobladder may be considered in patients with greater bladder and prostatic lesions with very small bladders (capacity less than 20 mL) and the presence of pelvic pain (36, 38, 40).

In only one retrospective and nonrandomized study was there a comparison between the techniques used for bladder augmentation (8). In this study, good results (voiding interval greater than or equal to two hours) were associated with the use of an ileocecal segment without detubularization and a sigmoid segment with detubularization. The use of sigmoid without detubularization as well as the presence of pelvic pain (a sign of tuberculous prostatitis) were associated with poor results.

Ureteral reimplantation should be performed in cases of stricture, but it is not necessary in cases of reflux (38). The presence of some degree of renal failure is not a contraindication to bladder enlargement, as it allows for a better quality of life due to improved voiding, and patients with an augmented bladder can appropriately receive a kidney transplant (8).

Recommendations:

1. In patients with bladder tuberculosis, bladder augmentation with an intestinal segment is indicated when the bladder capacity is less than 100 mL (GRADE: moderate, strong).
2. In patients with very small bladders (capacity less than 20 mL) or in those with UGT associated with pelvic pain, cystoprostatectomy and an orthotopic neobladder may be considered (GRADE: very low, weak).
3. When bladder augmentation or orthotopic neobladder surgery is performed, the ileum, sigmoid and ileocecal segments can be used. Detubularization and reconfiguration of the intestinal segment should be performed, but the ileocecal segment can be used in its original form without detubularization (GRADE: low, weak).
4. Ureteral reimplantation is indicated in patients with ureteral stricture but may not be performed in patients with reflux (GRADE: low, strong).
5. Spontaneous voiding occurs in most patients after bladder augmentation. In patients with a large volume of postvoiding residual urine, bladder outlet surgery, such as transurethral resection of the prostate or urethral surgery, should be performed to avoid self-catheterization (GRADE: very low, weak).

CONCLUSIONS

The diagnosis of UGT depends on a high degree of suspicion based on non-specific symptoms and radiological findings. Urinary bacteriological tests have low sensitivity, but even in the absence of diagnostic confirmation, treatment can be carried out through a combination of drugs for a period of six months. In the presence of ureteral stenosis or contracted bladder, complex but well stablished reconstruction procedures are necessary. A better knowledge of UGT features is essential to improve diagnosis and treatment management.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Pelvic Lymph Node Dissection Before Versus After Radical Cystectomy: A Systematic Review and Meta-Analysis

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ABSTRACT

Purpose: Radical cystectomy (RC) is the standard of care for patients with bladder cancer, and pelvic lymph node dissection (PLND) is a pivotal step that can be carried out either before or after RC. Evidence on the optimal timing for PLND remains limited.

Materials and Methods: We searched PubMed, Embase, Cochrane Central, Scopus and Google Scholar for studies comparing PLND before versus after RC. Outcomes assessed were total operative time, PLND time, RC time, number of lymph nodes (LN) dissected, and estimated blood loss. Mean differences (MDs) and 95% confidence intervals (CIs) were computed using a random-effects model. Subgroup analysis was conducted for robot-assisted RC (RARC).

Results: A total of 801 patients from six studies were included, of whom 360 (44.94%) underwent PLND before RC. There were no significant differences in total operative time (MD -17.49; 95% CI -41.65,6.67; p = 0.16; I2 = 94%), PLND time (MD -14.91; 95% CI -44.91,15.09; p = 0.33; I2 = 96%), LN yielded (MD -1.13; 95% CI -4.81,2.55; p = 0.55; I2 = 83%), and estimated blood loss (MD 0.17; 95% CI -51.33,51.68; p = 0.99; I2 = 81%). However, RC time was significantly reduced (MD -28.89; 95% CI -42.84,-14.93; p < 0.0001; I2 = 75%) when PLND was performed prior to RC. In RARC studies, PLND before RC decreased total operative time, RC time, and estimated blood loss.

Conclusions: The timing of lymphadenectomy was not associated with a significant reduction in total operative time, PLND time, LN yield, and estimated blood loss.

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INTRODUCTION

Bladder cancer (BCa) ranks as the nineth most frequently diagnosed malignant tumor worldwide, with over 60,000 new cases and more than 12,000 deaths reported annually among men in the United States (1, 2). Up to 40% of patients present with muscle-invasive bladder cancer (MIBC), and a quarter of them will harbor lymph nodal metastasis (3). Thus, early diagnosis and rapidly implemented interventions are essential in this type of tumor to reduce the risk of metastasis and improve survival rates. Radical cystectomy (RC) is currently regarded as the standard of care for patients with MIBC without systemic involvement, and also, though less frequently, for some non-muscle-invasive bladder (NMIBC) when intravesical treatments, such as BCG (Bacillus Calmette-Guerin), have failed (4, 5). RC is associated with a significant survival gain compared to observation, multiple resections, chemotherapy, or radiotherapy (6-8).

Pelvic lymph node dissection (PLND) is a pivotal stage of RC and can be carried out either before or after cystectomy. While current literature extensively discusses PLND templates, lymph node (LN) yield, density, positive pathological rates, and oncological benefits (9-11), there is limited evidence on the optimal timing of the procedure relative to RC, which is rarely addressed in guidelines. This uncertainty has raised concerns about potential impacts on perioperative outcomes, including operative time, blood loss, and postoperative recovery, which are critical for patient safety and long-term prognosis.

Furthermore, variability in clinical practices concerning the timing of PLND highlights the need for more concrete, evidence-based guidelines. Standardizing this component of RC could lead to improved consistency in outcomes across medical health centers and provide clearer instructions for urologists managing BCa cases. Therefore, we aimed to undertake a systematic review and meta-analysis to compare PLND performed before versus after RC to determine the optimal approach.

MATERIALS AND METHODS

This systematic review and meta-analysis were performed and reported following the Cochrane Collaboration Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement guidelines (12, 13). The prospective protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024550620)

Eligibility criteria

Inclusion in this meta-analysis was restricted to studies that met all the following eligibility criteria: (I) randomized controlled trials (RCTs) or nonrandomized studies; (II) involving patients undergoing RC; (III) comparing PLND before versus after RC; and (IV) reporting any of the outcomes of interest. We excluded studies with (I) no control group; (II) no outcome of interest; (III) overlapping population; or (IV) preliminary results from published studies.

Search strategy

We systematically searched PubMed (MEDLINE), Embase, Cochrane Central Register of Controlled Trials, Scopus, and Google Scholar from inception to June 2024. The search terms included 'radical cystectomy' and 'lymphadenectomy'. No filters or language limitations were applied in our search. A complete electronic search strategy is reported in the Supplementary Appendix. After removing duplicates, two authors (G.M.M.L. and L.G.S.G.) screened the titles and abstracts and independently assessed full-text articles for inclusion based on prespecified criteria. Discrepancies were resolved in a discussion panel with the senior author. We also searched for additional eligible studies through a review of the references from articles identified in the original search.

Data extraction

Two authors (G.M.M.L. and L.G.S.G.) independently extracted the data from each study using a

standardized data collection document to collect the following characteristics: inclusion and exclusion criteria, total number of participants in each group, baseline characteristics, RC technique, pathological staging, pathological LN metastasis, limitations of each study, endpoint data, and endpoint definitions. Our prespecified primary endpoints were total operative time, PLND time, and RC time. Our secondary outcomes included the number of dissected LN, and estimated blood loss. Baseline characteristics were reported as the mean and standard deviation for continuous variables and proportion for binary variables.

Quality assessment

We evaluated the risk of bias in randomized studies using version 2 of the Cochrane Risk of Bias assessment tool (RoB-2) (14), in which studies are scored as high, some concerns, low, or unclear risk of bias in 5 domains: selection, performance, detection, attrition, and reporting biases. Non-randomized studies were assessed with the Risk of Bias in Non-randomized Studies - of Interventions tool (ROBINS-I) (15). The two authors (G.M.M.L. and L.G.S.G.) independently conducted the assessments, and disagreements were resolved through consensus after discussing reasons for discrepancies.

Statistical analysis

Endpoints were primarily analyzed with a mean difference (MD) with 95% confidence interval (CI). Cochran Q test and I2 statistics were used to assess heterogeneity. We used the DerSimonian and Laird random-effect model to calculate pooled estimates, considering that the patients came from different populations. Review Manager 5.4 (Cochrane Centre, The Cochrane Collaboration, Denmark) was used for statistical analyses.

RESULTS

Study selection and characteristics

Our initial search yielded 10,770 results, as shown in Figure-1. After removing duplicate records and ineligible studies, 13 were retrieved and remained for full-text revision based on our previously detailed inclusion criteria. Six studies were ultimately included in the pooled analysis, comprising 801 patients from one RCT (16) and five cohort studies (17-21). Among these patients, 360 (44.94%) underwent PLND before RC, whereas 441 (55.06%) underwent PLND after RC. The main characteristics of the included studies are presented in Table-1. The mean age of all patients included was 60.17 years old, with no significant difference between both groups, and 658 (82.15%) were male. The clinical and surgical baseline characteristics of the included patients are detailed in Table-2.

Pooled analysis of all studies

In the group of patients that had PLND before RC, there was an overall trend towards decreased total operative time (MD -17.49; 95% CI -41.65,6.67; p = 0.16; I2 = 94%; Figure 2A) and significantly lower RC time (MD -28.89; 95% CI -42.84,-14.93; p < 0.0001; I2 = 75%; Figure-2B) when compared to those who underwent it after RC. Moreover, there was no statistical difference between both groups in PLND time (Figure-2C), number of LN dissected (Figure-3A), and estimated blood loss (Figure-3B).

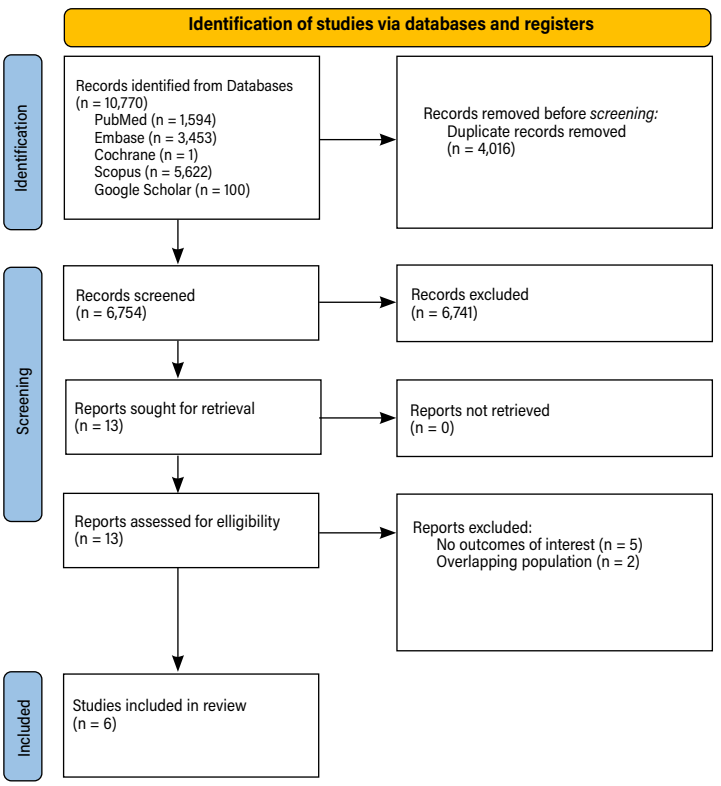
Subgroup analysis

In a subgroup analysis of studies that performed robot-assisted RC (RARC), there was a significant reduction in total operative time (MD -23.84; 95% CI -30.88,-16.81; p <0.00001; I2 = 0%; Figure-2A), RC time (MD -35.13; 95% CI -41.82,-28.44; p < 0.00001, I2 = 0%; Figure-2B), and estimated blood loss (MD -39.54; 95% CI -44.20,-34.88; p <0.00001; I2 = 0%; Figure-3B) in patients that had PLND before RC. Furthermore, there was no statistical difference between groups in the number of LN dissected (Figure-3A).

Quality assessment

Supplementary Appendix Figure-1 summarizes the individual risk of bias assessments of the included studies. The RCT was appraised using the Cochrane Collaboration's tool RoB-2, and it was con-

Figure 1 - PRISMA flow diagram od study screening and selection.



sidered to have an overall risk of bias classified as "some concerns", primarily due to the nature of the procedure, since it is inherently impossible to blind the surgeon. All five non-randomized studies were rated as "moderate risk" due to their potential to introduce confounding factors or bias in patient selection. Furthermore, the retrospective design of four of these studies might influence the determination of patient exclusion criteria based on specific findings such as outcomes and comorbidities.

DISCUSSION

In this systematic review and meta-analysis comprising six studies and 801 non-overlapping patients, we comprehensively compared performing PLND before or after RC. The main findings from our pooled analysis did not demonstrate statistically significant differences in total operative time, PLND time, number of LN dissected, and estimated blood loss. However, there was a significant reduction in RC time in patients that underwent PLND before RC.

Lymph node involvement in BCa is a crucial prognostic factor for oncological outcomes, and its incidence ranges from 5% in NMBIC and 18-27% in MBIC. Given the heightened risk of postoperative tumor recurrence associated with nodal metastases, PLND is a pivotal component of RC (22, 23). Multiple aspects have been studied to contribute to a safe and effective PLND, such as the extent of the dissection, the number of LN yielded, and the surgical technique.

The lymphatic drainage in bladder cancer surgery can follow two main templates: a limited PLND, which includes both sides of the obturator fossa, and an extended PLND, which covers a broader area, such as the aortic bifurcation, iliac vessels, and internal iliac nodes (24, 25). Studies have shown that extended PLND is associated with better relapse-free survival (RFS) due to improved local control, though extending beyond this (super-extended PLND) does not improve survival and may increase complications (3, 26-27).

Table 1 - Main characteristics of the included studies.

Study	Country; Period	Design	Exclusion criteria	RC technique
Moeen, et al. 2024 (16)	Egypt; 2014-2019	RCT, single-center	Palliative cystectomy, grossly enlarged LNs in MSCT or MRI, CKD, or refused to participate	Open
Kumaraswamy, et al. 2023 (17)	India; 2019-2022	Ambispective, single-center	Incomplete or missing data	Laparoscopic
Wang, et al. 2023 (18)	China; 2014-2022	Retrospective, single-center	Previous bladder or prostate surgery, previous RT, distant metastasis, coagulation dysfunction, important organ dysfunctions, or combined with other systemic malignant tumors	RARC
Salih Boga, et al. 2020 (19)	Turkey; 2017-2019	Retrospective, single-center	NA	RARC
Zhu, et al. 2013 (20)	China; 2003-2013	Retrospective, single-center	Non-extended or zoned PLND, distant metastasis, or neoadjuvant RT or CR	RARC
Ozen, et al. 2012 (21)	Turkey; 2005-2009	Prospective, multicenter	Previous pelvic RT, previous PLND, or neoadjuvant CT	Open

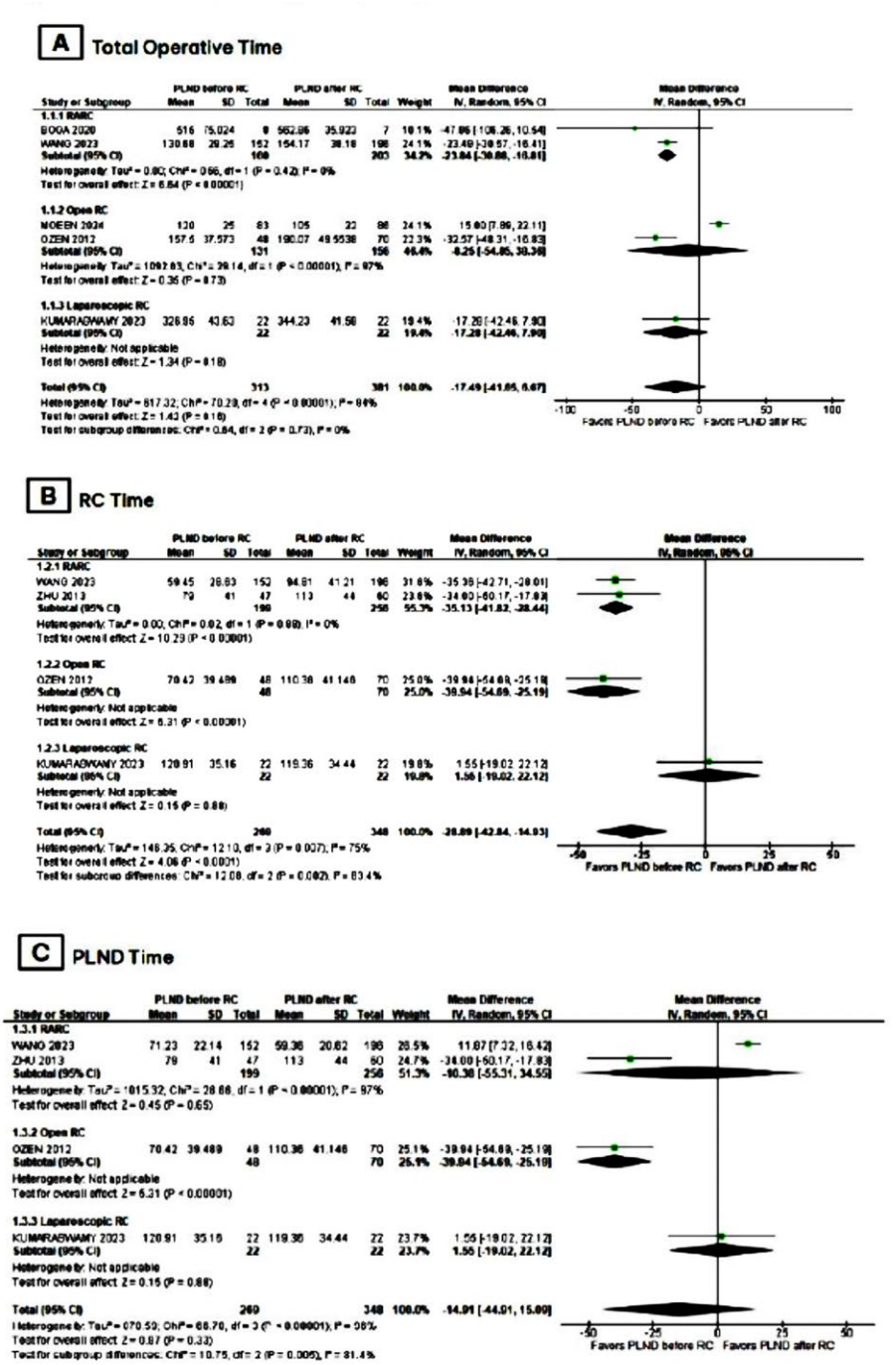
CKD = chronic kidney disease; CT = chemotherapy; LNs = lymph nodes; MRI = magnetic resonance imaging; MSCT = multi-sliced computed tomography; NA = not available; PLND = pelvic lymph node dissection; RARC = robot-assisted radical cystectomy; RC = radical cystectomy; RCT = randomized controlled trial; RT = radiotherapy

Table 2 - Clinical and surgical baseline characteristics of the included patients.

Study	Patients, n		Age, years (±SD)			Male, n (%)			Pathological stage, n (%)								Pathologic LN metastasis, n (%)		
	bRC	aRC	bRC	aRC	p	bRC	aRC	p	bRC				aRC				p	bRC	aRC	p
									≤T1	T2	T3	T4	≤T1	T2	T3	T4				
Moeen, et al. 2024 (16)	83	86	58.21 (±6.9)	55.03 (±7.6)	0.235	66 (79.5)	65 (75.5)	0.326	0 (0)	50 (60.3)	33 (39.7)	0 (0)	0 (0)	52 (60.5)	34 (39.5)	0 (0)	0.513	13 (15.7)	18 (20.9)	0.111
Kumaraswamy, et al. 2023 (17)	22	22	57.95 (±12)	57.95 (±9.97)	1.0	19 (86)	22 (100)	0.23	6 (27.3)	11 (50)	5 (22.7)	0 (0)	7 (31.8)	12 (54.54)	2 (9.09)	1 (4.54)	0.62	NA	NA	1.0
Wang, et al. 2023 (18)	152	196	61.08 (±7.66)	62.75 (±5.753)	0.588	114 (91.2)	157 (80.1)	0.158	24 (15.8)	56 (36.8)	53 (34.8)	19 (12.5)	30 (15.3)	62 (31.6)	67 (34.2)	37 (18.9)	0.228	34 (22.4)	53 (27.1)	0.376
Salih Boga, et al. 2020 (19)	8	7	61.00 (±7.67)	62.86 (±5.98)	0.608	7 (87.5)	7 (100)	NA	0 (0)	5 (62.5)	2 (25.0)	1 (12.5)	0 (0)	4 (57.1)	2 (28.6)	1 (14.3)	0.978	3 (37.5)	2 (28.6)	0.714
Zhu, et al. 2013 (20)	47	60	63.00 (±10)	61.00 (±10)	NA	44 (93.61)	50 (83.33)	NA	1 (2.1)	12 (25.5)	21 (44.7)	13 (27.7)	2 (2.3)	16 (26.7)	29 (48.3)	13 (21.7)	NA	16 (34.0)	19 (31.7)	NA
Ozen, et al. 2012 (21)	48	70	61.09 (±9.75)		NA	107 (90.7)		NA	10 (20.8)	12 (25.0)	21 (43.8)	5 (10.4)	15 (21.4)	20 (28.6)	21 (30.0)	14 (20.0)	0.181	19 (39.6)	24 (34.3)	0.385

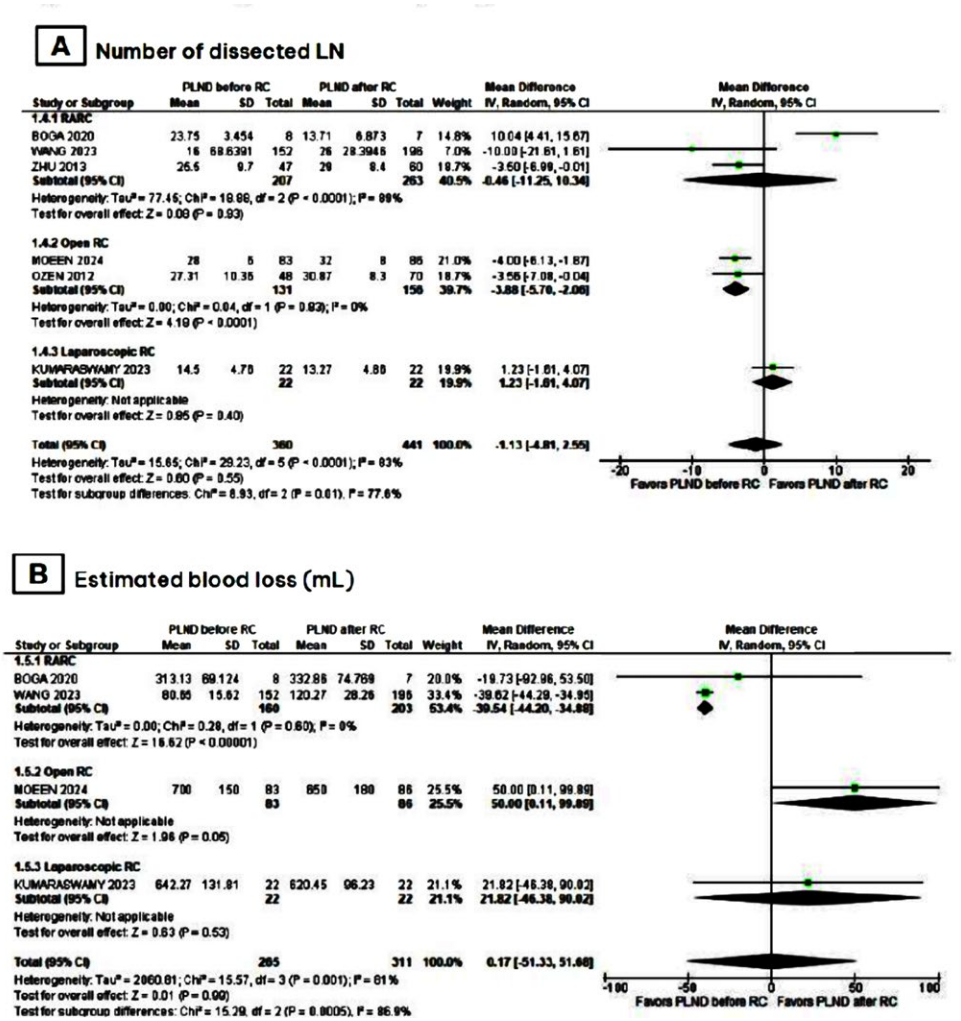
aRC = After radical cystectomy; bRC = Before radical cystectomy; LN = lymph node; NA = Not Available; RC = Radical cystectomy; SD = Standard deviation.

Figure 2 - Meta-analysis of primary endpoints.



(A) Recurrence rate; (B) Radical cystectomy time; (C) Pelvic lymph node dissection time.
CI = confidence interval; RARC = robot-assisted radical cystectomy; SD = standard deviation

Figure 3 - Meta-analysis of secondary endpoints.



(A) Number od dissected lymph nodes; (B) Estimated blood loos.

CI = confidence interval; RARC = robot-assisted radical cystectomy; SD = standard deviation

A higher number of lymph nodes (LNs) removed correlates with better survival rates, as it helps remove micrometastases and ensures more accurate staging (28-31). Research suggests that patients with at least 10 nodes removed tend to have better outcomes, and some recommend dissecting 15 to 20 nodes. However, rather than focusing solely on the number of nodes, the meticulous performance of the dissection within a well-defined template is more important for better oncological outcomes (32-34).

The optimal timing of PLND relative to RC has been controversial. Advocates for performing PLND before RC argue that this approach bares the vascular pedicles of the urinary bladder, which allows for

easier identification and control of these blood vessels, potentially reducing the risk of significant blood loss and making the subsequent steps of cystectomy faster and more efficient. However, the narrow pelvic space, especially in patients with large or locally advanced tumors, may make the procedure more challenging. On the other hand, proponents of performing PLND after RC emphasize the advantages of a wider operative field in the narrow pelvic cavity once the bladder is removed. The expanded surgical field facilitates the procedure, particularly in cases where previous pelvic surgery or tri-modality treatments have resulted in marked pelvic adhesions (16, 17, 21). Our study demonstrated a statistically significant reduction in RC time in patients who underwent early PLND, yet it did not find significant superiority in performing PLND before or after RC regarding the total operative time, PLND time, number of LNs yielded, and estimated blood loss. Moreover, this issue is not addressed in the guidelines of international medical associations, such as the American Urological Association (AUA) and the European Association of Urology (EAU) (4, 5, 35, 36). Consequently, the timing of PLND should be based on the surgeon's experience and preference, as well as the patient-related factors, to provide an effective procedure with minimal morbidity.

In recent years, advancements in surgical technology have impacted the approach to RC for BCa treatment. Despite typically requiring more operative time than open RC, RARC offers substantial benefits, such as smaller incisions, reduced blood loss, earlier bowel motility, fewer postoperative complications, and quicker recovery times. This increased surgical duration might be attributed to the complex setup of the robotic system, the docking of the robot, and the learning curve associated with mastering robotic surgical techniques (37-40). Our study showed that patients who had robotic PLND before RARC presented a statistically significant reduction in total operative time, RC time, and estimated blood loss. Therefore, performing PLND before cystectomy appears to be a favorable option for patients undergoing the robotic procedure.

This study has some limitations. Firstly, the scarcity of available literature on the optimal timing of PLND has led to a relatively small sample size, impacting the depth and robustness of our analysis and potentially restricting the generalizability of our results. Secondly, the generalizability of our findings may be affected by a geographical limitation, given that studies from Europe or the United States, regions known for their significant contributions to oncological research, were either not available or did not meet the inclusion criteria. Additionally, we observed significant heterogeneity in the outcomes studied. This increased heterogeneity could stem from multiple factors across the included studies, such as variability in surgical techniques used for RC and PLND, differences in surgeons' expertise, and inconsistencies in perioperative protocols. Moreover, patient-related variables, such as differences in tumor characteristics, baseline health status, and prior treatments, may further contribute to the observed heterogeneity, which underscores the need for more standardized protocols and reporting to reduce variability and improve comparability between studies. Lastly, there is a paucity of RCTs comparing PLND before and after RC, highlighting the importance of further research in this area.

CONCLUSION

In this meta-analysis including 801 patients who had PLND performed before or after RC, the timing of the lymphadenectomy was not associated with a significant reduction in total operative time, PLND time, number of LN dissected, and estimated blood loss. Additional RCTs are required to assess the comparative effectiveness of PLND before versus after RC and the oncological outcomes.

ABBREVIATIONS

BCa = Bladder cancer
MIBC = Muscle-invasive bladder cancer
RC = Radical cystectomy
NMIBC = Non-muscle-invasive bladder cancer
BCG = Bacillus Calmette-Guerin
PLND = Pelvic lymph node dissection
LN = Lymph node

RCT = Randomized controlled trial
MD = Mean difference
CI = Confidence interval
RARC = Robot-assisted radical cystectomy

CONFLICT OF INTEREST

None declared.

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Patient Outcomes After Penile Prosthesis Placement with Concomitant Non-Reconstructive Urologic Procedures

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ABSTRACT

Purpose: There is substantial literature demonstrating minimal to no increased risk of three-piece penile prosthesis (PP) complications for patients undergoing placement with concomitant reconstructive urologic procedures. However, there is a paucity of research investigating outcomes for patients suffering from erectile dysfunction (ED) who undergo concomitant non-reconstructive urologic procedures at the time of PP placement.

Materials and Methods: We performed a retrospective review of patients undergoing PP placement and a second non-reconstructive urologic procedure performed concomitantly at our institution between January 2007 and July 2021. This was compared to a control cohort of 127 patients who underwent PP placement only. Outcomes of interest were complications and device infections. Comparative statistics were used to compare the two groups, and the Kaplan-Meier method was used to estimate the rate of complications and infections over time.

Results: We identified 44 patients who underwent concomitant surgery and 127 patients who underwent single surgery only. The types of concomitant surgeries were as follows: 23 endoscopic (52.3%), 9 penile (20.5%), 10 scrotal (22.7%), 1 hardware placement (2.3%), and 1 oncologic (2.3%). Hypertension was the only comorbidity that was more prevalent in the concomitant group (65.9% vs. 43.8%, P<0.01). Patients undergoing concomitant surgery had similar complication (4.6% vs. 3.6%, P=0.79) and device infection (2.3% vs. 0.7%, P=0.43) rates as the single surgery group.

Conclusions: In the largest study of its kind, we observed that patients undergoing concomitant non-reconstructive urologic procedures at the time of PP placement are not at an increased risk of adverse events.

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INTRODUCTION

Erectile dysfunction (ED) is the inability to attain or maintain an erection firm enough for satisfactory sexual intercourse (1). Treatment options for ED include lifestyle modifications, oral therapy, vacuum pumps, intraurethral suppositories, intracavernosal injections, and surgery (2). Per the American Urological Association (AUA) guidelines, men may be offered all treatment options upfront with a clear understanding of the risks and benefits of each (1). However, penile prosthesis (PP) implantation remains the gold standard for patients who cannot tolerate or fail less invasive treatment options, as well as for those who are not candidates for such options.

Conventionally, PP implantation is performed as a standalone procedure. This dogma was founded on the tenet that concomitant procedures would increase operative time, local wound exposure, and post-operative edema – factors which can potentially increase infection risk and loss of the prosthesis. Thus, caution has been advised against concomitant procedures due to the presumed increased risk of bacterial seeding (3).

This tenet has been challenged in multiple series which demonstrated no increased risk of adverse events. In fact, potential advantages of concomitant reconstructive procedures were touted. For example, with concomitant PP and artificial urinary sphincter (AUS) or male sling implantation, patients returned to sexual activity and regained urinary continence faster than when these surgeries were performed independently (46). Furthermore, penile straightening procedures associated with Peyronie's disease were commonly performed with implantation of a PP, with high patient satisfaction rates and low risk of adverse events (7). Procedures such as suprapubic lipectomy, ventral phalloplasty, or suspensory ligament release can be carried out at the time of penile implant surgery with no increased risk of complications (8). While these observations are encouraging for the prospect of concomitant surgeries during device implantation, only reconstructive urologic procedures performed at the time of PP placement have been studied.

As such, there is a need to examine the outcomes of patients undergoing non-reconstructive urologic procedures at the time of PP placement. In this study, we sought to examine the long-term outcomes of patients undergoing PP placement with a concomitant non-reconstructive urologic procedure.

MATERIALS AND METHODS

This study was approved by the Johns Hopkins University Institutional Review Board (IRB00205900). A retrospective review of patients undergoing PP placement at Johns Hopkins between January 2007 to July 2021 was conducted. Our institutional records were queried for patients who underwent PP implantation along with any other procedure using Current Procedural Terminology (CPT) codes. Any patient who underwent adjunctive penile reconstructive procedures (e.g., penile modeling, penile plaque excision) or anti-incontinence surgeries were excluded. Additionally, patients with neurogenic bladders were excluded from the study because previous studies have documented an increased risk of complications after PP implantation in this patient population (9).

The control group consisted of patients who underwent PP implantation only between July 2016 and July 2021. It was not necessary to increase the time range for the control group as the ratio was 3:1 to the concomitant group, which was statistically adequate. These patients underwent first-time implants due to organic vasculogenic disease, a history of radical prostatectomy, or a history of pelvic radiation. Exclusion criteria for the control group was a history of priapism and prior gender-affirming surgery due to inherently increased risks of complications associated with these patients (10).

Patient records were examined for baseline patient characteristics, operative details, and follow-up information. Any complications attributable to the surgery were recorded for the entire duration of follow-up.

Comparative statistics (Mann-Whitney U test, χ^2 test, Fisher's exact test) were used to compare characteristics between the two groups. The time to post-operative complications was estimated using the Ka-

plan-Meier method. All analyses were performed using Stata 17.0, and statistical significance was set at α=0.05.

RESULTS

We identified 44 patients who underwent concomitant procedures and 137 patients who underwent PP implantation only. There were no significant differences in age, body mass index (BMI), total number of comorbidities, marital status, or smoking status between groups (Table-1). There was a significantly higher proportion of white patients undergoing concomitant surgery compared to single surgery (68.2% vs. 41.6%, P=0.007). Furthermore, while there were no differences in the rate of cardiovascular disease or diabetes mellitus between the two groups, there was a significantly higher proportion of hypertensive patients in the concomitant surgery group (65.9% vs. 43.8%, P=0.01).

Almost 90% of patients received an American Medical Systems (AMS) device (Boston Scientific, Marlborough, MA), with the remaining 10% receiving a Coloplast device (Coloplast A/S, Humlebaek, Denmark). No difference was seen between the concomitant or single surgery groups with respect to the device used (P=0.83). All patients in both cohorts underwent PP implantation via a penoscrotal approach. No cases were identified in which a patient had a two-piece or malleable PP and a concomitant procedure.

Twenty-two patients undergoing concomitant surgery had a cystoscopic procedure (50.0%) (Table-2). Scrotal surgeries, including vasectomy, or-

Table 1 - Baseline characteristics of patients undergoing concomitant surgery and single surgery.

Characteristic	Concomitant Surgery (n=44)	Single Surgery (n=137)	P-value
Median age at surgery, years (IQR)	63.8 (53.7-68.4)	65.0 (57.8-69.1)	0.16
Race, n (%)			0.007
White	30 (68.2%)	57 (41.6%)	
Black	13 (29.6%)	68 (49.6%)	
Other	1 (2.3%)	12 (8.8%)	
Median BMI, kg/m^2 (IQR)	31.2 (27.1-32.3)	28.1 (26.0-32.9)	0.30
Married, *n* (%)	29 (65.9%)	84 (61.3%)	0.58
Comorbidities, *n* (%)			
Cardiovascular disease	12 (27.3%)	23 (16.8%)	0.13
Diabetes mellitus	13 (29.6%)	53 (38.7%)	0.27
Hypertension	29 (65.9%)	60 (43.8%)	0.01
Number of comorbidities, n (%)			0.17
0	9 (20.5%)	35 (25.6%)	
1	20 (45.5%)	71 (51.8%)	
2	11 (25.0%)	28 (20.4%)	
3	4 (9.1%)	3 (2.2%)	
Smoker, n (%)	19 (43.2%)	56 (40.9%)	0.79

Table 2 - Operative and follow-up details of patients undergoing concomitant surgery and single surgery.

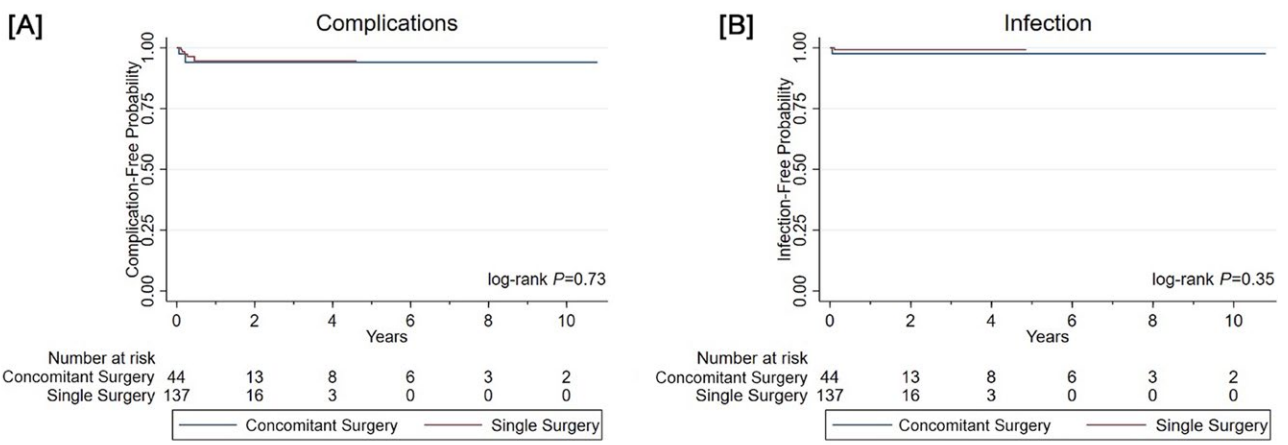
Detail	Concomitant Surgery (n=44)	Single Surgery (n=137)	P-value
Type of penile prosthesis, n (%)			0.83
AMS	39 (88.6%)	123 (89.8%)	
Coloplast	5 (11.4%)	14 (10.2%)	
Concomitant procedure type, n (%)			
Cystoscopy	22 (50.0%)		
Scrotal surgery	10 (22.7%)		
Vasectomy	5		
Orchiectomy	3		
Hydrocelectomy	1		
Spermatocelectomy	1		
Penile surgery	9 (20.5%)		
Circumcision	8		
Lysis of adhesions	1		
Lithotripsy	1 (2.3%)		
Hardware	1 (2.3%)		
Radical prostatectomy	1 (2.3%)		
Follow-up time, months (IQR)	7.4 (1.6-27.9)	4.9 (2.8-9.2)	0.28
Postoperative complication, n (%)	2 (4.6%)	5 (3.6%)	0.79
Device infection, n (%)	1 (2.3%)	1 (0.7%)	0.43

chiectomy, hydrocelectomy, and spermatocelectomy, comprised 10 cases (22.7%). Penile surgeries, including circumcision and release of glandular adhesions, were performed in 9 cases (20.5%). Ureteroscopy with laser lithotripsy, sacral neuromodulator device implantation, and radical retropubic prostatectomy were performed in 1 patient each (2.3% each).

The median follow-up time was 7.7 months for the concomitant surgery group and 4.9 months for the single surgery group (P=0.22) (Table-2). There was no significant difference in complications between the two groups (4.6% concomitant vs. 3.6% single, P=0.79). The device infection rate was comparable as well (2.3% concomitant vs. 0.7% single, P=0.43).

Patients who underwent concomitant surgery had the following complications (n=2): device infection at one month (release of glandular adhesions) and device erosion at two months (circumcision). Patients who underwent PP surgery only had the following complications (n=5): device infection at one month; pump failure at one month; fluid leak at three months; wound separation at six months; pump failure at six months. There was no difference in the time complication between the two groups (P=0.73) (Figure-1A). The rates of freedom from complication at 3, 6, and 12 months was 94.0% throughout for the concomitant surgery group and 97.4%, 94.6%, and 94.6%, respectively, for the single surgery group. Similarly, there was no difference in the time to infection

Figure 1 - Kaplan-Meier curves comparing concomitant surgery and single surgery for (A) freedom from complications and (B) freedom from device infections.



(P=0.35) (Figure-1B). The rate of freedom from infection was 97.6% for the concomitant surgery group and 99.2% for the control group at 3, 6, and 12 months.

DISCUSSION

In recent years, the dogma that PP implantation should not be performed in conjunction with other procedures has been challenged. However, it is unknown whether non-reconstructive urologic procedures can be performed safely without compromising outcomes. To this end, we examined patients undergoing PP implantation and concomitant non-reconstructive urologic procedures over a 14- year span at a high-volume institution and found no increased risk of postoperative complications or device infections.

Concomitant surgeries with PP implantation have been increasingly performed over the past decade, the majority of which are reconstructive. Examples of reconstructive procedures include the correction of Peyronie's disease, stress urinary incontinence, and penile length (4–8,11,12). These studies have shown that reconstructive urologic procedures performed concurrently with PP implantation confer no increased risk of adverse outcomes. However, there are limited studies evaluating concomitant non-reconstructive urologic procedures at the time of PP implantation.

Case reports have been published demonstrating the feasibility of non-reconstructive urologic procedures at the time of PP placement, and early evaluation suggests that patient-reported quality of life is improved with concomitant surgery without compromising surgical outcomes (13–15). However, these case reports were very limited in sample size. To our knowledge, the present study is the largest to date rigorously examining outcomes in this patient population. Importantly, we found that complication rates in patients undergoing concomitant procedures were similar to those of individuals undergoing first-time implantation.

Furthermore, we found that when complications arise, they tend to do so within the first three months, and of those complications, infection rates between the concomitant surgeries and PP implantation alone were comparable. Overall infection rates for the concomitant surgery group resemble those in the literature for implantation of a PP alone (1% to 3%) (16,17). These data offer additional support for performing concomitant procedures. Notably, most of the patients in both groups opted for an AMS device as opposed to a Coloplast device. At our institution, we provide patients with both options and review the pros and cons of each device prior to selection.

Apparent benefits of concomitant procedures include one setting for surgical intervention,

obviating the need for further induction of anesthesia during subsequent procedures. Financial savings may also be potentially realized by utilizing the same operating room equipment and staff. Conversely, depending on the institutional setting, reimbursement for concomitant procedures may be reduced for the surgeon performing the operation (18). Thus, while concomitant procedures appear feasible and safe, the relative paucity of data may be driven in part by non-medical processes which disincentivize these types of procedures.

Insertion of a PP remains a common procedure for patients with ED and is performed by both fellowship-trained urologists and general urologists. While a urologist who is a high-volume implanter may feel comfortable performing concomitant procedures at the time of PP implantation, a general urologist may be apprehensive. Our report may seem more applicable for high-volume implanters, and such surgeons may have performed concomitant surgeries occasionally in the past with a modest sense of their routineness. Our report serves to affirm the success of concomitant procedures with PP implantation.

There are several limitations which should be noted. The number of patients undergoing urologic procedures at the same time as PP implantation in our series is relatively low at 44 patients. However, we present the largest examination of this patient population to date, and with a dataset spanning over 14 years, the low numbers suggest the infrequency with which these concomitant procedures are performed. Furthermore, the outcomes we observed are thankfully relatively rare, which limits the amount of analysis that can be soundly performed (i.e., multivariable regression). Nevertheless, even without adjusting for baseline patient characteristics, which were not significantly different between the two groups, we found no difference in both short- and long-term postoperative complications and infections. Finally, our sample consisted of patients undergoing surgery at a high-volume tertiary care center and may not be generalizable to the broader community.

In this study of patients undergoing PP implantation with a concomitant non-reconstructive urologic procedure, we find no increased risk of complications or device infections when compared to patients undergoing first-time PP placement only. While further investigation is needed, our findings challenge the traditional dogma that secondary urologic procedures should be avoided at the time of PP implantation.

DISCLOSURES

Institutional Review Board Approval Number: IRB00205900

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Ridwan Alam, William S. Du Comb contributed similarly as first author

CONFLICT OF INTEREST

None declared.

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Efficacy and Safety of Mirabegron Compared to Solifenacin in Treatment of Non-neurogenic Overactive Bladder in Children: A Randomized Controlled Trial

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ABSTRACT

Purpose: Non-neurogenic overactive bladder (OAB) is a common problem in children. Anti-muscarinics have been widely used as first-line medical treatment. However, their frequent side effects necessitate searching for therapeutic alternatives. We aimed to assess the efficacy and safety of the beta 3 agonist, mirabegron.

Materials and Methods: A randomized controlled trial enrolled child with non-neurogenic OAB refractory to behavioral urotherapy. Patients were randomized to receive either Mirabegron 25/50 mg based on a 40-kg body weight cutoff or solifenacin 5 mg for 12 weeks. Patients were assessed using Dysfunctional Voiding Scoring System questionnaire (DVSS), 3-day voiding diary and uroflowmetry. Vital signs and adverse effects were recorded at baseline and follow-up. The study primary endpoint was ≥50% reduction of the baseline DVSS.

Results: Among 128 patients screened, 72 patients (36 in each group) completed the study with a mean age of 9.2±2.3 years. Both groups had significant improvement of DVSS and voiding diary (p<0.001) at 12 weeks. In mirabegron group, 94.4% (34/36) had greater than 50% improvement of DVSS compared to 75% (27/36) of solifenacin group (P=0.02). Complete symptom resolution was observed in 22.2% (8/36) patients on mirabegron versus 8.3% (3/36) on solifenacin (P=0.1). Patients on mirabegron had less adverse effects (19.4% vs 47.2%; p=0.01).

Conclusion: Mirabegron is more effective with fewer adverse effects than solifenacin for treatment of children with OAB. Mirabegron treatment improves daytime symptoms and nocturnal enuresis with less risk of constipation. It may be considered as first-line pharmacotherapy in this patient population.

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INTRODUCTION

Voiding dysfunction is a common problem in the pediatric population. It affects 17-22% of children older than 5 years, the age for diagnosis (1). The term describes abnormalities of urinary bladder functions in children, either during filling or emptying (2).

Overactive bladder (OAB) is a subset of pediatric voiding dysfunction characterized by frequency, urgency, and nocturia with or without urinary incontinence in the absence of UTI or other obvious pathologies. The diagnosis relies on history taking, voiding diaries, and specific questionnaires such as the Dysfunctional Voiding Scoring System (DVSS). Evaluation of associated bowel dysfunction is important, as children with constipation are 6.8 times more likely to have voiding dysfunction (3). Clinical examination, uroflowmetry, and bladder US should be done to exclude underlying neurogenic or anatomic problems. Urodynamic studies are only considered in patients refractory to pharmacological treatment due to their invasive nature (4, 5).

The first line of treatment is behavioral urotherapy, which consists of patient education, timed voiding, proper voiding position, balanced fluid intake, and restriction of caffeine and bladder irritants. Symptoms should be evaluated after at least two months of urotherapy. For children with more severe LUTS, behavioral therapy alone has a low response and high discontinuation rate (6).

Pharmacotherapy, primarily antimuscarinics, is used as a second-line treatment for patients with OAB. However, they are frequently discontinued due to lack of efficacy or bothersome adverse effects, such as dry mouth, headache, and constipation which in turn aggravates the OAB symptoms (7, 8).

Mirabegron has been recently developed for treatment of OAB. It is a selective beta-3 adrenergic agonist that causes bladder wall relaxation. Mirabegron has shown great efficacy and safety in treating OAB in adults (8). However, a few studies have evaluated mirabegron in children, with promising results (9, 10). It was only in 2021 that the FDA approved its use in children (11, 12). We hypothesize that mirabegron is equally effective as anticholinergics in treating children with OAB refractory to behavioral therapy. The better safety profile of mirabegron can favor its use as a first-line pharmacotherapy for children with OAB,

This study aimed to assess the efficacy and safety of mirabegron for treatment of pediatric non-neurogenic OAB, compared to the antimuscarinic, solifenacin.

MATERIALS AND METHODS

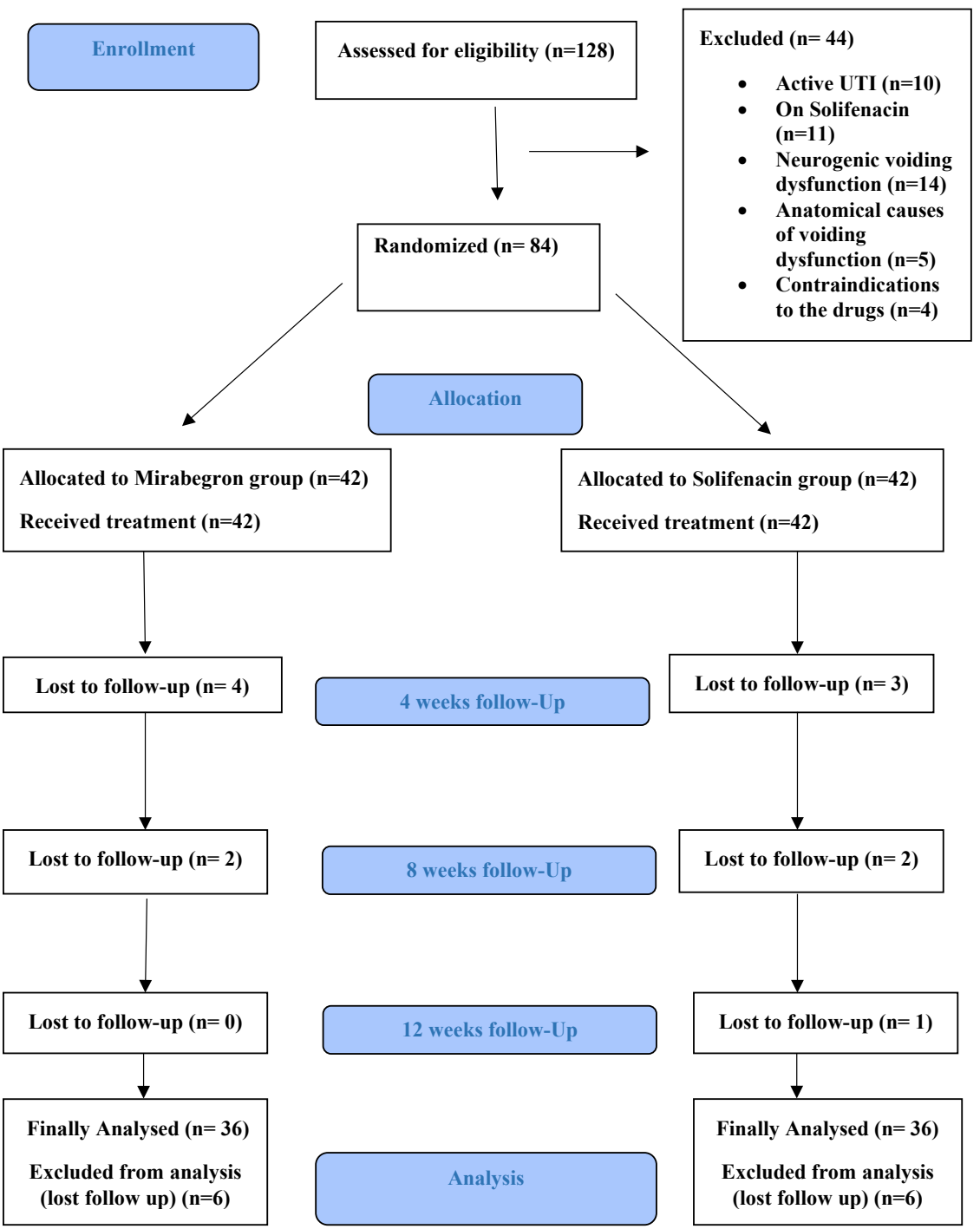
Study design and enrollment:

This was a single-blinded randomized controlled trial (RCT), conducted at a single tertiary center, between February 2022 and January 2023. The study was approved by the Institutional Review Board (**MS.21.09.1680**) and registered on ClinicalTrials.gov (**NCT05240456**). Children 5-12 years of age with OAB and a DVSS score ≥ 6 for females and ≥ 9 for males, unresponsive to at least 2 months of urotherapy with or without concomitant anticholinergic treatment, were screened for eligibility (Figure-1) (13). Neurogenic or anatomical LUT abnormalities, active UTI, unresponsiveness to prior solifenacin treatment, and contraindications to solifenacin or mirabegron were the exclusion criteria. Patients who were on other anticholinergic medications at screening were instructed to discontinue anticholinergics at least 2 weeks before starting the study medication. Parents who agreed to enroll their children provided informed consent according to the Declaration of Helsinki.

Randomization and intervention

Using the closed envelope method, patients were randomly assigned to one of the two treatment groups in a 1:1 ratio. Group 1 received 25/50 mg mirabegron orally according to their body weight. Patients <40 kg received 25 mg and patients >40 kg received 50 mg, once daily in the morning after a meal, for 12 weeks (14). Group II patients received 5 mg of oral solifenacin once daily in the morning after a meal, for 12 weeks (15). Patients were asked to fill daily dosing logs to assess compliance. Patients in

Figure 1 - CONSORT flow chart of the progress of the parallel groups through the phases of the randomized trial.



both groups were asked to continue behavioral urotherapy. Constipation, if present, was concomitantly treated by increasing daily fluid and dietary fiber intake. Osmotic laxative (lactulose) was used if dietary measures were not sufficient.

Baseline evaluation

Baseline evaluation included history and physical examination to exclude underlying neurological conditions. Heart rate and blood pressure were measured. All patients underwent urinalysis with reflex urine culture, renal bladder ultrasound, PVR measurement, and uroflowmetry. If present, UTI was treated before enrollment. Patients and their guardians were asked to complete the Arabic version of the DVSS questionnaire, a three-day voiding diary, a four-week wet night chart, and an Arabic version of the Bristol stool scale to evaluate constipation (defined as Bristol stool score of I or II) (16-18).

Follow-up

During the 12-week study period, follow-up visits were scheduled every four weeks. During each visit, vital signs and PVR were measured. Treatment-related adverse effects were specifically questioned. Patients or their guardians were asked to refill the DVSS questionnaire. Additionally, a new uroflowmetry, three-day voiding diary, four-week wet night chart, and Bristol stool scale were obtained at the study conclusion (Table-1).

Endpoint

The primary endpoint was treatment efficacy, defined as ≥50% reduction of the DVSS relative to the baseline. The secondary endpoint was treatment-related adverse effects assessed at each follow-up visit. According to the American Academy of Pediatrics Clinical Practice Guidelines, clinically relevant blood pressure changes were defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or blood pressure more than 95th percentile for age +12 mmHg, whichever is lower (19). Clinically relevant heart rate changes were defined as ≥15 beat/minute change from baseline (20). Adverse effects were considered mild if they didn't interfere with patients' usual functioning, moderate if they to some extent interfered, and severe if they significantly interfered.

Table 1 - Plan for treatment assessment & follow up.

Parameters	Visit 1 (evaluation)	Visit 2 (4 weeks)	Visit 3 (8 weeks)	Visit 4 (12weeks)
History taking & complete examination	✓			
Vital signs measurement	✓	✓	✓	✓
DVSS (Arabic version)	✓	✓	✓	✓
3-day voiding diary	✓			✓
Abdomino-pelvic Ultrasound	✓			
PVR	✓	✓	✓	✓
Urine analysis ± Culture	✓			
Uroflowmetry	✓			✓
Bristol stool scale	✓			✓
4-week wet night chart	✓			✓

Sample size calculation

Assuming type I statistical error of 5% and type II statistical error of 20%, the study was powered at 80%. An average difference of 5 points in symptom score was defined as clinically relevant (21). We assumed that anticholinergic treatment would result in improved DVSS in 50% of patients. A minimum of 75% improvement of the DVSS with the new treatment was considered clinically significant, giving an effect size of 25%. With a dropout rate of 15%, a sample size of 34 patients in each study arm was estimated.

Statistical analysis

Data were statistically analyzed using SPSS Inc., Chicago, IL, USA, version 21. Independent sample t-test, paired sample t-test, chi-square test, Mann-Whitney test, or Wilcoxon signed-rank test were used for comparisons, as appropriate. P-value ≤0.05 was considered statistically significant.

RESULTS

Patients

A total of 128 patients were screened for eligibility. Of them, 84 patients were included and randomized in the study (42 patients in each arm). Twelve patients did not complete the study: 2 discontinued treatment due to adverse effects and 10 lost follow-up. Therefore, the final analysis included 72 patients who completed the study (36 patients in each group). The CONSORT flow chart of the study is shown in (Figure-1). The mean age at enrollment was 9.2±2.23 years, and the mean baseline DVSS score was 15.5±3.97. A total of 27(37.5%) patients had associated constipation according to the Bristol stool scale at baseline, and 66(91.7%) patients had associated nocturnal enuresis. The baseline demographics of patients in both groups were comparable (Table-2).

Efficacy

DVSS

At 12 weeks, the mean DVSS significantly decreased compared to baseline in both study groups (p<0.001) (Figure-2). DVSS was significantly lower in mirabegron group compared to solifenacin at 8 and 12 weeks (p=0.005).

A total of 34 of 36 (94%) patients had ≥50% reduction of their baseline DVSS in mirabegron group compared to 27 of 36 (75%) patients in solifenacin group (p=0.02). Complete symptom resolution, a DVSS score of zero, was reported in 8(22%) patients in mirabegron group, and 3(8%) patients in solifenacin group (P=0.1).

Three-day voiding diary

Both groups also had significant improvement in the three-day voiding diary parameters at the end of the study compared to baseline values (P<0.001). When comparing both groups, patients on mirabegron had significantly fewer daytime incontinence episodes compared to solifenacin (p<0.001). Other variables showed no statistically significant differences (Table-3).

Uroflowmetry

In mirabegron group, the median voided volume increased from 160.5(30-475) mL at baseline to 177(40-375) mL at 12 weeks (p=0.27). In solifenacin group, it increased from 138(32-523) mL at baseline to 149(36-483) mL at 12 weeks (p=0.39). These differences were not statistically significant (Table-3).

Four-week wet night chart

In mirabegron group, the number of wet nights per 4 weeks improved from a baseline median of 23.5(0-28) to 6(0-28), (p<0.001). A greater than 50% reduction in the number of wet nights was achieved in 22 of 33(67%) patients who had associated nocturnal enuresis. Complete nighttime dryness was achieved in 5 of 33 patients (15%). While in solifenacin, the number of wet nights improved from baseline median 25(0-28) to 6(0-28), (p<0.001). Improvement ≥50% was achieved in 23 of 33(69%) patients who had nocturnal enuresis. Complete nighttime dryness was achieved in 7 of 33(21%) patients.

Bristol stool scale

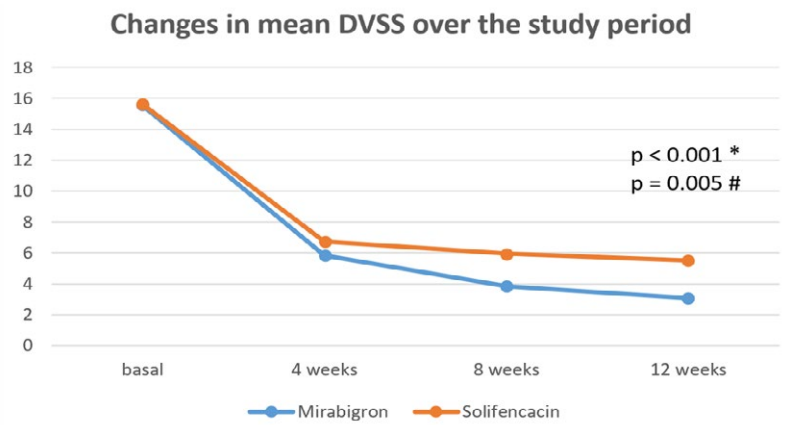
At the end of treatment, mirabegron group had significantly fewer patients suffering constipation, defined as Bristol I or II, compared to solifenacin (P=0.04) (Table-3).

Table 2 - Baseline patient demographics.

Demographics	Mirabegron (group 1) (N=36)	Solifenacin (group 2) (N=36)	P-value
Mean age ± SD, years *	9.4 ± 2.14	9.1 ± 2.34	0.64
Gender: N (%) #			
Male	14 (39%)	10 (28%)	0.32
Female	22 (61%)	26 (72%)	
Stressful life events: N (%) #	29 (81%)	29 (81%)	1
Previous anticholinergic treatment: N (%) #	27 (75%)	25 (69%)	0.6
Mean baseline DVSS Score ± SD *	15.6 ± 4.1	15.4 ± 4	0.81
Three-day voiding diary:			
Mean number of voids per day ± SD *	9 ± 2.37	9.14 ± 2.02	0.79
Median voided volume (range), mL +	100 (30-200)	137.5 (50-300)	0.23
Median number of daytime incontinence episodes per day, (range) +	2 (0-5)	2 (1-4)	0.34
Nocturnal enuresis: N (%) #	33 (92%)	33 (92%)	1
Median number of wet nights in 4-week wet night chart: (range) +	23.5 (0-28)	25 (0-28)	0.94
Uroflowmetry:			
Median voided volume (range), mL +	160.5 (30-475)	138 (32-523)	0.87 0.79
Median Q-max (range), mL/s +	21 (6-56.9)	20.9 (4.7-52.1)	
Median PVR:(range), mL +	10 (0-60)	10 (0-50)	0.69
Bristol stool scale: N (%) #			
Bristol I, II (Constipation)	14 (39%)	13 (36%)	0.97
Bristol III, IV (normal)	21 (58%)	22 (61%)	
Bristol V, VI (diarrhea)	1 (3%)	1 (3%)	

Comparisons done using: * Independent sample t-test; + Mann-Whitney test; # Chi square test

Figure 2 - Changes in the mean DVSS scores of both groups in relation to baseline values.



*: Comparison of DVSS at the end of the study with baseline DVSS scores in each group.

#: Comparison of mean DVSS between both groups at the end of the study.

Safety

No clinically significant blood pressure or heart rate changes were observed in both groups. Only one patient discontinued mirabegron due to chest pain, which was reversible after treatment discontinuation. Also, one patient discontinued solifenacin due to an extensive skin rash. Mirabegron showed a significantly better safety profile. Side effects were reported in 7 of 36 (19.4%) children on mirabegron, with headache (n=3) being the commonest. While 17 of 36 (47.2%) children on solifenacin had side effects of which constipation and headache were the commonest (n=6 each) **(P=0.01)**. All reported side effects were mild and fully reversible after treatment discontinuation (Table-3).

DISCUSSION

Anticholinergic drugs have been widely used as primary pharmacological agents for children with OAB refractory to behavioral urotherapy. Solifenacin, an M3 selective antimuscarinic, has proven superior efficacy and safety compared to the traditional anti-muscarinic drugs (22-24). In this RCT, both mirabegron and solifenacin were equally effective in reducing daytime frequency, nocturnal enuresis, and increasing the median voided volumes. Notably, patients treated with mirabegron had lower DVSS and fewer daytime incontinence episodes on the 3-day voiding diary compared to those treated with solifenacin. A limited number of prospective studies have compared the efficacy of both drugs in children with OAB. A placebo-controlled RCT compared the efficacy and safety of mirabegron and solifenacin in children with newly diagnosed OAB. Based on the 3-day voiding diary for symptom evaluation, the authors reported comparable efficacy of mirabegron and solifenacin (25). Two other studies showed improved bladder capacity and daytime continence with mirabegron in children with OAB refractory to anticholinergics (9, 10).

To our knowledge, this is the first prospective trial to evaluate mirabegron efficacy in treatment of nocturnal enuresis associated with OAB using the standard 4-week wet night charts. Both groups had significant and comparable improvement in the median number of wet nights. Improvement of ≥50% of wet nights post-treatment was achieved in 67% of patients on mirabegron versus 69% on solifenacin. Two retrospective studies reported improved nocturnal enuresis in children treated with mirabegron. In one study, improvement >50% was achieved in 87.5%

Table 3 - Study outcomes.

Parameters	Mirabegron (group I) (N= 36)	Solifenacin (group II) (N= 36)	P-value
Mean DVSS score ± SD *			
At baseline	15.6 ± 4.1	15.4 ± 4	0.81
At 4 weeks	5.8 ± 0.52	6.7 ± 0.52	0.23
At 8 weeks	3.8 ± 0.49	6 ± 0.54	0.005
At 12 weeks	3.1 ± 0.51	5.5 ± 0.66	0.05
Improvement of DVSS score: N (%) #			
> 50% improvement	34 (94%)	27 (75%)	0.02
Complete symptom resolution	8 (22%)	3 (8%)	0.1
Three-day voiding diary at 12 weeks			
Mean number of voids per day ± SD *	5.3 ± 1.58	6.1 ± 2.04	0.08
Median voided volume (range), mL +	200 (50-250)	150 (85-300)	0.07
Number of daytime incontinence episodes (range) +	(0-1)	(0-2)	<0.001
Uroflowmetry at 12 weeks			
Median voided volume (mL), (range), +	177 (40-375)	149 (36-483)	0.37
Median Q-max (mL/s), (range), +	20.7 (5.7-43.9)	23.4 (4.9-77.7)	0.96
Median PVR at 12 weeks (range), mL +	6.5 (0-50)	6 (0-50)	0.73
Four-week wet night chart at 12 weeks			
Median number of wet nights: N (range) +	6 (0-28)	6 (0-28)	0.81
Improvement > 50%: N (%) #	22 (67%)	23 (69%)	0.79
Complete dryness: N (%) #	5 (15%)	7 (21%)	0.53
Bristol stool scale			
Bristol I, II (constipation): N (%) #	7 (19.4%)	15 (41.7%)	0.04
Treatment related adverse effects			
Total Number (%) #	7 (19.4%)	17 (47.2%)	0.01
Constipation	1 (2.8%)	6 (16.7%)	
Headache/drowsiness	3 (8.3%)	6 (16.7%)	
Dry mouth	0	2 (5.6%)	
Blurring of vision	0	1 (2.8%)	
Abdominal pain	1 (2.8%)	1 (2.8%)	
Acne like rash	1 (2.8%)	0	
Sweating	0	1 (2.8%)	
Behavioral changes (Hallucination)	1 (2.8%)	0	

DVSS = Dysfunctional Voiding Symptom Score, PVR = postvoid residual. Comparisons were made using: * independent sample t-test, + Mann-Whitney test, # Chi-square test. Significant differences are in bold.

vs. 63.2% of patients using mirabegron and solifenacin respectively (26). In the other study, 35% of patients on mirabegron showed improvement >50% after 6 months of follow-up (27).

An overwhelming majority of 85.7% of patients assigned to mirabegron in this study were compliant to their treatment. Only one of 42(2.4%) patients discontinued mirabegron due to chest pain that resolved after treatment discontinuation. Unfortunately, that patient was lost to follow-up and the cause of his chest pain could not be investigated. This is consistent with a recent meta-analysis that reported a high likelihood of drug adherence in >80% (12). Cardiovascular adverse effects are well known with mirabegron and are a common cause for treatment discontinuation. Palpitation was reported in 8 of 279 (2.9%) adult patients who received mirabegron for OAB, 3 of those patients (1%) had chest pain. Chest pain and palpitations resolved once therapy was stopped (28). Chest pain was also reported in 1 of 41 children in a recent retrospective study of mirabegron (29). Cardiovascular side effects, like hypertension and prolonged QT interval on ECG are one of the main concerns with mirabegron treatment in adults (30). Although the same concern was raised in the pediatric population, clinically significant cardiovascular side effects were uncommon in a recent meta-analysis in children (12). The lower incidence may be explained by careful selection of cases and exclusion of patients with cardiovascular risk factors, which are uncommon in children, unlike adult patients.

Overall, adverse effects were less common with mirabegron compared to solifenacin in the current study. The most common side effects with mirabegron were headache or drowsiness in 3 (8.3%) patients, constipation, abdominal pain, acne-like rash, and behavioral changes or hallucination were reported in one patient (2.8%) each. These results were in line with the most recent studies on mirabegron safety (9, 12, 25). On the other hand, the most common side effects with solifenacin were constipation, headache or drowsiness in 6 (16.7%) patients each. Other side effects included dry mouth in 2 (5.6%) patients, visual blurring, sweating, and abdominal pain in one patient (2.8%) each. One patient (2.8%) discontinued solifenacin due to a significant skin rash. These adverse effects are also in agreement with the available literature (17, 19).

This study is limited by the relatively small sample size and the short treatment duration. The lack of external funding for the study limited the ability to enroll more patients and extend the study duration beyond 12 weeks. This study also lacked an evaluation of the treatment effect on the patients' quality of life. The drop-out cases could not be tracked to identify drop-out causes. Patients treated with mirabegron were not evaluated with ECG before or after treatment to evaluate prolonged Q-T interval. Despite the superior efficacy and safety of mirabegron, treatment costs may limit its use as a first-line treatment in children with OAB. We look forward to future studies with longer follow-ups to demonstrate the durability of treatment effects and evaluate long-term safety and patient compliance.

Despite these limitations, to our knowledge, this is the first randomized controlled trial to demonstrate that mirabegron is more effective with fewer adverse effects than solifenacin in children with OAB. Another important advantage of this study is the use of multiple tools to assess patient symptoms including the DVSS, 3-day voiding diary, and 4-week wet night chart. The combined use of these tools permitted the concurrent evaluation of nocturnal enuresis alongside daytime symptoms and assessment of both storage and voiding symptoms. Further, the Bristol stool scale demonstrated a lower risk of constipation with mirabegron. This could have contributed to the better symptom improvement seen with mirabegron. This multi-parametric evaluation fits the complex and multi-faceted nature of voiding dysfunction in children.

CONCLUSION

Mirabegron is more effective with fewer treatment-related adverse effects compared to solifenacin in children with OAB refractory to behavioral therapy and other anticholinergic medications. Mirabegron treatment improves daytime symptoms and nocturnal enuresis with less risk of constipation. It may be considered as a first-line pharmacotherapy for select patients with non-neurogenic OAB.

ABBREVIATIONS

BMI = Body mass index
DVSS = Dysfunctional voiding scoring system
ECG = Echocardiogram
FDA = Food and Drug Administration
LUT = Lower urinary tract
LUTS = Lower urinary tract symptoms
OAB = Overactive bladder
US = Ultrasonography
PVR = Post voiding residual
RCT = Randomized controlled trial
UTI = Urinary tract infection

CONFLICT OF INTEREST

None declared.

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Testicular Implant Complications after Transmasculine Gender Affirming Surgery

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ABSTRACT

Purpose: Complications from testicular implantation in transgender men can cause significant distress, repeat visits to the emergency department, and require reoperation for explantation. Outcomes for these implants have not been well described in the literature. This study compares patient and surgery specific factors with complications from testicular implants in transgender men.

Materials and Methods: We performed a retrospective review of patients who underwent testicular implantation. Surgery was standardized across patients with placement through incisions at the top of the labia majora or medially during metoidioplasty. Complication rates, including infection, erosion, migration, and pain requiring removal was compared with patient factors, including body mass index (BMI), smoking status, and implant size.

Results: Of the 116 testicular implants, 12% had a complication requiring removal. The most common reason for removal was erosion of the prosthesis, which occurred in 6 instances. Migration was a relatively frequent complaint, with 10% of patients noting relocation of an implant. However, only 4 implants ultimately underwent reoperation for migration. Four implants caused enough pain to require reoperation. On logistic regression of BMI, age, smoking status, and immunocompromised state on removal of prosthesis, no factor was found to be a significant predictor of removal. Increasing implant size was not associated with an increased likelihood of removal.

Conclusions: Complications after testicular implants in transgender men are not uncommon events. Although there appears to be a growing trend toward smaller prostheses in the literature, our data suggest that implant size is not a significant predictor of complications requiring prosthetic removal.

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INTRODUCTION

Testicular prostheses have been used since the 1940s for the variety of etiologies that cause a testicle to be absent, such as castration for prostate cancer, after testicular torsion, undescended testicles, or orchiectomy for testicular cancer (1, 2).

The complications of testicular prostheses in cis-gendered men have been well documented and include extrusion, pain, and infection. Testicular prostheses in the modern era with saline-filled implants have been reported to be safe and well-tolerated in cisgender adult and pediatric patients (3, 4). The removal rate of testicular prostheses placed after radical orchiectomy for testicular cancer has been reported to be <0.5% (5).

A variety of techniques have been described for scrotoplasty with masculinizing gender affirming surgery including those without testicular implants or placed in a staged fashion such as the Ghent technique (6) or scrotoplasty with concomitant testicular implants. The complication rates of testicular prostheses for gender affirming surgery are not well studied. There is a dearth of revision and explantation rates in transgender men who have had implantation of testicular prostheses (7). Placement of testicular implants in transgender men is potentially different from cisgender men for a variety of hypothetical reasons including differences between labial and scrotal sizes, potential differences in skin thickness and fat distribution. Furthermore, transgender men can often be undergoing a significantly larger surgery at the time of implant placement (metoidioplasty with or without hysterectomy (8)) compared to cis-gender men (orchiectomy). Different factors have been proposed to contribute to prosthetic complications, including smoking, surgical technique, and implant size (9, 10). We hypothesized that the rate of complications in testicular implants would be higher in transgender men compared to that of cisgender men, and that larger implant size would be associated with an increased complication rate. The purpose of this study is to identify the risk of removal of testicular implants in transgender men and factors that contribute to complications.

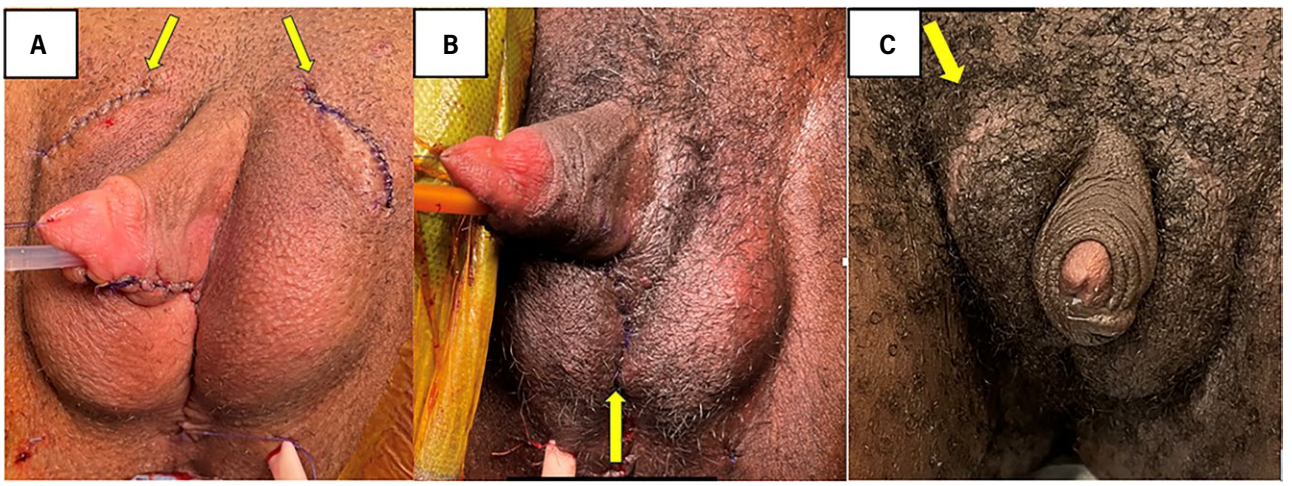
MATERIALS AND METHODS

A retrospective review was performed of patients who underwent transmasculine gender affirming surgery from 2021 to 2023 at a single institution, as part of an IRB-approved study (IRB 20-01505). Patients were included if their surgery was a metoidioplasty with scrotoplasty and insertion of testicular prostheses. Patients were excluded from analysis if their surgery was not their index surgery or if data of interest were omitted on record review, such as implant size.

Two senior surgeons performed all testicular prosthesis implantations. Implantation was standardized across all patients with one of two techniques, with Coloplast® Torosa silicone prostheses placed in pockets created by incisions at the top of the labia majora or blunt dissection of the labia majora medially during metoidioplasty. Incisions at the top of the labia majora, labeled a superolateral approach, create dartos pockets in the newly formed scrotum for the implants. The implants are placed superficial to the Martius fat pad and have not typically been anchored in place with a suture (Figure-1A). In the medial approach, the labia majora are dissected and joined in the midline to create the scrotum. Each side is then opened bluntly on the medial aspect to create pockets for the implants. These implants are also placed superficial to the labial fat pads. Medial insertion of implants avoids the need for additional incisions and minimizes scar (Figure-1B).

Demographic variables were collected for each patient, including age, body mass index (BMI), and current or former smoking status. The presence of any comorbid immunocompromising disease, including diabetes, HIV infection, or chronic steroid use, was also measured. The primary outcome of interest was a post-operative complication, such as infection, erosion of the prostheses, implant migration, or pain, that required implant removal. Implant removal was compared with patient factors, including age, body mass index (BMI), smoking status, implant size, and immunocompromised state. For the purposes of analyzing implant removal, each implant was considered an observation since not all patients who underwent removal had bilateral explantation.

Figure 1 - Approaches to Testicular Prosthesis Implantation.



A) Superolateral approach: Incisions are made at the superolateral aspects of the labia majora to create dartos pockets for the silicone testicular implants; B) Medial approach: Pockets for the silicone implant are created at the medial aspects of the labia majora; C) Example of migrated right testicular prosthesis.

Statistics were performed using Stata 16 (StataCorp, College Station, TX). Pearson's chi-squared test was performed to evaluate differences in rates of implant removal between implant technique. Logistic regression was performed to identify patient factors associated with complications requiring implant removal. Statistical test results were deemed significant for p-values less than 0.05. Institutional Review Board approval for this observational study was obtained through our institution's Program for the Protection of Human Subjects.

RESULTS

Fifty-eight patients who underwent scrotoplasty with bilateral testicular prostheses insertion met the inclusion criteria for this study. The median follow-up period was 28 weeks, and the median patient age was 30 years old. Nearly 75% of study participants had a BMI < 30. Twenty-six patients (45%) were current or former smokers, and three patients had a comorbid immunocompromising condition. Forty-seven patients (81%) had testicular prosthesis placement via the superior-lateral approach.

Of the different complications, migration (Figure-1C) was the most frequent complaint noted in postoperative visits, with 10% of patients noting relocation of one or more of their prostheses postoperatively. However, only 4 implants (3%) ultimately underwent reoperation for migration. Five patients experienced prosthesis erosion requiring removal, while two others had implant-related pain that also required removal. One patient developed cellulitis overlying their implants, which was managed conservatively with antibiotics. The median time to complication was 22 days postoperatively.

Of the 116 testicular implants, 14 implants (12%) had a complication that required removal. The most common reason for post-operative removal was erosion of the prosthesis, which occurred in 6 instances (5%). Eroded implants were removed in the clinic or emergency department. They required either aspiration or manipulation out of skin opening followed by packing. Four implants (3%) caused significant enough pain to require reoperation for removal. By technique, 1 of 22 (5%) implants by medial approach underwent removal compared to 13 of 94 (14%) implants by superior-lateral approach (p=0.23).

The rate of implant removal was compared against patient factors (Table-1). On univariable logistic regression of BMI, age, smoking status, and immunocompromised state on post-operative removal

Table 1 - Implants Removed by Patient-specific and Surgical Factors.

	Implants Removed (%)	Total Implants
Age (Years)		
20-29	6 (10)	58
30-39	0 (0)	28
40-49	8 (33)	24
50-59	0 (0)	6
BMI		
<18.5	0 (0)	2
18.5 - 24	3 (8)	36
25 - 29	5 (11)	46
30 - 39	6 (20)	30
>= 40	0 (0)	2
Smoker		
Yes	9 (14)	64
No	5 (10)	52
Immunocompromised		
Yes	2 (33)	6
No	12 (11)	110
Implant Size		
Small	7 (18)	40
Medium	3 (7)	44
Large	4 (13)	32
Prosthetic Technique		
Superolateral	13 (14)	94
Medial	1 (5)	22
Univariate Logistic Regression on Post-operative removal		
	Odds Ratio (95% (CI)	p value
Age	1.03 (0.96 – 1.11)	0.41
BMI	1.01 (0.88 – 1.16)	0.32
Implant Size		
Small (referent)	-	-
Medium	0.80 (0.14 – 4.51)	0.80
Large	1.23 (0.21 – 7.15)	0.82
Current or Former Smoker	0.98 (0.23 – 4.10)	0.98

of prosthesis, no factor was found to be a significant predictor of subsequent removal. Furthermore, increasing implant size was not associated with an increased odds ratio of prosthetic removal.

DISCUSSION

Rates of testicular prosthesis complications from transgender surgery described in a review by Fascelli et al. are wide-ranging, including infection rates of 3-11% and extrusion rates of 7-14% (7). These rates are subject to overlapping etiologies, however, such as an infection causing wound breakdown and ultimately implant extrusion. Therefore, in our study, we focused on rates of post-operative removal to compare against potential risk factors.

A study of 206 patients who underwent scrotoplasty and testicular implants from Amsterdam University Medical Center found an explantation rate of 13% for their prostheses (9). At this center, implants were increasingly placed during a second stage surgery. Prior studies have also suggested a delayed prosthetic implantation approach to gender affirming surgery of at least six months after the index procedure (6, 7, 10-12). In our study patients underwent a one-stage metoidioplasty surgery, which includes lengthening of the clitoris and urethra along with scrotoplasty with testicular prosthesis implantation as described by Djordjevic et al. (13). However, the comparable rate of explantation (12%) in our one-stage cohort suggest that, at least for testicular prostheses, immediate implantation is possible.

There was a slightly higher rate of explants for patients who were current or former smokers (14% vs. 10%), however the likelihood of post-operative removal was not increased by smoking status on regression analysis. This is in contrast to the study from Amsterdam University that found smoking to be a significant risk factor for infection. The idea that poor wound healing could contribute to higher rates of implant removal led us to examine rates of comorbid immunocompromising conditions, such as diabetes, HIV infection, or chronic steroid use, in patients requiring removal. If a significant risk factor, strategies such as lowering HgA1c or delaying prosthetic implantation after metoidioplasty, may be advisable. Only 3 patients in our data set had an immunocompromising condition, with one of them requiring explantation of both prostheses. This higher rate of explantation requires future examination of a larger sample of immunocompromised patients.

We found that migration was the most common complication after testicular implant placement. This complication is significant for altering the appearance of the scrotum but can also interfere with urination and directing the urinary stream. During the study period we did not routinely suture the implant in place as we had found, anecdotally, prior to the study period that implant migration occurred despite the placement of anchoring sutures and these sutures can distort the appearance of the scrotum.

Given that one of the most common complications is prosthesis extrusion, technique must be given careful consideration. Our study documented two techniques for implant pouch creation. There was not a significant difference between explantation rate on chi-squared analysis; however, the vast majority of implants were performed via the superior-lateral approach. Going forward, surgical techniques can be compared and trialed against each other to minimize erosion rates. Kang et al. emphasizes the importance of minimizing skin tension for the prosthesis pouch to prevent erosion (12). They cite an example of pouch formation in the scrotal reconstruction of a patient who suffered scrotal trauma; surgeons used Foley catheter balloons as tissue expanders in the perineal-scrotal region to create new pockets for the native testes (14). Postoperative care is yet another area of study that can improve rates of complications and prosthesis explantation. In our institution, all patients after testicular implants are given the same post-operative instructions to avoid sitting, heavy lifting, and walking more than 200 steps per day.

In addition to understanding complication rates and their risk factors, another future area of research is patient satisfaction with testicular implants. Patients who have had testicular prostheses implanted after surgical castration for prostate cancer report

greater satisfaction compared to orchiectomy alone (15). The complication rate for transgender men is much higher than that of cisgender men and can cause significant distress. It would be important to understand the level of patient satisfaction for various prosthesis factors, such as size, positioning, and comfort, so that we can weigh these against the costs and risks of implantation.

A major limitation of our study is the duration of follow-up, with a median follow-up of just over 6 months. This poses the problem of underestimating the complication rate, if patients were to seek care outside of our institution or experience complications going forward. We also only have one type of silicone implant available at our center, which limits the comparison of different implant types on complication rates. The retrospective nature of our study is another limitation of the data to predict an implant complication based on risk factors. For example, if surgical technique was chosen based on a perceived likelihood of complication, it loses its predictive power in a regression analysis.

Testicular prostheses have become increasingly used for gender affirming surgery. The growth of their use in the transgender population requires increased attention to complication rates, which thus far have been reported to be at least twenty-fold greater than in cisgender men.

In our series, the complication rate of testicular implants requiring removal was 12%. Our study contributes to the existing literature by showing that single-stage testicular implantation during metoidioplasty carries the same rate of postoperative removal compared to a staged approach. We also showed that the size of implants did not correlate to complication rate, suggesting that placement of the largest size implant that labial size and cosmetic appearance permits is reasonable. Given our sample size, we could not evaluate medial versus superior-lateral placement of implants. Further prospective study is needed to understand patients at higher risk of implant complications to preempt them during an already long and arduous process of transition.

CONFLICT OF INTEREST

None declared.

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Percutaneous Cryotherapy and Radiofrequency Ablation of Renal Masses: Multicenter Comparative Analysis with Minimum 3-Year Follow-up

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ABSTRACT

Background: Different modalities of percutaneous thermal ablation (PTA) have been used as possible minimally invasive nephron-sparing treatments for small renal masses (SRMs). The present study aimed to compare long-term outcomes of two guidelines-recommended ablative techniques, cryotherapy (CRYO) and radiofrequency ablation (RFA).

Materials and Methods: Data of patients with single cT1 solid renal mass undergoing CRYO or RFA between 2004 and 2020 were retrospectively retrieved from a multi-institutional international database. Oncologic outcomes included "technical success", local recurrence-free survival (RFS), distant metastasis-free survival (MFS), and overall survival (OS). Intraoperative and postoperative complications, length of stay (LOS), and re-admission rate within 30 days were registered. Major complications were defined as CD grade ≥III. Baseline features and treatment outcomes were analyzed using descriptive statistics. RFS, MFS, and OS were estimated using the Kaplan-Meier method.

Results: Overall, 643 patients were included, of which 492 (71.2%) underwent CRYO, and 151 (21.8%) RFA, with a median follow-up of 43 and 37 months, respectively (p=0.07). Technical success was achieved in 96.5% of CRYO vs 93.4% of RFA (p=0.09). No difference in terms of overall (CRYO: 10.4% vs RFA: 6%; p=0.1) and "major" (CRYO: 0.8% vs RFA: 1.3; p=0.06) postoperative complications were observed. RFS (CRYO:85.7%; RFA:84.9%, p=0.2), MFS (CRYO: 96.9%; RFA: 95.8%, p=0.4) and OS (CRYO: 89%; RFA: 87.4%; p=0.8) were comparable.

Conclusions: CRYO and RFA are both valid minimally invasive options for the treatment of small renal tumors. They are particularly suitable for patients who are not good surgical candidates as they offer very low risk of major procedure-related complications. For the right indication, they both offer favorable mid to long term oncologic outcomes.

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INTRODUCTION

Different thermal ablation (TA) approaches have been developed as minimally invasive nephron-sparing surgery for small renal masses (SRMs). Among the others, percutaneous cryotherapy (CRYO) and radiofrequency ablation (RFA) are widely used techniques for treating SRMs through a minimally invasive, nephron-sparing approach. CRYO involves the application of extreme cold to induce cellular damage and tumor cell death, while RFA relies on thermal energy generated by radiofrequency waves to achieve tumor necrosis (1). Both procedures are performed under imaging guidance, typically using computed tomography or ultrasound, with CRYO providing enhanced visualization through the formation of an 'ice ball' around the treated area. These techniques are especially valued for preserving renal function, reducing hospital stay, and decreasing complications compared to partial nephrectomy (PN), particularly in patients who are poor surgical candidates (2).

Indeed, according to American Urological Association (AUA) guidelines, CRYO and/or RFA should be considered as options for patients with SRMs less than 3 cm. Great emphasis on the need to discuss the higher risk of tumor recurrence and the potential need for re-treatment during patient counseling (3). European Association of Urology (EAU) adopts a more cautious position, reserving percutaneous TA (PTA) to frail and/or comorbid patients, due to the existing uncertainties regarding its clinical effectiveness (4). Such a discrepancy is mainly because current evidence on PTA approaches is predominantly based on single-center and population-based retrospective studies (5–7).

We hypothesized that CRYO and RFA would yield comparable long-term oncologic outcomes in patients with SRMs. Therefore, the aim of the present study is to describe and compare the long-term outcomes of these two guidelines-recommended PTA procedures in a large international multicenter cohort.

MATERIALS AND METHODS

Study design and population

Data were retrieved from a multi-institutional international database including patients undergoing PTA in seven U.S. and European centers between 2004 and 2020. Inclusion criteria were adult patients (18 years) with single cT1 solid renal mass who had undergone either CRYO or RFA. Exclusion criteria included multifocal or metastatic renal cell carcinoma at presentation, incomplete follow-up data or missing data in outcomes of interest, and lack of post-procedural imaging confirming ablation outcomes. As an analysis of deidentified data, the study obtained exempt status after being reviewed by the local Ethics Committee. Data sharing across participating centers was obtained.

Baseline characteristics, together with clinical, treatment, and post-treatment data were collected. Baseline patient features included demographic data, body mass index (BMI), American Society of Anesthesiologists (ASA) score, history of smoking, diabetes mellitus and hypertension, preoperative estimated glomerular filtration rate (eGFR) calculated by using the Chronic Kidney Disease Epidemiology Collaboration formula (8), and medical history of chronic kidney disease (CKD) ≥ class III. Clinical staging included tumor size, tumor staging according to TNM status, RENAL nephrometry score (9), hilar location, and tumor biopsy.

Treatment details and outcomes included intraoperative and postoperative complications overall, and ≤30 days major according to Clavien-Dindo [CD] classification (10), length of stay (LOS), and readmission rate within 30 days. Complications with CD grade ≥ III were defined as "major complications".

Oncologic outcomes included: "technical success", defined as the extension of ablation defect beyond tumor margin with the absence of residual enhancement in the ablation bed on imaging obtained immediately after the procedure (11), local recurrence-free survival (RFS), defined as a new focal enhancement in the ablation bed or enlargement of the ablation defect on follow-up imaging, distant metastasis-free survival (MFS), as extrarenal disease on imaging, with or without pathologic confirmation, and overall survival (OS), as death by any cause.

A trifecta composite outcome was evaluated for each treatment, including: "technical success", as

a surrogate for oncological outcome; absence of major perioperative complications, as a proxy for surgical outcome; <10% reduction in eGFR at 90 days, as a surrogate for functional outcome. A trifecta outcome as surrogate of overall treatment quality was considered achieved only if all three above conditions were satisfied.

Statistical analysis

Statistical analysis was conducted according to guidelines (12). Patients were stratified into two groups according to treatment modalities. Means and standard deviations (SD) or median and interquartile range (IQR) were adopted to report normally distributed and non-normally distributed continuous variables, respectively. Proportion and frequencies were used to report categorical variables. Patient demographic characteristics and treatment outcomes of each cohort were analyzed using descriptive statistics, as appropriate.

Local RFS, distant MFS, and OS were estimated using the Kaplan-Meier method. The follow-up duration for RFS and MFS was determined from the treatment to recurrence and/or metastasis, respectively. For OS, the follow-up duration was calculated from treatment to the last follow-up visit. Patients with benign histology at pre-treatment biopsy were censored for the assessment of oncological outcomes. To identify significant predictors of "trifecta" achievement, we conducted logistic regression analysis adjusting for age, BMI, ASA score, RENAL Nephrometry Score, and procedure type.

All statistical tests were performed with SPSS® 25.0 (IBM Corp. Armonk, NY, USA) and statistical significance was set at $p<0.05$.

RESULTS

Baseline characteristics

Table-1 summarizes demographics and tumor characteristics. Overall, 643 patients who underwent PTA were included in the analysis. Of these, 492 (71%) and 151 (29%) were treated with CRYO and RFA with a median follow-up of 43 and 37 months, respectively (p=0.07).

No differences in terms of mean age (p=0.1), ASA score (p=0.9), median BMI (p=0.8) were observed between the two cohorts. Also, tumor features like median clinical tumor size (p=0.4), rate of cT stage (p=0.1), and RENAL nephrometry score (p=0.6), were comparable for both RFA and CRYO. The RFA group had a lower median baseline eGFR of (62.5 vs 67.0 mL/min; p=0.015) and a higher rate of CKD ≥ III stage (34.4 vs 23.9%; p=0.011).

At preoperative biopsy, 77.8% of the whole cohort presented malignant histology and 7.6% of the patients did not have data on the biopsy. among which the most common subtype was clear cell RCC at 29.6%.

Treatment outcomes

Treatment outcomes are described in Table-2. Imaging-based "technical success" was achieved in 95.8% of the whole cohort, with no difference between the approaches (CRYO: 96.5% vs RFA: 93.4%; p=0.09). A significantly higher number of intraoperative complications was observed during CRYO (3.3% vs 0%, p=0.02). No difference in overall (CRYO: 10.4% vs RFA: 6%; p=0.1) and "major" (CRYO: 0.8% vs RFA: 1.3; p=0.06) postoperative complications were reported.

Overall, 94 (14.6%) patients who had a benign histology report were excluded from the analysis of oncological outcomes, as well as patients without an oncologic follow-up. Therefore, oncological outcomes were evaluated in 536 patients, including 417 patients treated with CRYO and 119 with RFA.

Within the overall cohort, local recurrence was observed in 96 (17.9%) patients. Of these, 65 (15.6%) and 27 (22.7%) patients after CRYO and RFA, respectively.

After 5 years, local RFS rates were 85.7% for CRYO and 84.9% for RFA, with 124 and 41 patients still at risk, respectively. There was not a statistically significant difference in local RFS between different subgroups (p=0.2) (Figure-1A).

Distant metastasis developed in 24 (4.5%) patients with a median onset time of 23 months. The 5-year MFS rates were 96.9% for CRYO and 95.8% for RFA without any difference (p=0.4) (Figure-1B). Overall, 114 patients died over an average of 31 months after PTA treatment. The 5-year OS rates for CRYO

Table 1 - Demographics and tumor characteristics.

	Overall	CRYO	RFA	p
Patients, n (%)	643	492 (71)	151 (29)	-
Female Gender, n (%)	200 (29.2)	155 (31.5)	45 (29.8)	0.693
ASA score, n (%)				0.9
1	7 (0.9)	6 (1.2)	1 (0.7)	
2	156 (24.2)	118 (24.0)	38 (25.2)	
3	406 (63.2)	309 (62.8)	97 (64.2)	
4	74 (11.6)	59 (12.0)	15 (9.9)	
Age, years, mean (SD)	68.8 (10.7)	68.5 (10.7)	69.8 (10.6)	0.181
BMI, kg/m^2, median (IQR)	27 (24-30)	27 (26-32)	27 (26-32)	0.8
CKD ≥ III stage, n (%)	170 (26.4)	118 (23.9)	52 (34.4)	**0.011**
Diabetes history, n (%)	166 (25.8)	132 (26.9)	34 (22.5)	0.278
Preop. eGFR, mL/min, median (IQR)	65.4 (63-66)	67.0 (63-71)	62.5 (58-66)	**0.015**
Clinical size, cm, median (IQR)	2.5 (1.5-2.5)	2.5 (1.5-2.5)	2.5 (1.5-2.5)	0.4
Clinical T stage, n (%)				0.1
T1a	604 (93.9)	462 (93.9)	142 (95.3)	
T1b	37 (6.1)	30 (6.1)	7 (4.7)	
RENAL score, median	6 (4-6)	6 (4-6)	6 (4-6)	0.6
Malignant, n (%)	500 (77.8)	384 (78.1)	116 (76.8)	0.5
Clear cell	204 (29.6)	169 (34.4)	35 (23.2)	
Papillary	96 (14.0)	73 (14.8)	23 (15.2)	
Chromophobe	26 (3.8)	22 (4.5)	4 (2.7)	
Other/Unspecified	174 (25.3)	120 (24.1)	54 (35.8)	
Benign histology, n (%)	94 (14.6)	69 (14.0)	25 (16.6)	
Oncocytoma	48 (6.9)	23 (4.6)	24 (15.8)	
Angiomyolipoma	4 (0.6)	4 (0.8)	0	
Others	43 (-)	42 (-)	1 (-)	
No Biopsy/Data not available, n (%)	49 (7.6)	39 (7.9)	10 (6.6)	

Table 2 - Treatment and oncological outcomes.

	Overall (n=643)	CRYO (n=492)	RFA (n=151)	P value
Technical success*, n (%)	616 (95.8)	475 (96.5)	141 (93.4)	0.09
Intraoperative complications, n (%)	11 (1.7)	11 (3.3)	0	0.02
Overall postop. complication, n (%)	60 (9.3)	51 (10.4)	9 (6.0)	0.1
Major postop. complications, n (%)	6 (0.9)	4 (0.8)	2 (1.3)	0.06
Hospital stays, days, median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	0.3
Last follow-up, months, median (IQR)	41.5 (39-42)	43 (42-44)	37 (35-39)	0.07
30-day readmission, n (%)	4 (0.8)	3 (0.6)	1 (0.6)	0.5
Local recurrence, n (%)	96/536 (17.9)	65/417 (15.6)	27/119 (22.7)	0.07
Time to recurrence, months, median (IQR)	12 (10-14)	12 (10-14)	11 (10-13)	0.4
Distant metastasis, n (%)	24/536 (4.5)	17/417 (4.1)	7/119 (4.6)	0.4
Time to distant metastasis, months, median (IQR)	23 (22-25)	17 (15-19)	26 (24-28)	0.26
Deaths, n (%)				
Overall	114/536 (21.3)	80/417 (19.2)	34/119 (28.6)	0.3
Cancer-related	11/536 (2)	8/417 (1.9)	3/119 (2.5)	0.7
Time to Death, months, median (IQR)	31 (28-34)	40 (37-43)	39 (38-40)	0.1

* Treatment and oncological outcomes of patients undergoing cryotherapy and radiofrequency ablation

and RFA were 89% and 87.4%, respectively (p=0.8) (Figure-1C). At 5 years, there were 124 patients still at risk in the CRYO group, and 41 in the RFA group.

Trifecta outcome was achieved by 496 patients (76.3%), of which 324 (77.7%) received CRYO, and 85 (71.4%) underwent RFA, with no statistically significant difference between the two groups (p=0.3). According to logistic regression analysis, both BMI (odds ratio [OR] 1.08, 95%CI 1.02-1.15) and RENAL score ≥7 (OR 1.21, 95%CI 1.08-1.57) was related to a decreased likelihood of trifecta achievement.

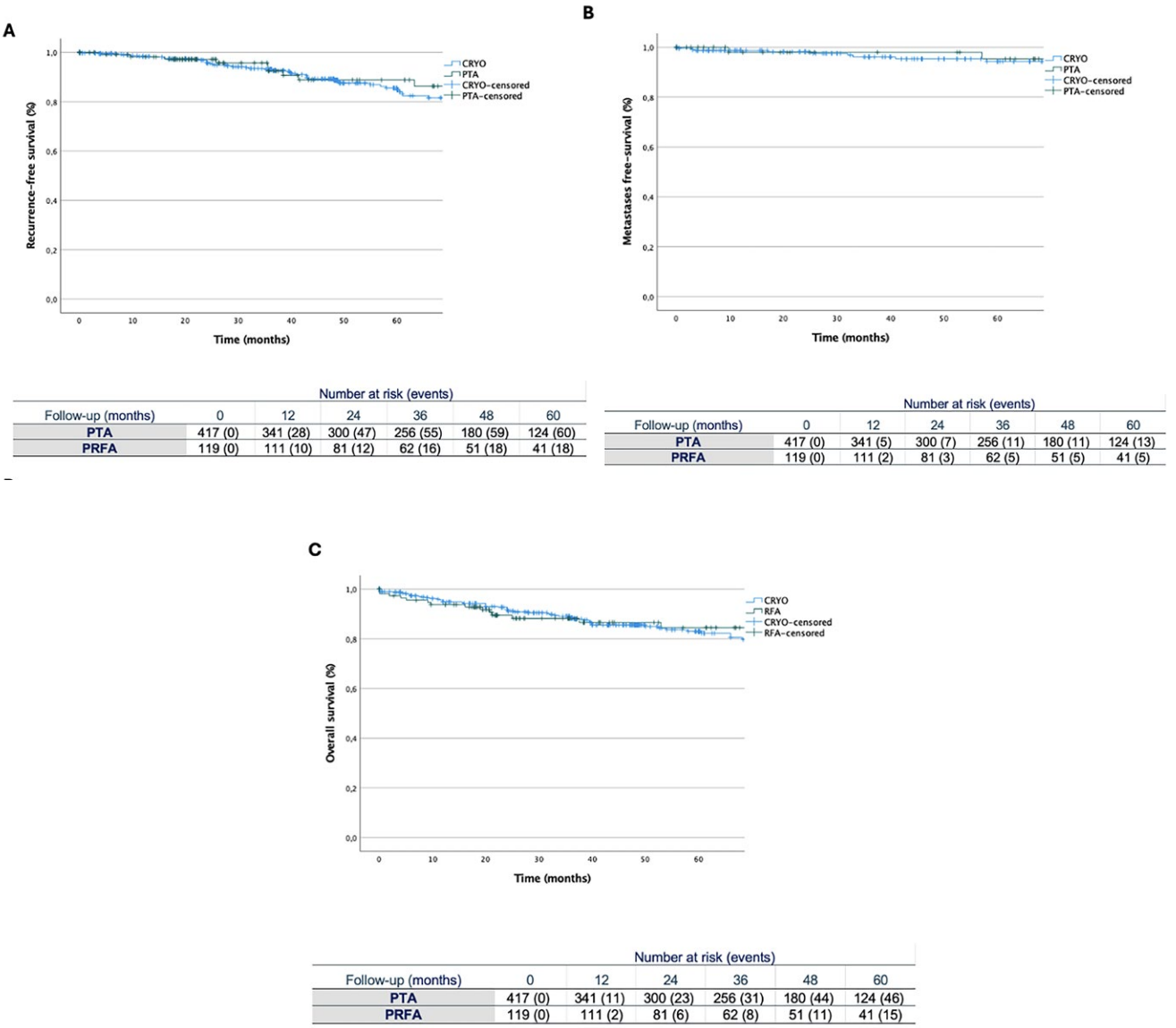
DISCUSSION

To the best of our knowledge, this study represents among the few to compare mid to long-term oncological outcomes of CRYO and RFA in a large multicenter setting. Our findings corroborate the existing evidence which is mostly based on single-center case series (Table-3).

Analyzing patients' baseline characteristics, our groups showed comparable features. Looking at those that can potentially influence the PTA outcomes such as BMI (13), tumor position (14), and complexity of the renal mass (15) we found no differences in the two groups. This mitigates potential selection bias and confounding factors, especially analyzing the oncological outcomes.

No significant difference between CRYO and RFA was observed in terms of oncological outcomes. Image-based technical success was achieved in 96.5% of patients after CRYO and 93.4% after RFA, without difference (p=0.09). Concerning RFA, early results by Tracy et al. indicated a technical success rate of 97% after the primary procedure, with a mean follow-up of 27 months (16). More recent data with a

Figure 1 - Kaplan-Meier curves of oncological outcomes for patients undergoing percutaneous thermal ablation: A) recurrence-free survival; B) metastasis-free survival; C) overall survival.



Number at risk (events)

Follow-up (months)	0	12	24	36	48	60
PTA	417 (0)	341 (28)	300 (47)	256 (55)	180 (59)	124 (60)
PRFA	119 (0)	111 (10)	81 (12)	62 (16)	51 (18)	41 (18)

Number at risk (events)

Follow-up (months)	0	12	24	36	48	60
PTA	417 (0)	341 (5)	300 (7)	256 (11)	180 (11)	124 (13)
PRFA	119 (0)	111 (2)	81 (3)	62 (5)	51 (5)	41 (5)

Number at risk (events)

Follow-up (months)	0	12	24	36	48	60
PTA	417 (0)	341 (11)	300 (23)	256 (31)	180 (44)	124 (46)
PRFA	119 (0)	111 (2)	81 (6)	62 (8)	51 (11)	41 (15)

longer follow-up at 62.8 months showed a success rate of 90% after RFA treatment (17). As for CRYO, our success rate aligns with those reported in the literature. Indeed, two single-arm retrospective studies assessed a success rate of 95% (14, 18). Our comparative analysis reaffirms these promising results of percutaneous TA, extending them to a large multi-institutional setting (19). It can be argued that the use of computed tomography during the percutaneous approach offers a more precise visualization of the ice ball for CRYO and facilitates treatment monitoring for both modalities, in contrast to the use of ultrasound in laparoscopic technique (20). Indeed, intraoperative ultrasound guidance can play a valuable role in developing a tailored surgical approach during kidney surgery (21).

When we look at time-to-event outcomes, our cohort shows encouraging results, without sig-

Table 3 - Review of the available literature on percutaneous thermal ablation.

Author	Year	Design	Technique	Patients	Outcomes*				Follow-up (months)
					RFS	CSS	OS	Success rate	
Tracy, et al. (16)	2010	Single center Single arm Retrospective	RFA	215	93%		85%	97%	27
Marshall, et al. (17)	2020	Single center Single arm Retrospective	RFA	100	92%		75%	^100%	62.8
Kim, et al. (39)	2013	Single center Single arm Retrospective	CRYO	124	85%	100%	85%	87%	30.2
Knox, et al. (18)	2020	Single center Single arm Retrospective	CRYO	277				95.6%	27.4
Bhagavatula, et al. (40)	2020	Single center Single arm Retrospective	CRYO	307	RFS: 88% Local RFS: 95%	99%	76%		41
Stacul, et al. (14)	2021	Multicenter Single arm Retrospective	CRYO	338	82.4%		91%	95.9%	26.9
Andrews, et al. (25)	2019	Single center Comparative Retrospective	PN vs CRYO/ RFA	1422	PN: 97.7% RFA: 95.9%, CRYO: 95.9% p>0.05	PN: 99.3% RFA: 95.6% CRYO: 100% p>0.05	PN: 92% RFA: 72% CRYO: 77% p<0.05		6.3-9.4 years
Millan, et al. (24)	2022	Multicenter Comparative Retrospective	PN vs CRYO/ RFA	2276	PN: 97.4% PTA: 88.1% p<0.05		PN: 99% PTA: 97.4% p=0.9		24-28.8

* Review of the available literature on percutaneous thermal ablation

nificant differences between the two groups. RFS rates were 85.7% and 84.9% at 5 years after CRYO and RFA, respectively (p=0.2). MFS rates of 96.9% for CRYO, and 95.8% for RFA were reported (p=0.4). Moreover, OS was 89% and 87.4% for CRYO and RFA, respectively (p=0.8). While these outcomes are in line with those previously reported in literature (22), evidence comparing ablative treatments to PN remains inconclusive (23). Millan et al. directly compared PN to PTA, revealing a significantly higher 2-year local or distant RFS for the former (97.4% vs 88.1%, p=0.003) (24). However, the relatively short follow-up period and potential sample size discrepancies after propensity-score matching may account for these conflicting results. Conversely, Andrews et al. reported no significant differences in local RFS (PN: 97.7%, RFA: 95.9%, CRYO: 95.9%, all p>0.05), and distant MFS (PN: 98%, RFA: 93%, CRYO: 100%, all

p>0.05) for cT1a renal masses, with a longer follow-up (25). In our prior experience with PN compared to PTA, we observed similar outcomes, with local recurrence occurring in 4% vs. 6.7% (p=0.3) and the onset of metastasis in 6% vs. 7.5% (p=0.4) of patients, respectively. Moreover, a superior safety profile for PTA emerged as evidenced by lower postoperative complication rates and better preservation of renal function (26). This may confer an additional advantage to PTA over PN, particularly in more fragile patients (27).

Our findings revealed a low rate of postoperative overall (9.3%), and major complications (0.9%) in the overall cohort, with no significant difference between the two techniques. Interestingly, CRYO showed significantly higher intraoperative complications when compared to RFA (3.3% vs. 0%, p=0.02). However, the clinical significance of this result is uncertain. The overall percentage of intraoperative complications remains low, and consistent with those of previous studies (28, 29). The low incidence of intra- and postoperative complications may speculate an advantage of the percutaneous approach when compared to laparoscopic procedures, as higher complication rates have been previously reported in studies on following laparoscopy TA (30). For this reason, AUA recommends a percutaneous approach when ablation is considered as a therapeutic option (3).

Another paramount outcome of nephron-sparing surgery is the preservation of renal function (31). According to a retrospective analysis by Woldu et al., PTA techniques allowed better preservation of renal parenchyma, especially when compared to PN. In their analysis, the authors observed that the kind of surgery was the strongest predictor of renal parenchyma volume preservation (32). In a multicenter comparative analysis of trifecta outcomes, we reported a significant worsening of postoperative renal function 1 year after PN, compared to PTA (33). Nevertheless, some other studies did not identify any significant differences between PN and CRYO (34) or RFA (35), making it difficult to draw conclusions on this subject. However, potential reasons for poorer parenchymal preservation after PN include the greater complexity of treated renal masses, as well as the vascular clamping and the tension created by renorrhaphy, which may contribute to additional tissue loss (32). Therefore, a comprehensive evaluation of oncological, surgical, and functional outcomes becomes pivotal when counseling patients on potential treatment options, to provide patient-tailored solutions, especially when a nephron-sparing treatment is mandatory.

We evaluated the efficacy of these techniques using a surrogate of surgical success as the trifecta, which has been extensively reported for PN (36). However, it is not routinely used for PTA studies. The trifecta can help authors compare different studies and techniques. In our cohort, CRYO and RFA appeared comparable in trifecta achievement rates. Our analysis suggested that BMI and a higher RENAL score could adversely affect trifecta achievement. Similar findings were observed in the trifecta analysis of patients undergoing PN, where these same variables, among others, were inversely related to trifecta achievement (37). Indeed, this composite outcome corroborates the overall success quality of these procedures and the comparability of their long-term results.

This study provides novel insights into the long-term efficacy of CRYO and RFA as nephron-sparing treatments for SRMs in a multicenter international cohort, differing from prior studies limited to single-center data. Moreover, the application of trifecta outcomes as a comprehensive measure of treatment quality, an approach rarely used in PTA research, advances our understanding of the optimal application of these techniques.

Our study has limitations that should be recognized when interpreting our findings. Firstly, the retrospective design has inherent biases that could undermine the accuracy of our results. Furthermore, its multicentric nature could imply dissimilarities in terms of surgical techniques and follow-up protocols, potentially resulting in discrepancies in outcomes. However, despite these constraints, our study presents a large multicenter cohort comparison of long-term oncologic outcomes between CRYO and RFA. Future research and prospective clinical trials are warranted to address the need for high-quality prospective data regarding the clinical effectiveness of PTA in treating SRMs. A recent feasibility study demonstrated the viability of a cohort-embedded randomized controlled trial comparing PTA and robot-assisted PN (38).

CONCLUSIONS

CRA and RFA ablation both provide favorable and durable cancer control and preservation of renal function in the treatment of cT1a renal masses. While complication profiles between the two techniques vary slightly, their comparable long-term oncologic outcomes support their use as effective nephron-sparing alternatives for poor surgical candidates. Prospective studies are encouraged to further substantiate these findings and refine patient selection criteria.

COMPLIANCE WITH ETHICAL STANDARDS

Ethics approval and consents

This study was conducted in accordance with the Declaration of Helsinki on ethical principles for medical research involving human subjects. It obtained exempt status after being reviewed by the local Ethics Committee. All patients provided written informed consent for the inclusion of their data in the database and for their use for scientific research purposes.

Availability of Data and Materials

The database and the raw results of the data analysis are available upon reasonable request to the corresponding author.

CONFLICT OF INTEREST

Jihad Kaouk is a speaker for Intuitive, a consultant to Method AI and VTI, and research sponsorship PI Medtronics. Authors have no other conflict of interest to declare

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Biplanar or Monoplanar Prostate Biopsy: Should Transrectal and Transperineal Approaches be Combined for Prostate Cancer Detection?

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ABSTRACT

Purpose: The accurate diagnosis of prostate cancer (PCa) remains challenging, particularly because standard biopsy techniques do not routinely include anterior zone, leading to potential missed diagnoses in this region. This study evaluates the accuracy and safety of biplanar stereotactic biopsy for diagnosing anterior clinically significant PCa (csPCa).

Materials and Methods: After propensity score matching analysis, data from 256 patients were retrospectively analyzed, including 128 in the biplanar group (transrectal targeted biopsy with transperineal systematic biopsy) and 128 in the monoplanar group (transperineal targeted biopsy with transperineal systematic biopsy). PCa detection rates, lesion locations, csPCa, clinically insignificant PCa (ciPCa), and complication incidences were compared. Univariable and multivariable logistic regression models evaluated factors influencing biopsy outcomes.

Results: No significant differences were observed in overall PCa detection, ciPCa, posterior lesions, or postoperative complications between biplanar and monoplanar groups. The biplanar group demonstrated a higher detection rate for anterior csPCa (P=0.025). The overall International Society of Urological Pathology grade group (ISUP GG) distributions for Prostate Imaging Reporting and Data System (PI-RADS) scores 3 to 5 were not significantly different. Logistic regression identified age and PSA levels as independent predictors of higher detection rates, while univariable analysis showed that prostate volume had a significantly smaller effect on PCa detection rates in the biplanar group compared to the monoplanar group. Postoperative complications showed no statistically significant differences.

Conclusions: In conclusion, biplanar stereotactic biopsy was superior to monoplanar biopsy in detecting anterior csPCa. Both methods demonstrated no significant differences in overall PCa detection rates and safety.

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INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed cancer in males worldwide, ranking first in Europe and the United States (1). In recent years, the incidence of PCa has been increasing in China (2). Transrectal prostate biopsy (TRBx) primarily detects PCa in the posterior region of the prostate, but it has limited effectiveness in identifying cancers located in the anterior portion (3). Transrectal ultrasound (TRUS)-guided biopsies have been the routinely performed technique for detecting PCa, however, this method suffers from inadequate visualization of the target, leading to the underdiagnosis of clinically significant PCa (csPCa) (4).

Transperineal prostate biopsy (TPBx), by improving the sampling of the anterior prostate, has been shown to increase the detection of csPCa in patients under active surveillance, which underscores the importance of early intervention in reducing the likelihood of disease progression and associated morbidity (5). Furthermore, the development of multiparametric magnetic resonance imaging (mpMRI) and the introduction of Prostate Imaging Reporting and Data System (PI-RADS) have significantly influenced the diagnostic approach to PCa, particularly for csPCa (6). Studies indicate that MRI-TBx achieves higher detection rates of csPCa while reducing the identification of clinically insignificant prostate cancer (ciPCa) compared to systematic biopsy (7). The biplanar stereotactic biopsy method, which combines transrectal targeted biopsy with transperineal systematic biopsy, is designed to capitalize on the sensitivity of mpMRI. It was observed that prostate evasive anterior tumors were detected late and often presented with high grades (8). Both biopsy methods were performed by the same group of urologists, all with the same qualifications and expertise.

In our study, we aimed to investigate whether biplanar stereotactic biopsy could offer an advantage in detecting anterior csPCa compared to monoplanar biopsy, which combines transperineal targeted biopsy with transperineal systematic biopsy. To minimize confounding factors, we applied propensity score matching (PSM) to control for selection bias. This study has the potential to propose a prostate biopsy method that enhances the detection rate of csPCa, particularly in the anterior region.

MATERIALS AND METHODS

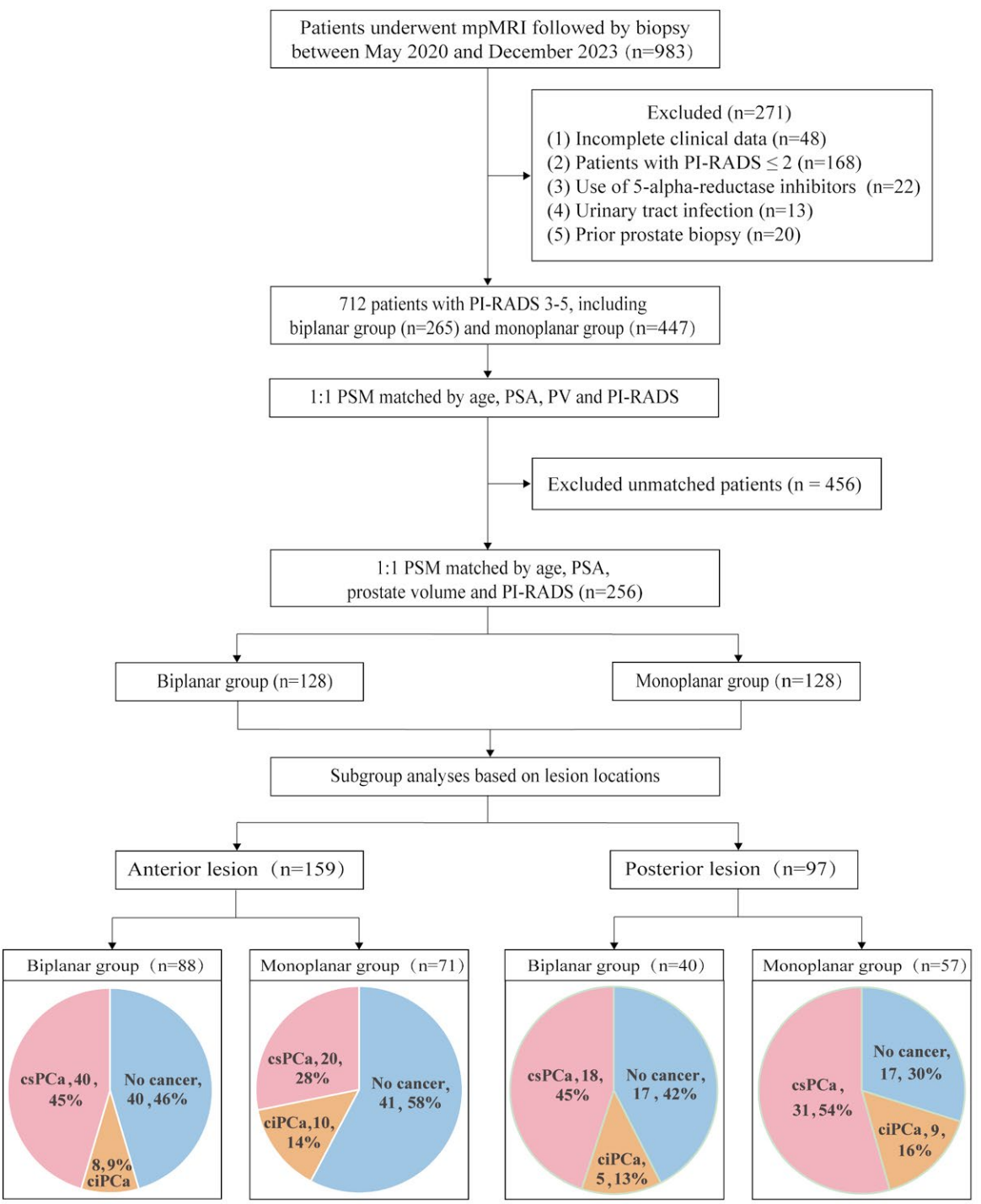
Study population

The study retrospectively included the clinical data of 983 patients admitted to Shanghai General Hospital for prostate biopsy from May 2020 to December 2023. After applying the exclusion criteria, 271 patients were excluded, leaving a total of 712 patients. The cohort was subdivided into two groups based on the technique used at the two campus divisions of Shanghai General Hospital: 265 patients at the northern campus underwent biplanar biopsy, while 447 patients at the southern campus underwent monoplanar biopsy. Following 1:1 PSM, a final cohort of 256 patients was selected, including 128 patients in the biplanar group and 128 in the monoplanar group. Eligible patients for the study were those with the following criteria: (1) elevated prostate-specific antigen (PSA>4 ng mL-1); (2) abnormal digital rectal examination; (3) monitoring of PCa; (4) PI-RADS score greater than 2. Exclusion criteria included the following: (1) a negative multiparametric MRI (PI-RADS ≤ 2); (2) incomplete clinical data; (3) use of 5-alpha-reductase inhibitors in the past 6 months; (4) presence of a urinary tract infection or prostatitis within the preceding three months; (5) patients with prior prostate biopsy. Figure-1 illustrates the flowchart of subject selection. This study was approved by the Shanghai General Hospital Clinical Research Ethics Committee (Institutional Review Board number: IRB: K-2024-011) and registered in the Chinese Clinical Trial Register (ChiCTR2400087842).

Clinical characteristics

In this retrospective study, all available cases were collected for comprehensive evaluation of both methods using medical records and medical coding information. The study gathered data on patient age, pre-biopsy PSA levels, MRI reports prior to biopsy,

Figure 1 - Flow chart and diagnostic accuracy for detection of anterior and posterior PCa between biplanar and monoplanar groups. PI-RADS, Prostate Imaging Reporting and Data System; ciPCa, clinically insignificant prostate cancer; csPCa, clinically significant prostate cancer.

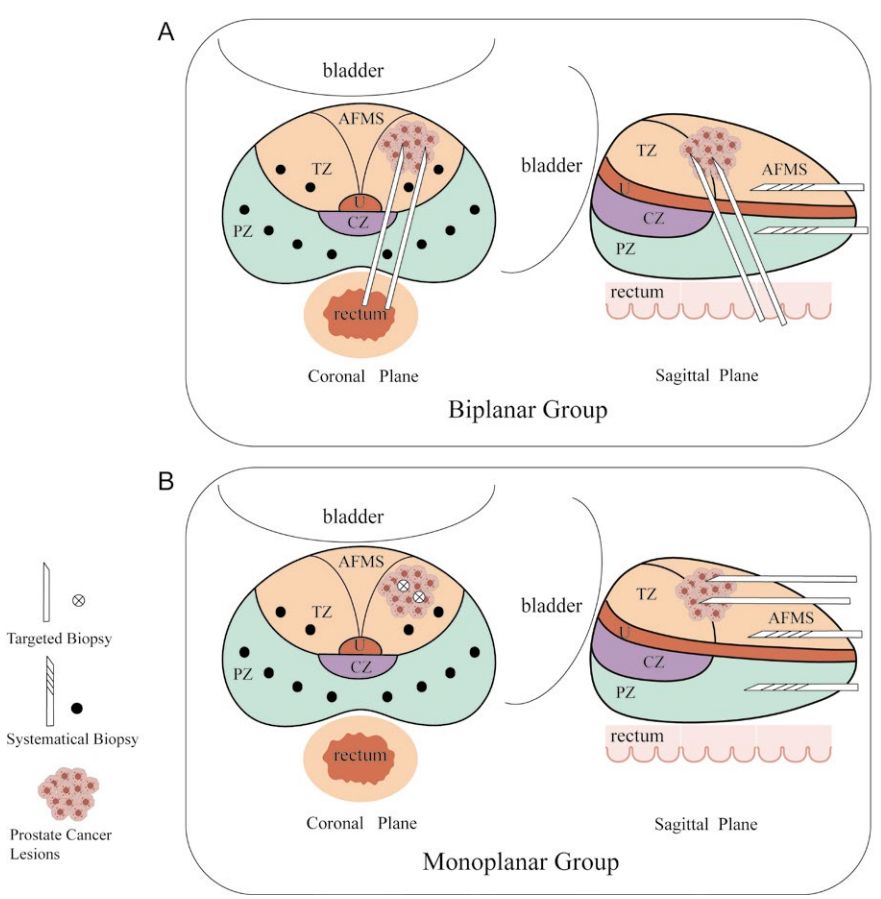


biopsy indications, and results of histopathological examination. Prostate volume was measured using TRUS and calculated with the ellipsoid volume formula: Prostate volume (mL) = (π/6) × (anterior-posterior diameter [cm]) × transverse diameter (cm) × superior-inferior diameter (cm).

Biopsy protocol

All patients received either biplanar stereotactic biopsy or monoplanar biopsy within one week following their mpMRI examination. A rectal needle guider was used to target suspicious cancer regions identified on mpMRI, guided by an ultrasound fusion device (GE Logic E9, GE Healthcare, Milwaukee, WI, USA). Biopsies were performed using a Bard biopsy gun equipped with disposable 18-G needles (MC1616 and MC1820, Bard Company, USA). Figure-2 illustrates the biplanar and monoplanar biopsy schemes. In the biplanar group, TRBx were performed to obtain 2-4 cores from each lesion, with assistance from MRI-TRUS image fusion software (Supplementary Figure-1). For the monoplanar group, 2-4 targeted TPBx cores were acquired from each lesion, utilizing the ultrasound device for transperineal targeted biopsy (HI VISION Preirus, Hitachi Medical Systems, Japan). After the targeted biopsy, a 12-core systematic transperineal biopsy was performed, and the standardized biopsy specimens were sent for patho-

Figure 2 - Schemes of biplanar biopsy and monoplanar biopsy. (A) Schemes of biplanar biopsy on prostatic coronal and sagittal plane. (B) Schemes of monoplanar biopsy on prostatic coronal and sagittal plane. TZ, transition zone; PZ, peripheral zone; CZ, central zone; AFMS, anterior fibrous muscle matrix; U, urethra.



logical analysis. Both biopsy methods were performed by the same group of urologists, all with the same qualifications and expertise.

Pathology and PCa diagnosis

The pathologic evaluation of the biopsy cores, which was conducted and cross-verified in a blinded manner to reduce potential bias, reported the number of total positive cores/total cores, Gleason score, and the International Society of Urological Pathology grade group (ISUP GG). The cancer suspicious regions identified through mpMRI offered relevant information about the location of PCa lesion. Regarding the urethral level as a reference, PCa were further classified into anterior and posterior lesions (Supplementary Figure-2). Lesions identified on MRI were characterized according to the PI-RADS criteria. Histopathology results were classified using the ISUP GG, with PCa lesions scoring ISUP GG 2–5 deemed csPCa. Lesions with a maximum ISUP GG of 1 were regarded as clinically insignificant PCa (ciPCa).

Propensity score matching

To minimize confounding factors and reduce bias between the two groups, the cohorts were matched using propensity scores derived from logistic regression based on patients' age, PSA, prostate volume, and PI-RADS scores. Biplanar group patients were matched to monoplanar group patients at a 1:1 ratio using a nearest neighbor matching algorithm. A caliper width of 0.25 standard deviations of the logit of the propensity score was applied. After matching, 128 patients were selected in each group, with unmatched patients excluded from further analysis. This achieved balance across covariates as confirmed by standardized mean differences below 0.1 for all variables. Post-matching, the balance was assessed and confirmed through visual inspection of propensity score distributions and by calculating standardized mean differences. Additionally, a jitter plot of individual cases, a histogram of individual differences, and a histogram of standardized differences were generated (Figure-3). PSM was conducted using the 'matching' package in R version 4.2.0 (R Project for Statistical Computing) (9).

Statistical analysis

Measurement data were expressed as mean ± standard deviation for normally distributed data, or median with interquartile range (IQR) for non-normally distributed data. Count data were expressed as frequency (n) and percentage (%) with the chi-square test, and differences were considered statistically significant at $P < 0.05$. To compare the clinical characteristics of patients between the groups, we employed Student's t-tests and Mann–Whitney U tests. The chi-square test, univariate and multivariate logistic regression analyses were used to compare the two groups. In both multivariable and univariable analyses, the effects were quantified using odds ratios with 95% confidence intervals. All analyses were conducted using SPSS (version 27.0) for general statistical tests, and the R package was utilized for PSM to ensure precise bias control and group balance.

RESULTS

Characteristics of patients

From May 2020 to December 2024, we identified 983 patients underwent mpMRI followed by prostate biopsy and 271 patients were excluded after the exclusion criteria were applied. A total of 256 patients were included in this study after PSM, with 128 men in the biplanar group and 128 men in the monoplanar group (Figure-1). The characteristics of patients in the two groups are shown in Table-1. A comparison of pre-procedure demographics, including age, PSA, and prostate volume, showed good match between the two groups ($P \geq 0.05$). The differences in the number of biopsy cores taken, number of targeted biopsy cores taken, positive cores, and PI-RADS scores between the two groups were not statistically significant ($P \geq 0.05$). The monoplanar group had a significantly higher mean number of positive targeted biopsy cores compared to the biplanar group ($p = 0.004$), indicating a statistically significant difference.

Prostate cancer detection rate based on lesion location

Table-2 outlines the diagnostic outcomes for both anterior and posterior prostate lesions in the bi-

Figure 3 - Equitable comparison of baseline covariates (age, PSA levels, prostate volume, and PI-RADS) distribution between the biplanar and monoplanar groups for diagnostic assessment. (A) Jitter plot showing individual patients' propensity score distribution for biplanar and monoplanar groups. (B) Histogram depicting the distribution of patients' propensity scores in the biplanar and monoplanar groups. (C) Baseline covariate differences before and after matching.

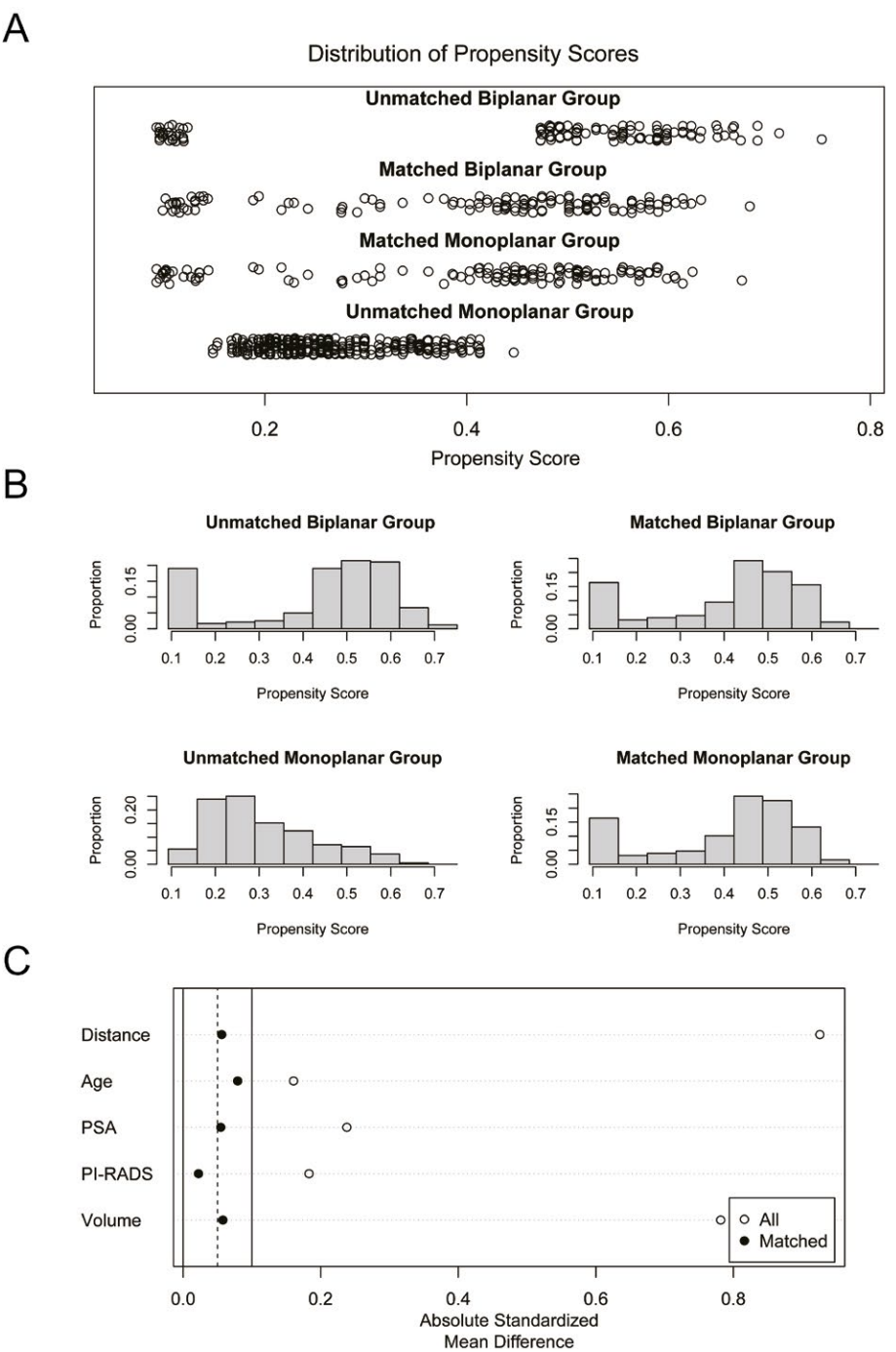


Table 1 - Characteristics of patients according to prostate biopsy method.

	Biplanar group (n=128)	Monoplanar group (n=128)	p value
Age, year, median (IQR)	67 (62-73)	67 (62-72)	0.434 [a]
PSA, ng/mL, median (IQR)	9.8 (8.0-13.9)	9.2 (7.5-13.6)	0.193 [b]
Prostate volume, mL, mean (IQR)	52.1 (40.6-61.4)	51.0 (41.8-59.9)	0.506 [b]
PI-RADS			
PI-RADS=3	73 (56.0%)	71 (55.5%)	0.801 [c]
PI-RADS=4	18 (14.4%)	21 (16.4%)	0.602 [c]
PI-RADS=5	37 (29.6%)	36 (28.1%)	0.953 [c]
Number of cores taken, mean (IQR)	14.37 (14-15)	14.62 (12-15)	0.162 [b]
Number of targeted biopsy cores taken, mean (IQR)	2.6 (2-3)	2.6 (2-3)	0.962 [b]
Positive cores, mean (IQR)	2.2 (1-4)	2.3 (1-3)	0.653 [b]
Positive targeted biopsy cores, mean (IQR)	0.2 (0-1)	0.4 (0-1)	0.054 [b]
Number of positive cores, n (%)	Biplanar group (n=71)	Monoplanar group (n=70)	
1	15 (21.1%)	14 (20.0%)	0.835 [c]
2-3	22 (31.0%)	25 (35.7%)	0.591 [c]
4-12	33 (46.5%)	30 (42.9%)	0.610 [c]
>12	1 (1.4%)	1 (1.4%)	1.000 [d]

SD = standard deviation; PSA = prostate-specific antigen; IQR = Interquartile Range

[a] student`s t test; [b] Mann–Whitney U test; [c] chi-square test; [d] Fisher's exact test

Table 2 - PCa detection rates stratified by PCa lesion's location.

Biopsy outcomes per subanalysis			p value [a]
	Biplanar group (n=128)	**Monoplanar group (n=128)**	
Overall detection rate	71 (55.5%)	70 (54.7%)	0.900
ciPCa	13 (10.2%)	19 (14.8%)	0.257
csPCa	58 (45.3%)	51 (39.8%)	0.376
	Biplanar group (n=40)	**Monoplanar group (n=57)**	
Positive biopsy rate of posterior lesion	23 (57.5%)	40 (70.2%)	0.198
Posterior ciPCa	5 (12.5%)	9 (15.8%)	0.650
Posterior csPCa	18 (45.0%)	31 (54.3%)	0.514
	Biplanar group (n=88)	**Monoplanar group (n=71)**	
Positive biopsy rate of anterior lesion	48 (54.5%)	30 (42.3%)	0.123
Anterior ciPCa	8 (9.1%)	10 (14.1%)	0.323
Anterior csPCa	40 (45.5%)	20 (28.2%)	0.025

PCa = prostate cancer; ciPCa = clinically insignificant prostate cancer; csPCa = clinically significant prostate cancer

[a] chi-square test.

planar and monoplanar groups. Overall, 71 (55.5%) of the patients had PCa detected in the biplanar group, of which 58 (45.3%) were csPCa. The monoplanar group identified 70 cases (54.7%) of PCa and 51 cases (39.8%) of csPCa. Comparing the biplanar group and the monoplanar group, we found no statistically significant difference in terms of the overall detection rate, csPCa detection rate and ciPCa detection rate (P > 0.05). The detection efficiency of biplanar biopsy compared to monoplanar biopsy, stratified by ISUP GG, is detailed in Supplementary Figure-3. When comparing the detection rates of anterior and posterior PCa lesions for the two biopsy methods separately, it was found that the biplanar biopsy had an advantage in detecting anterior PCa lesions. The histopathological findings of the posterior PCa lesion biopsy indicate that there is no statistically significant difference between the two biopsy groups in detecting posterior PCa lesion and ciPCa (P > 0.05). The anterior csPCa lesion detection rate in the biplanar group was 45.5%, which was higher than that in the monoplanar group (28.2%), and the difference was statistically significant (P = 0.025; Table-2).

To investigate whether there was a selection bias in PI-RADS scores between the two groups that could affect the detection rates of PCa, we compared the detection rates of patients in both groups under different PI-RADS scores. Supplementary Table-1 presents the breakdown of PI-RADS scores for cases identified as csPCa and ciPCa in the biplanar and monoplanar biopsy groups. There was no statistically significant difference in the distribution of patients with PI-RADS scores of 3-5 between the two groups (P > 0.05). Supplementary Table-2 presents the biopsy pathology results of patients in both groups under different PI-RADS scores, stratified by tumor location. Therefore, the advantage of biplanar biopsy in detecting anterior csPCa is not attributable to differences in PI-RADS scores between the two groups.

ISUP distribution by PI-RADS scores

Supplementary Table-3 shows the distribution of ISUP GG in patients with different PI-RADS scores for both biplanar and monoplanar biopsy groups. The data highlight that for patients with a PI-RADS score of 5, the probability of having an ISUP GG ≥ 4 was 51.4% in the biplanar group compared to 38.9% in the monoplanar group. Despite this observed difference, no statistically significant differences were found between the two groups in terms of the distribution of ISUP GG for PI-RADS scores 3 to 5 (P > 0.05). This suggests that while the biplanar method shows a higher detection rate of more aggressive cancers (ISUP GG ≥ 4) in patients with a PI-RADS score of 5, both biopsy methods provide comparable pathological results overall for PCa detection.

Predictors of prostate cancer detection

Multivariable and univariable logistic regression analyses identified age and PSA levels as independent predictors of higher detection rates in both the biplanar and monoplanar groups (Table-3). Patients with lower prostate volume who underwent monopla-

Table 3. Univariable and multivariable binary logistic regression for analyzing the effects of biopsy methods and patients` clinical characteristics on prostate cancer detection rate

	Univariable analysis		Multivariable analysis	
	Biplanar group, OR (95% CI), p value [a]	Monoplanar group, OR (95% CI), p value [a]	Biplanar group, OR (95% CI), p value [a]	Monoplanar group, OR (95% CI), p value [a]
Age	1.026 (0.989-1.065), 0.011	1.068 (1.015-1.123), 0.012	1.071 (1.018-1.127), 0.008	1.058 (0.996-1.124), 0.047
PSA	1.032 (1.023-1.041), < 0.001	1.041 (1.026-1.055), < 0.001	1.042 (1.037-1.078), < 0.001	1.039 (1.022-1.055), < 0.001
Prostate volume	0.953 (0.874-1.039), 0.271	0.983 (0.902-1.071), 0.039	0.907 (0.805-1.021), 0.107	0.958 (0.862-1.066), 0.432
PI-RADS				
PI-RADS=3*	-	-	-	-
PI-RADS=4	2.677 (0.927-7.728),0.069	4.896 (1.685-14.228), 0.004	3.041 (3.010-3.163), <0.001	5.621 (1.753-18.022), 0.004
PI-RADS=5	14.056 (4.489-44.006), <0.001	12.142 (4.186-35.217), <0.001	13.106 (13.021-13.527), 0.006	15.169 (4.689-49.074), <0.001

PSA = prostate-specific antigen; CI = confidence interval; OR = odds ratio.
[a] multivariable binary logistic regression; *reference group.

nar biopsy initially showed a higher detection rate (OR: 0.983, 95% CI: 0.902–1.071, P = 0.027). However, this association lost significance after multivariate adjustment (OR: 0.958, 95% CI: 0.862–1.066, P = 0.432). Stratifying the cohort by maximal PI-RADS score showed that detection rates of PCa were significantly higher for patients with PI-RADS scores of 4 or 5 compared to those with a score of 3 in both groups.

Comparison of biopsy complications

The comparison of biopsy complications between the two groups revealed no statistically significant differences in postoperative hematuria, acute urinary retention, infection, and rectal bleeding (P > 0.05). Specifically, 28 patients (21.9%) in the biplanar group and 41 patients (32.0%) in the monoplanar group presented with hematuria, with the difference in incidence not being statistically significant (P=0.067). Additionally, two patients (1.6%) in the biplanar group and three patients (2.3%) in the monoplanar group experienced acute urinary retention, with no statistically significant difference in the incidence between the two groups (P > 0.05). Importantly, no cases of infection or rectal bleeding were observed in either group.

DISCUSSION

Since Hodge introduced the 6-core TRUS-guided biopsy as the standard for prostate biopsy, it still faced a high rate of missed diagnoses (10). To refine biopsy techniques, we aim to explore whether biplanar stereotactic biopsy can enhance PCa detection rates while minimizing complications. In this study, mpMRI-TRUS targeted biopsy was employed in both groups combined with systematic biopsy, as it offers significant advantages in detecting csPCa compared to systematic biopsy (42% vs. 26%, respectively) (11). Recent studies have shown that combining targeted biopsy with systematic biopsy significantly increased the overall detection rate of PCa (12). Additionally, MRI-TRUS targeted biopsy reduces the overdiagnosis of ciPCa, leading to less overtreatment (13). Siddiqui observed a 30% increase in csPCa detection with MRI-TRUS fusion targeted biopsy compared to systematic biopsy, while the detection rate of ciPCa decreased by 17% (14). This study utilized a 12-core transperineal systematic biopsy, which has been shown to improve the detection rate of PCa without increasing complications compared to the 6-core transperineal systematic biopsy (15).

The results of our study showed no significant difference in the overall detection rate of PCa, ciPCa, and posterior PCa between the biplanar and monoplanar groups (P > 0.05). Specifically, systematic biopsies in both groups were performed via the transperineal route. Prostate evasive anterior tumor syndrome describes anteriorly located tumors that can evade standard biopsy techniques but are detectable through MRI, highlighting the need for further examination to rule out PCa (16). Given these challenges in detecting anterior lesions, TPBx offers greater flexibility and accuracy, allowing for more extensive sampling of the peripheral zone tissue and a higher detection rate of csPCa in the anterior prostate, which might be missed by TRBx. Pepe et al. demonstrated that the transperineal route achieved a markedly higher detection rate of anterior zone csPCa compared to the transrectal approach, with rates of 93.3% versus 25% (17). Therefore, the use of TPBx for systematic biopsy in both groups in this study helps to mitigate the potential bias of missing anterior lesions with TRBx, strengthening the credibility of the biplanar biopsy's advantage in detecting anterior lesions.

In comparing the detection rates of anterior csPCa between the two groups of PSM-matched patients, the biplanar approach demonstrated superiority over the monoplanar biopsy method (P < 0.05). This difference may be attributed to the advantages of biplanar stereotactic biopsy, which combines transperineal and transrectal approaches, allowing biopsies in both transverse and sagittal planes, thus providing a broader sampling area. Both systematic and targeted biopsies encounter difficulties in detecting apical lesions, but a combined biopsy approach can significantly enhance detection rates of PCa (18). Targeted biopsy frequently misses cancers in the

posterior region, while TRUS-guided biopsy often fails to identify lesions located in the anterior region (19). The biplanar biopsy method combines transrectal and transperineal approaches, offering broader access to different prostate regions and improving detection, particularly for hard-to-reach anterior lesions. The transrectal approach may be more effective in patients with prostate volumes of 30–80 mL and advanced stages (T3–T4), whereas the transperineal approach shows greater efficacy in detecting cancers at earlier stages (T1–T2) (20). The increased sampling area of the biplanar method, similar to the regional saturation biopsy approach shown to improve the detection of clinically significant prostate cancer by enhancing coverage of suspected regions, potentially reduces the chance of missing significant cancerous lesions, leading to more accurate diagnoses (21). Additionally, the biplanar biopsy technique incorporates transrectal image fusion-guided biopsy, enabling the clinician to integrate TRUS and mpMRI images for precise lesion localization in the coronal plane, thereby enhancing the accuracy of targeting. In contrast, the monoplanar approach, limited to coronal plane biopsies, lacks sagittal plane sampling, which complicates precise localization of anterior lesions using transrectal ultrasound alone (22). This limitation requires exceptional biopsy skills and accurate spatial judgment by urologists, increasing the risk of localization errors and leading to a lower detection rate of clinically significant PCa (23). This makes the biplanar biopsy an effective screening method for anterior PCa when indicated by mpMRI.

The results of both univariable and multivariable logistic regression analyses identified age and PSA levels as significant independent predictors of PCa detection in both biplanar and monoplanar groups. Interestingly, in the monoplanar group, lower prostate volume initially appeared to be associated with higher detection rates, but this lost significance after multivariate adjustment, suggesting other factors like age and PSA were more impactful (24, 25). Furthermore, when stratifying by PI-RADS scores, patients with PI-RADS 4 or 5 had notably higher detection rates compared to those with a score of 3 in both biopsy groups (26). The strong predictive value of PI-RADS scores, aligns with findings from prior studies, including the recent validation of the BCN-MRI PM, which demonstrated that mpMRI could reliably predict csPCa, further emphasizing their utility in PCa detection (27, 28). While both biopsy methods showed similar predictive trends, the data suggest that a more individualized approach considering patient-specific factors such as age, PSA levels, and PI-RADS scores could optimize diagnostic accuracy.

There was no significant difference in the incidence of hematuria or urinary retention between the two groups following biopsy ($P > 0.05$). This aligns with the findings of the recent ProBE-PC trial, which demonstrated that there were no significant differences in postoperative complication rates between TRBx and TPBx (29). In the biplanar group, transrectal targeted biopsy with only 2-4 cores per lesion was employed, reducing the likelihood of intestinal flora entering the bloodstream via the intestinal wall and prostate tissue, suggesting a safer procedure with a lower risk of infectious prostatitis, as seen in the lower complication rates of TPBx compared to TRBx (30). This substantial reduction in infectious complications significantly improved the safety profile of the biopsy. The remarkably low postoperative complication rates observed in this study suggest that both methods were comparably safe and effective for urological procedures.

This investigation has several limitations. Firstly, as a retrospective study, it may be subject to inherent limitations. Although we attempted to minimize confounding factors such as age, PSA, and prostate volume through PSM, the process could not fully eliminate selection bias. A prospective study and blinded data processing would be valuable in further validating our result. Secondly, this was a single-center study with limited PSM samples. Future studies with larger sample sizes and multicenter designs are needed to validate these findings. Finally, there may be pathological verification bias, particularly in patients diagnosed as cancer-free, since biopsy outcomes were used as the reference rather than surgical pathology results.

CONCLUSION

Biplanar stereotactic biopsy demonstrates a notable advantage over monoplanar biopsy in the detection of anterior csPCa lesions. Both biplanar stereotactic biopsy and transperineal monoplanar biopsy effectively detect PCa and ciPCa, while maintaining comparable safety. In both biopsy groups, age and PSA levels were key independent predictors of PCa detection, with the biplanar biopsy showing less impact from prostate volume compared to the monoplanar biopsy. Biplanar stereotactic biopsy may serve as an effective screening approach for detecting anterior csPCa identified by mpMRI.

ABBREVIATIONS

ISUP = International Society of Urological Pathology
PI-RADS = Prostate Imaging Reporting and Data System
PCa = Prostate cancer; csPCa: Clinically significant prostate cancer
ciPCa = Clinically insignificant prostate cancer
TRUS = Transrectal Ultrasound-Guided
TPB = Transperineal biopsy
TRB = Transrectal biopsy
mpMRI = Multiparametric Magnetic Resonance Imaging
PSA = Prostate-specific antigen
IQR = Interquartile Range
OR = Odds ratio
CI = Confidence interval
SD = Standard deviation

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AVAILABILITY OF DATA AND MATERIALS

Data for this study can be accessed by contacting the corresponding author with a reasonable request.

COMPLIANCE WITH ETHICAL STANDARDS

This study was registered in the Chinese Clinical Trial Register (ChiCTR2400087842). Written informed consent for participation was waived due to the study's retrospective nature.

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Zeng Zhou, Tiewen Li, Yichen Zhang contributed similarly as first author

CONFLICT OF INTEREST

None declared.

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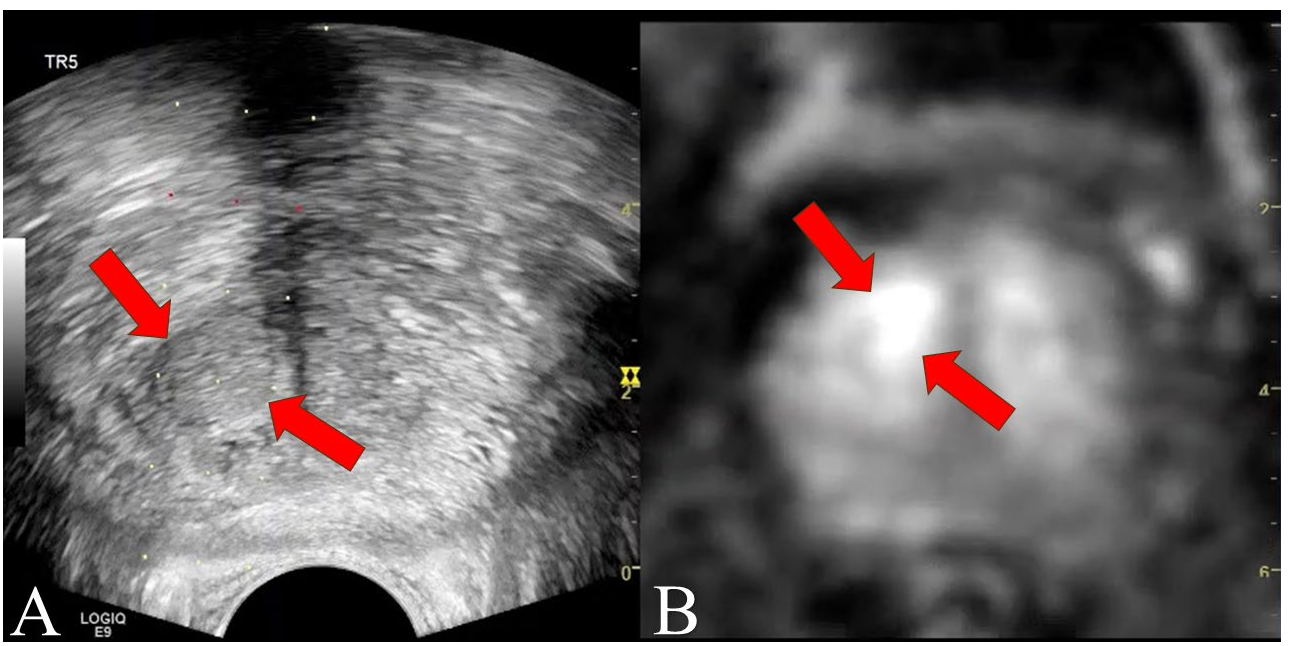
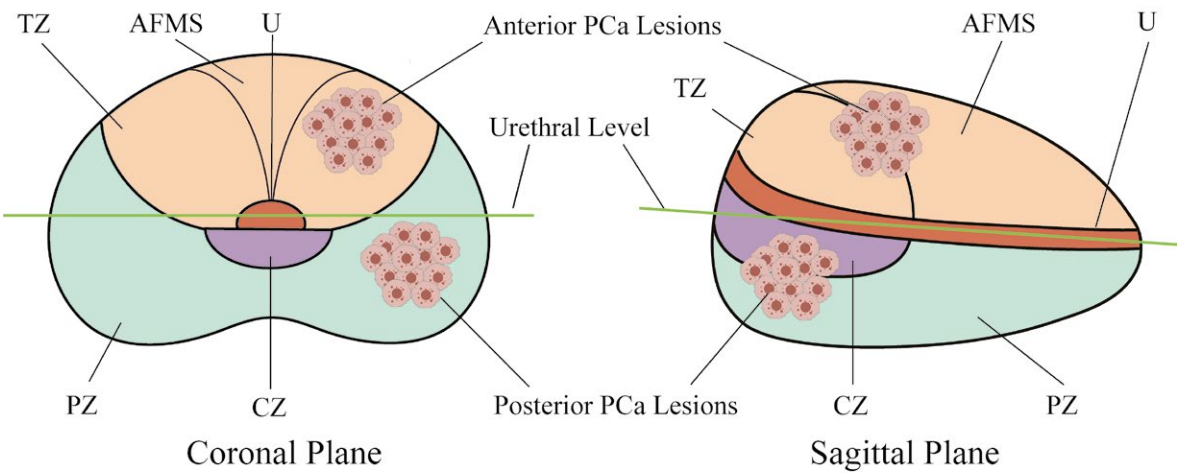
APPENDIX

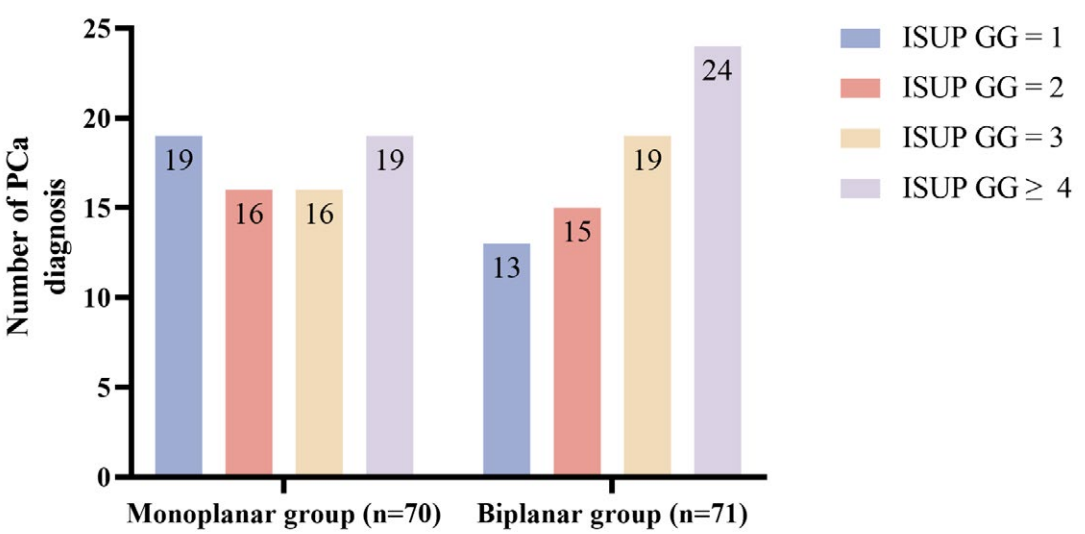
Supplementary Figure 1 - Software-assisted MRI-TRUS image fusion targeted biopsy. (a) Under transrectal ultrasound, a hypoechoic lesion is observed on the right prostate (arrows). (b) Axial diffusion weighted images (DWI) showed a large hyperintense signal lesion developed in the peripheral zone.



Supplementary Figure 2 - Anterior and Posterior Classification of Prostate Cancer Lesions in Coronal and Sagittal Planes. TZ, transition zone; PZ, peripheral zone; CZ, central zone; AFMS, anterior fibrous muscle matrix; U; urethra.



Supplementary Figure 3 - Distribution of ISUP grade group in monoplanar and biplanar groups for prostate cancer diagnosis. ISUP: International Society of Urological Pathology.



Supplementary Table 1 - Prostate cancer detection rates of three PI-RADS scores using different biopsy methods.

PI-RADS	Core Positive	Biplanar group (n=128)		Mono-planar group (n=128)		p value
3	No PCa	58.9%	(46/73)	66.2%	(47/71)	0.690[a]
	PCa	37.0%	(27/73)	33.8%	(24/71)	
	ciPCa	16.4%	(12/73)	18.3%	(13/71)	0.767[a]
	csPCa	20.5%	(15/73)	15.5%	(11/71)	0.430[a]
4	No PCa	38.9%	(7/18)	28.6%	(6/21)	0.520[b]
	PCa	61.1%	(11/18)	71.4%	(15/21)	
	ciPCa	16.7%	(3/18)	19.0%	(4/21)	0.110[b]
	csPCa	38.9%	(7/18)	52.4%	(11/21)	0.523[b]
5	No PCa	10.8%	(4/37)	13.9%	(5/36)	0.736[b]
	PCa	89.2%	(33/37)	86.1%	(31/36)	
	ciPCa	2.7%	(1/37)	5.6%	(2/36)	0.615[b]
	csPCa	86.5%	(32/37)	80.6%	(29/36)	0.494[a]

PI-RADS = Prostate Imaging Reporting and Data System; PCa = prostate cancer; ciPCa = clinically insignificant prostate cancer; csPCa = clinically significant prostate cancer
[a] chi-square test; [b] Fisher's exact test

Supplementary Table 2 - Prostate cancer detection rates of three PI-RADS scores in anterior and posterior lesions.

PI-RADS	Core Positive	Anterior Lesions (n=159)		p value	posteriors Lesions (n=97)		p value
		Biplanar group	Mono-planar group		Biplanar group	Mono-planar group	
3	PCa	35.4% (17/48)	26.1% (12/46)	0.328[a]	40.0% (10/25)	48.0% (12/25)	0.569[a]
	csPCa	20.8% (10/48)	10.9% (5/46)	0.187[a]	20.0% (5/25)	21.0% (6/25)	0.733[a]
4	PCa	54.5% (6/11)	50.0% (3/6)	1.000[b]	71.4% (5/7)	80.0% (12/15)	1.000[b]
	csPCa	54.5% (6/11)	33.3% (2/6)	0.620[b]	71.4% (5/7)	60.0% (9/15)	1.000[b]
5	PCa	86.2% (25/29)	78.9% (15/19)	0.695[b]	100% (8/8)	94.1% (16/17)	1.000[b]
	csPCa	82.8% (24/29)	68.4% (13/19)	0.304[b]	100% (8/8)	94.1% (16/17)	1.000[b]

PI-RADS = Prostate Imaging Reporting and Data System; PCa = prostate cancer; ciPCa = clinically insignificant prostate cancer; csPCa = clinically significant prostate cancer
[a] chi-square test; [b] Fisher's exact test

Supplementary Table 3 - ISUP of mono-planar and biplanar group according to the PI-RADS of the patients.

PI-RADS	Biplanar group						Mono-planar group						Total
	No PCa	ISUP=1	ISUP=2	ISUP=3	ISUP≥4	Patients	No PCa	ISUP=1	ISUP=2	ISUP=3	ISUP≥4	Patients	
3	46 (63.0%)	12 (16.4%)	8 (11.0%)	4 (5.5%)	3 (4.1%)	73	47 (66.2%)	13 (18.3%)	4 (5.6%)	3 (4.0%)	4 (5.6%)	71	144
4	7 (38.9%)	0 (0%)	4 (22.2%)	5 (27.8%)	2 (11.1%)	18	6 (28.6%)	4 (19.0%)	6 (28.6%)	4 (19.0%)	1 (4.8%)	21	39
5	4 (10.8%)	1 (2.7%)	3 (8.1%)	10 (27.0%)	19 (51.4%)	37	5 (13.9%)	2 (5.6%)	6 (16.7%)	9 (25.0%)	14 (38.9%)	36	73
Total	54 (43.2%)	13 (10.4%)	15 (8.1%)	19 (15.2%)	24 (19.2%)	128	61 (46.6%)	19 (14.5%)	16 (12.2%)	16 (12.2%)	19 (14.5%)	128	256

ISUP = International Society of Urological Pathology; PI-RADS = Prostate Imaging Reporting and Data System

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Bladder Mucosa Harvested with Holmium Laser for Treatment of Urethral Strictures: Does the Graft Have its Tissue Integrity Preserved?

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ABSTRACT

Objective: The aim of this study is to evaluate the integrity and the microstructural characteristics of the bladder mucosa graft harvested using a minimally invasive technique with the Holmium laser (Ho-YAG) for the treatment of urethral stricture.

Materials and Methods: We studied patients with urethral strictures greater than 2 cm, with a urethroplasty indication. The patients were submitted to urethroplasty with the dorsal onlay reconstruction by a single surgeon. After the urethral dissection we use the Ho-YAG laser with a 550µg end fire laser fiber to obtain a fragment of bladder mucosa for the graft confection. A fragment of the bladder mucosa was fixed in a 10% buffered formalin to HE and Masson's trichrome analysis for the tissue integrity. Five sections were stained, and five fields of each section were selected. We used the Image J software, version 1.46r, loaded with its own plug-in to determine tissue integrity.

Results: We studied 11 patients (Mean age= 47.64); 9 (81.8%) with bulbar stricture and 2 (18.2%) with penile stricture (mean size = 4.63mm). The mean of bladder graft size was 53.64mm and the meantime of harvesting was 47.63 minutes. The histological study of the bladder wall graft showed an organization in accordance with normal standards, with the presence of an intact urothelium in the bladder graft. The submucosal layer is preserved, joining the detrusor to the urothelium and the collagen and elastic fibers are well organized.

Conclusion: The graft harvested from the bladder uroepithelium using Ho-YAG has its histological integrity preserved, which makes this technique a viable option for reconstructive surgery. However, more studies are needed to establish its long-term efficacy and safety of this new technique.

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INTRODUCTION

The use of oral mucosa as a graft for the treatment of urethral stricture is well established, but not free from morbidity (1). Bladder mucosa has been utilized in various forms of urethral reconstruction, particularly in cases where other graft materials are not suitable or available (2, 3). For instance, Ozgök et al. demonstrated the use of bladder mucosa grafts in urethral reconstruction for patients with penoscrotal or scrotal hypospadias, showing a complication rate of 28.6% (4). Similarly, Monfort et al. reported successful outcomes using bladder mucosa grafts for urethral strictures in children, with most patients achieving satisfactory results (5). Additionally, Garat and Villavicencio described the use of tubularized bladder mucosal grafts for posterior urethroplasty, indicating good initial results in challenging cases (6).

More recent techniques, such as those described by Westin et al., involve the use of Holmium:YAG laser for transurethral harvesting of bladder mucosa, which has shown promising preliminary results for dorsal onlay urethroplasty (7). These studies collectively support the feasibility and effectiveness of bladder mucosa as a graft material in urethroplasty, particularly in complex or recurrent cases where other graft options may be limited.

Studies showing the histological integrity of bladder mucosa graft removed using laser have never been done. Our hypothesis is that laser removal of the bladder mucosa preserves the tissue integrity of the graft. The aim of this study is to evaluate the integrity and the microstructural characteristics of the bladder mucosa graft harvested using a minimally invasive technique with the Holmium laser (Ho-YAG) for the treatment of urethral stricture.

MATERIALS AND METHODS

The study was approved according to the ethical standards of the hospital's institutional committee on experimentation with human beings (IRB number 51456521.8.0000.5259).

We prospectively analyzed 11 patients, admitted to our service between November 2021 and January 2024. Inclusion criteria consisted of patients having a diagnosis of anterior urethral stenosis, with or without recurrence, and were indicated for urethroplasty with graft (strictures greater than 2.5 cm). Exclusion criteria included: genitourinary malformations, a history of pelvic radiotherapy, a history of bladder cancer, and those with an indication for staged urethroplasty. Every patient was staged using cystourethrography and uroflowmetry except in those using a suprapubic urinary diversion.

All surgeries were performed by a single surgeon with experience in urethral surgery. Due to the physical characteristics of the bladder mucosa (soft and tenacious tissue), we chose to perform dorsal onlay (8) or dorsum lateral onlay urethroplasty (9) to avoid diverticula formation. After placing the patient in the lithotomy position, a perineal incision was made permitting access to the bulbar urethra. The next step proceeded with either the dorsal or lateral dorsum urethral dissection and following with location of the stenosis aided by a urethral catheter, longitudinal section, and measurement of the strictured urethral segment until reaching the suspected healthy proximal and distal urethral areas.

A 22 or 18.5F resectoscope with a working element adapted for the laser fiber was then passed through the proximal urethrostomy followed by a urethroscopy and cystoscopy using a 0.9% saline solution as irrigation fluid (10). This is performed to aid in identifying possible bladder and/or urethral pathologies and anatomical landmarks for marking the graft donor region. The Holmium Laser settings for energy were 0.5 to 0.8J and frequency of 30 to 40 Hz. After filling the bladder to full capacity, a rectangular marking of the donor graft area was made immediately above the inter-ureteral bar (10).

Dissection of the graft was then performed using the 550μm laser fiber, always going from lateral to medial and subsequently from proximal to distal, being that the deepest plane is the muscular layer of the bladder. Upon completing dissection, the graft is extracted from the bladder's interior using forceps and hemostasis then performed on the edges of the donor area and a small fragment of the graft was removed for histological analysis.

The fragment of bladder mucosa was fixed in 10% buffered formalin, and routinely processed for paraf-

fin embedding, after which 5µm thick sections were obtained at 15 µm intervals and studied by histochemical methods. The sections were stained with hematoxylin-eosin to assess the integrity of the tissue. We also performed the staining with Masson's trichrome Five sections were stained, and five fields of each section were selected. All selected fields were photographed with a digital camera (Olympus DP70, Tokyo, Japan) under the same conditions at a resolution of 2040 x 1536 pixels, directly coupled to the microscope (Olympus BX51, Tokyo, Japan) and stored in a TIFF file. We used the Image J software, version 1.46r, loaded with its own plug-in to determine tissue integrity.

RESULTS

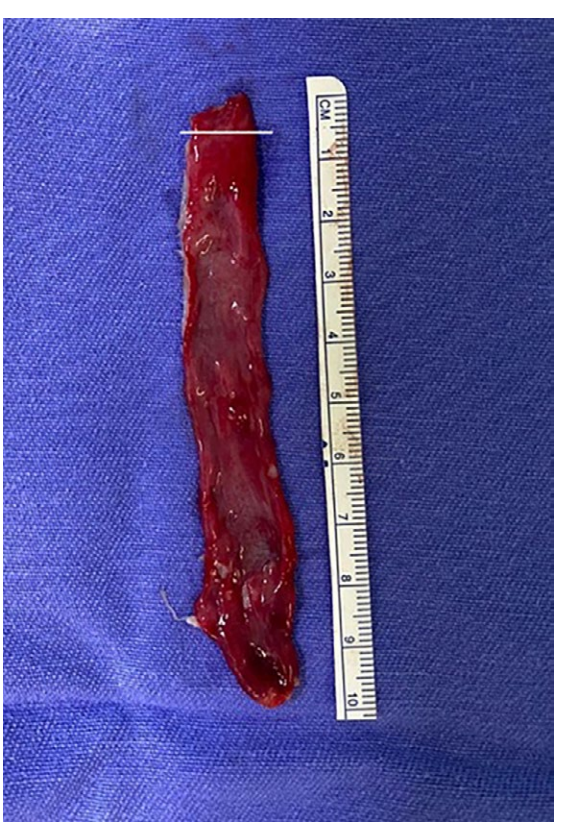
We can observe the demographic data and the etiology of urethral strictures of the patients studied in Table-1. The patients' ages ranged from 31 to 70 years old (mean= 53.45). The mean of bladder graft size was 53.64mm (4 to 7 cm) and the meantime of harvesting was 47.63 minutes (75 to 25 minutes).

TABLE 1 - The table shows the demographic data of the 11 patients submitted to urethroplasty with bladder mucosa graft.

Patient	Age	Comorbidities	Etiology	Prior Urethral Manipulation	Preoperative urethrocystogroma	Operative technique	Graft harvest duration	Grafit Size
1	39	No	Idiopathic	No	Bulbar urethral stricture 5 cm	Kulkarni	60 min	6 cm
2	48	SAH	Straddle Injury	No	Bulbar urethral stricture 3 cm	Augmented Anastomotic Urethroplasty	25 min	5 cm
3	63	Morbid obesity and SAH	Pelvic Trauma	No	Bulbar urethral stricture 4 cm	Kulkarni	30min	6 cm
4	53	No	Pelvic Trauma	Urethroplasty	Bulbar Stop	Augmented Anastomotic Urethroplasty	45 min	4 cm
5	45	No	Idiopathic	No	Bulbar urethral stricture 3 cm	Kulkarni	45 min	7 cm
6	46	No	Pelvic trauma	Urethroplasty	Bulbar urethral stricture 3,5 cm	Kulkarni	60min	5 cm
7	31	Morbid obesity and SAH	Idiopathic	No	Bulbar urethral stricture 4 cm	Kulkarni	75 min	6 cm
8	62	SAH	Idiopathic	No	Bulbar urethral stricture 3 cm	Kulkarni	35 min	5 cm
9	62	SAH	Indwelling Urinary Catheter	No	Bulbar urethral stricture 3 cm	Kulkarni	30min	6 cm
10	49	No	Idiopathic	DVRU	Bulbar urethral stricture 4 cm	Kulkarni	25 min	6 cm
11	70	SAH and Diabetes	Indwelling Urinary Catheter	No	Bulbar urethral stricture 3,5 cm	Kulkarni	32min	4 cm

The histological study of the bladder wall graft showed an organization in accordance with normal standards, with the presence of an intact urothelium in the bladder graft with no signs of compromise after laser removal (Figure-1). The bladder mucosa graft was lined by transitional epithelium (urothelium), which is composed of multiple layers of cells. The submucosal layer was preserved, joining the detrusor to the urothelium and the collagen and elastic fibers were well organized. The lamina propria lies beneath the urothelium and is composed of loose connective tissue containing blood vessels, nerves, and lymphatics and contains wispy, slender fascicles of the muscularis mucosae (MM), which can appear as individual or small groups of wavy muscle fibers (Figure-2).

Figure 1 - The figure shows the final aspect of bladder mucosa graft harvested with Holmium laser. The white line shows the fragment that was used to histological analysis.



DISCUSSION

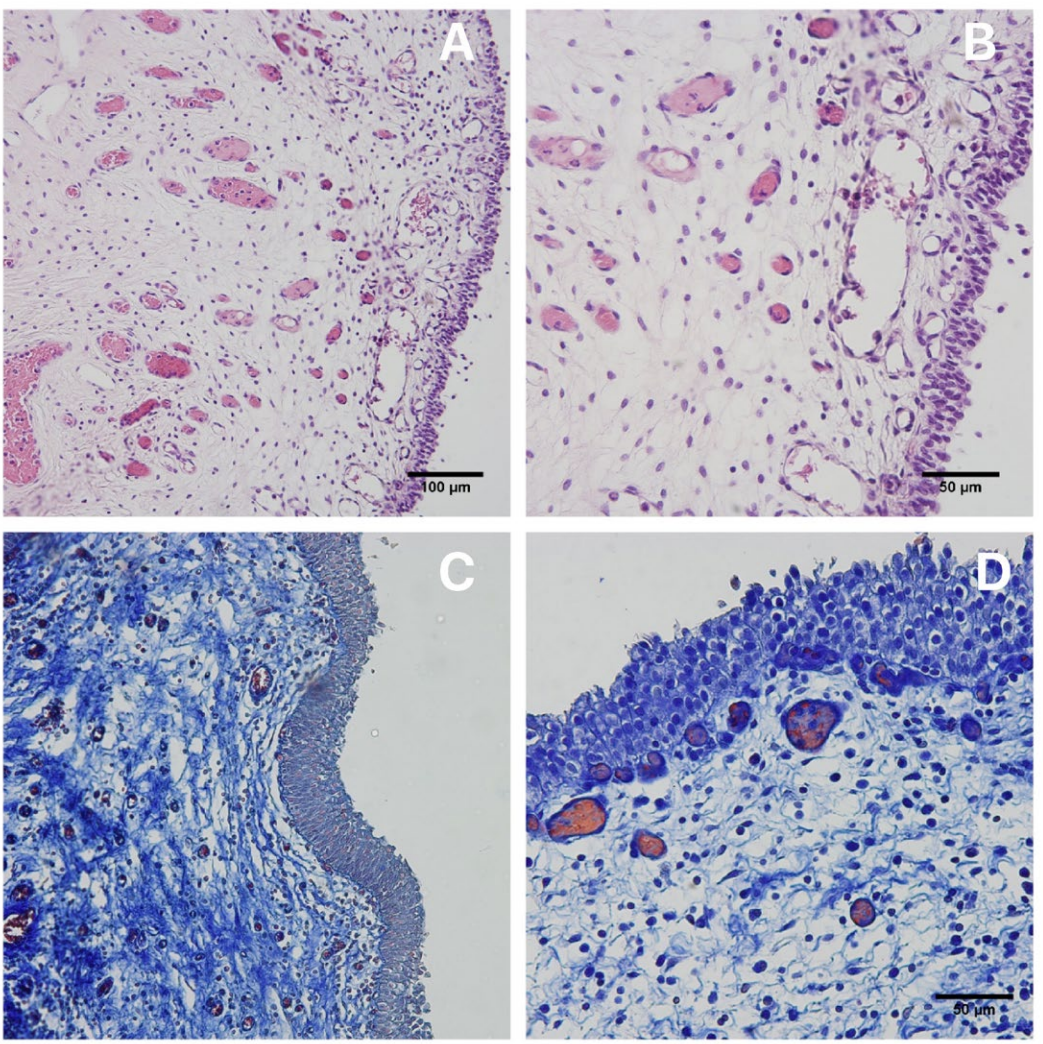
The use of a laser to collect bladder mucosa for urethroplasty is possible and was described for the first time by Joseph Memmelaar, in 1947 (11) for the treatment of 4 patients with hypospadias. Applying the knowledge and technology of that time, the grafts were harvested using an open technique and tubularized for the repair of hypospadias in a 1-stage procedure, obtaining patency in 3 out of 4 patients after 1 year.

Specifically, the Holmium:YAG (Ho:YAG) laser has been utilized for this purpose. A recent study shows a technique for transurethral harvesting of bladder mucosal grafts using the Ho:YAG laser. This technique was applied in a series of patients undergoing dorsal onlay urethroplasty for anterior urethral stricture. The results indicated that the procedure is feasible and reproducible, with comparable outcomes to other graft types used in urethroplasty (7). Another study by Figueiredo et al. also supports the feasibility of using the Ho:YAG laser for endoscopic harvesting of bladder mucosal grafts (10). This study described the successful application of this technique in a patient with a bulbar urethral stricture, further suggesting that bladder mucosal grafts harvested with the Ho:YAG laser could be a viable alternative to buccal mucosa grafts in urethral reconstruction (10).

The use of buccal mucosa for urethroplasty has been shown to retain its histopathological characteristics after engraftment to the urethra. Soave et al. found that buccal mucosa transplants maintain their structure and are not overgrown with urothelium after being integrated into the urethra (12). In our study we observed the preservation of the histology of bladder mucosa during the resection of graft with laser. According to a study by Li et al., the freeze-thaw technique can maintain the structure and biological function of bladder mucosa. The study demonstrated that no significant histological changes were observed in the frozen-thawed bladder mucosa compared to fresh bladder mucosa, and the urethral epithelial cells grew well postoperatively (13).

In our paper we studied the bladder histology with hematoxylin and eosin (H&E) and Masson's

Figure 2 - A) Photomicrograph showing the integrity of the bladder mucosa graft harvested with Holmium laser. HE X20 Masson's trichrome X1000; B) Photomicrograph showing of the bladder mucosa graft in higher augmentation. HE X40. C) Photomicrography showing the integrity of bladder mucosa. Masson's trichrome X20; and D) Photomicrography showing the bladder epithelium and mucosa structure of the graft harvested with Holmium laser Masson's trichrome X20.



trichrome. The bladder mucosa, when stained with H&E, exhibits several distinct histological characteristics characterized by the transitional epithelium, a supportive lamina propria with variable muscle fiber patterns, and a deeper muscularis propria with more organized muscle bundles (14), which gives us support for the structural analysis of bladder mucosa in our study. In the study by Julio Junior et al., Masson's trichrome stain was used to quantify connective tissue and smooth muscle in the bladder structure of fetuses with Prune Belly syndrome (15). This demonstrates the utility of Masson's trichrome stain in analyzing the structural components of the bladder mucosa. Additionally, Paner et al. utilized Masson's trichrome stain to differentiate between muscularis propria and muscularis mucosae in the urinary blad-

der, further supporting its application in detailed structural analysis of bladder tissues (16). Thus, Masson's trichrome stain is a valuable tool for examining the structural details of the bladder mucosa, particularly in distinguishing between different tissue types such as collagen and smooth muscle.

The present paper has some limitations: small sample, lack of ultra-structural analysis of bladder mucosa and longer follow-up.

In conclusion, our findings suggests that the graft harvested from the bladder uroepithelium using Ho-YAG has its histological integrity preserved, which makes this technique a viable option for reconstructive surgery. However more studies are needed to establish its long-term efficacy and safety of this new technique.

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CONFLICT OF INTEREST

None declared.

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Shock Wave Therapy in the Treatment of Erection Dysfunction: How to Define Clinical Outcomes? A Comparison Between Penile Doppler Ultrasound and a New Visual Erection Hardness Score (V-EHS) During a Blinded, Sham-Controlled Trial

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ABSTRACT

Background: In the last decade, several studies have proven the effectiveness of low-intensity shock waves (LI-ESWT), but with several factors that make it difficult to carry out systematic reviews.

Aim: To demonstrate the effectiveness of LI-ESWT and define the best tool for routine clinical assessment of erectile dysfunction.

Materials and Methods: Twenty-one participants with purely vasculogenic erectile dysfunction were selected and randomized to LI-ESWT or placebo. All patients underwent evaluation with The International Index of Erectile Function (IIEF-5), V-EHS (new visual scale), and standardized penile doppler ultrasound before and after shock wave therapy.

Outcomes: LI-ESWT has proven effective in the treatment of moderate erectile dysfunction, and the new V-EHS has demonstrated greater accuracy than Doppler in the diagnosis and follow-up of erectile dysfunction.

Results: Using the IIEF-5 as a control tool, we observed a clinical response after 1 month, with a greater increase in the shock wave therapy arm of +3.21 points compared to + 0.57 in the sham group. At six months, the treated group showed a mean increase of 4.71 points compared to baseline (p = 0.006), while those who received sham therapy had a decrease (case = +4.71 points vs. sham control = -1.0, p = 0.006). Based on this observed difference, we performed a comparative analysis between the V-EHS and penile doppler ultrasound to observe whether the test results corroborated the IIEF-5 findings. The correlation between V-EHS and IIEF-5 in the therapy group in the pre-therapy period was strong (r = 0.816, p < 0.001), and at 6 months it increased to very strong (r = 0.928, p < 0.001). Penile Doppler ultrasound did not show the same correlation strength with IIEF-5, presenting a moderate

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correlation at 6 months (Pearson correlation score = 0.540), as also demonstrated in the ROC curve through the V-EHS AUC = 0.963 (p = 0.001) vs. Doppler AUC = 0.713 (p = 0,290). ***Strengths and Limitations:*** The main strengths of the present study are the blinded, randomized, placebo-controlled clinical trial and the comparison between penile Doppler and a new visual classification for erection hardness score. The limitations are the number of patients and the short follow-up. ***Conclusions:*** LI-ESWT has proven effective in the treatment of moderate vasculogenic erectile dysfunction, with optimal results at 6 months. The new V-EHS offers a simple, reliable and reproducible assessment of erectile function.

INTRODUCTION

Erectile dysfunction (ED) is a common condition that affects approximately 18 million men in the United States. It is characterized by the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual activity, which significantly affects the quality of life (1). Among the current treatment options, low-intensity extracorporeal shock wave therapy (LI-ESWT) has shown good results. Many studies and international guidelines recommend it as an extra treatment for men with mild to moderate vasculogenic erectile dysfunction (2, 3).

This new therapy emerged with the hope of being the only modality capable of acting directly on the pathophysiology of ED, offering remodeling of the erectile tissue and, therefore, some degree of recovery of erectile function by promoting neovascularization, which has a positive effect on penile hemodynamics (2-4). However, like all new technologies especially those involving highly technical aspects such as new devices and different types of energy, along with physical aspects that are not familiar to the urologist's routine, this therapy requires time and continuous verification to gain the trust of doctors necessary for recommending it (4).

In this scenario, finding tools that allow clinicians to ensure the results obtained from this new treatment modality can be considered a turning point in the certification of this technology and in the safety of the method's indication. Since the validation of the Erection Hardness Score by Dr. John Mulhall and colleagues in 2007, this functional score has been extensively used in clinical practice (5). However, the lack of standardization in studies aimed at evaluating the improvement of erectile dysfunction after shock wave therapy is notorious. The established use of the IIEF-5, in addition to the EHS and penile Doppler ultrasound, has been conducted without standardization to determine which parameters demonstrate the most accurate results (6-8). Despite the recognition of both the EHS and penile Doppler ultrasound as established tools in the evaluation of patients with erectile dysfunction, the absence of a visual scale for the EHS and the lack of standardization in penile Doppler protocols complicates the interpretation of results. Recent efforts have been published in the sexual medicine literature to address this need for standardization (9-12).

In the present study, we observed the effects of shock wave therapy using the International Index of Sexual Function in its summarized version (IIEF-5) as a control parameter to verify the correlation of the results obtained through penile Doppler and an evaluation of a new visual scale for the Erection Hardness Score (visual erection hardness score – V-EHS). Our hypothesis is that the LI-ESWT improves mild and moderate ED. We aim to prospectively evaluate the efficacy of low-intensity shockwave therapy in patients with mild and moderate ED.

MATERIALS AND METHODS

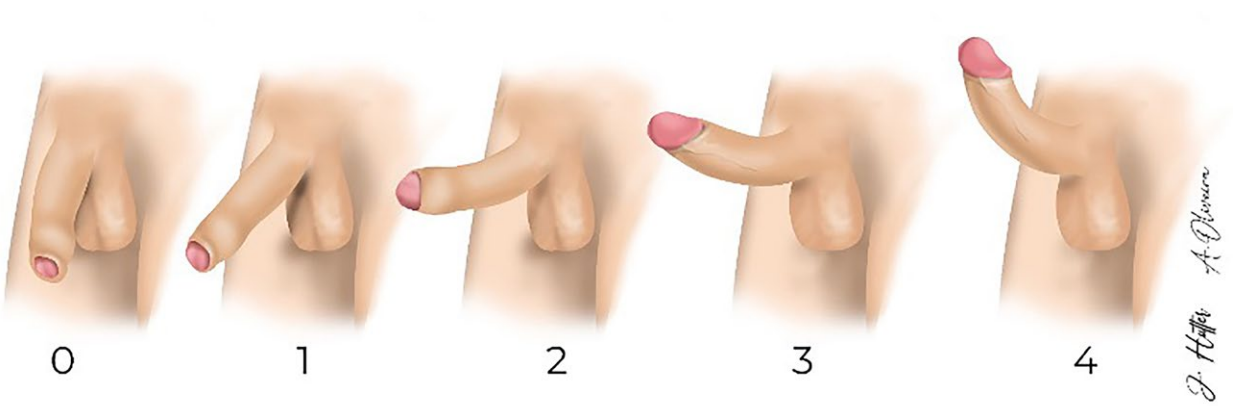
The present study was approved according to the ethical standards of the hospital's institutional committee on experimentation with human beings. We implemented a 2-arm stratified single-blinded randomized controlled clinical trial to determine the impact of sham versus LI-SWT on erectile function (IRB: 72872821.5.0000.5259). We confirm that all methods used in this paper were carried out in accordance with relevant guidelines and regulation in compliance to the declaration of Helsinki.

Data were collected between June 2022 and March 2024. The initial selection of patients was ac-

cording to the baseline clinical complaint of erectile dysfunction and the presence of moderate erectile dysfunction based on the validated International Index of Erectile Function questionnaire (IIEF-5 - 8 to 21) in use of tadalafil 5 mg daily. All pre-selected patients were referred for the Visual Erection Hardness Score (V-EHS), which is derived from the original EHS (5) with the inclusion of some modifications that are described in the Figure-1 and dynamic Doppler ultrasonography of the penis in order to confirm the presence of vasculogenic erectile dysfunction.

The criteria used in the positive determination of vasculogenic ED were: clinical history with cardiovascular risk factors and penile doppler ultrasound with peak systolic velocity (PSV) < 30 cm/s, end-diastolic velocity (EDV) > 5 cm/s, or cavernous resistance index (RI) <0,9. The V-EHS and penile doppler ultrasound evaluations were performed during a pharmaco-induced erection test by recording the time after intracavernous injection of trimix - 0.3 mL (prostaglandin 20 mcg/mL + phentolamine 4 mg/mL + pa-

Figure 1 – The figure shows the Visual Erection Hardness Score (V-EHS). This score is derived from the original Erection Hardness Score (5) but some modifications are incorporated: 1) The patient does not subjectively score; 2) It presents a new image, facilitating the perception and differentiation between the stages; 3) The scale itself, as we see above, is differentiated according to the axial resistance that the penis supports, which is functionally and directly related to the penetrative capacity and 4) It allows standardizing the erection test and the time of the re-dose (which should be done if a consistently hard erection (>3) is not obtained). In the figure we can observe: 0: Penis does not enlarge; 1: Penis is larger but not hard; 2: The penis is hard, but not hard enough to resist an axial force - it bends under a manual pulling force = not consistently hard erection; 3: Penis is hard, not completely hard, but resists an axial force - does not bends under a manual pulling force = consistently hard erection; 4: Penis is completely hard and fully rigid.

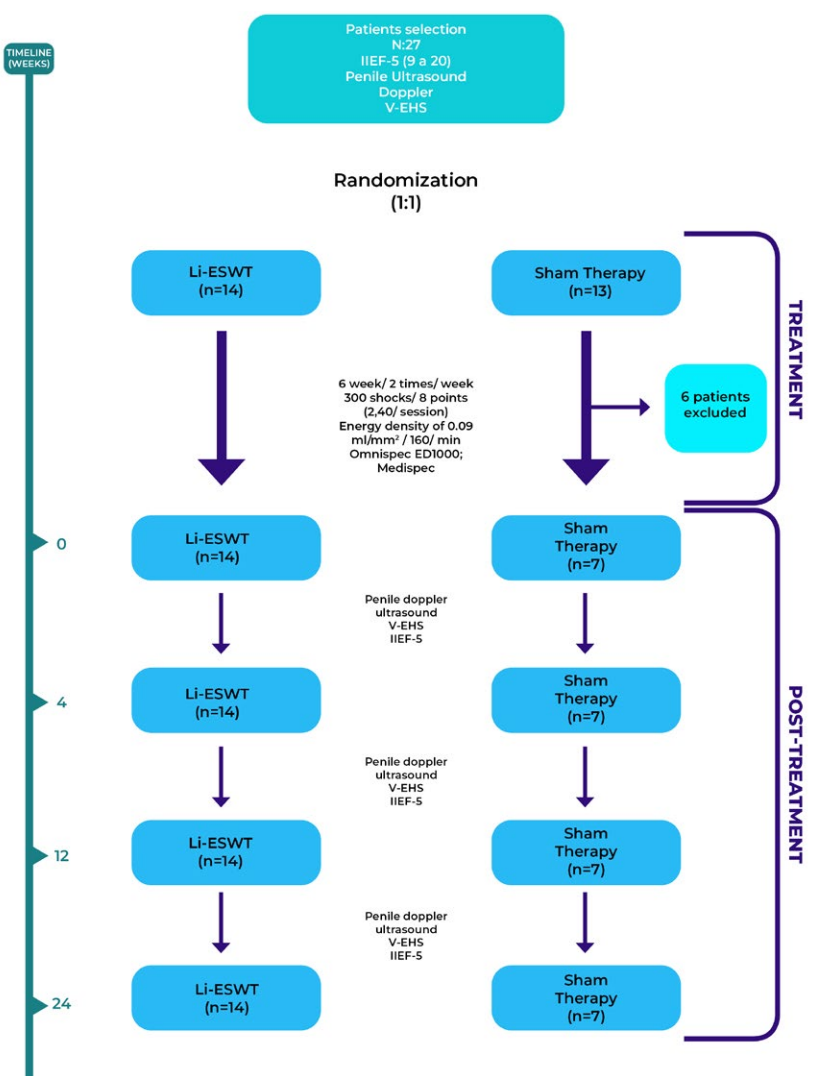


paverine 25 mg/mL) using as a basis for a re-dose the visual rigidity score (V-EHS) (Figure-1). If, after 20 minutes, the patient did not achieve a consistently hard erection (V-EHS = 3), a second dose was administered with the same concentration and volume.

Patients were excluded in cases of: (1) unstable psychiatric condition, (2) previous history of e penile/urethral surgery, (3) proven hypogonadism and (4) severe erectile dysfunction. The protocol of the present study is shown in Figure-2. Patients were randomized in a ratio of 1:1 into two groups: case-low intensity shock wave therapy (n = 14) or control (sham group) (n = 7).

Our LI-ESWT protocol was performed in 12 sessions, twice a week, for 6 weeks. We used the electro-hydraulic generating unit with a focal shock wave source (Omnispec ED1000; Medispec, Germantown, MD, USA). For the shock wave therapy session, the patient remained lying down in a supine position, the penis was manually stretched, and a standard commercial gel normally used for ultrasound was applied to the entire area of interest. The shock waves were distributed through the application probe to 8 sites: the distal, middle, and proximal penile shafts (both sides) and to the crura bilaterally, considering the final point

Figure 2 - The figure shows the protocol used during the present study.



of interest to be the corpora cavernosa and not only the penile shaft. Sessions consisted of 300 shocks for each treatment site (2,400/session) at an energy density of 0.09 mJ/mm2 and a frequency of 160/min. For the sham group, the sessions occurred in a similar manner, with the application probe being applied in an identical manner and the sound reproduced by a speaker located attached to the generator. Patient monitoring was performed in the outpatient clinic at 1, 3, and 6 months with IIEF-5, penile Doppler ultrasound, and V-EHS.

The erection tests, the V-EHS assessment, and penile Doppler ultrasound were performed by the same examiner. Treatment success was defined as an improvement of 4 points or more in the IIEF-5, as it had greater clinical significance. All patients continued to use tadalafil 5 mg throughout the study protocol.

Statistical analysis

The statistical analyses were performed using IBM SPSS, version 20. Data were presented in tables of means and standard deviations. A student's t-test for independent samples was used to statistically evaluate the differences between the Case and Sham groups for the quantitative interval variables. To evaluate the differences over time (pre, 1 month, 3 months, and 6 months) of the IIEF-5 and V-EHS scales, the nonparametric Friedman test was used, followed by Dunn's paired comparison tests. The differences between the Case and Sham groups at each time point of the IEEF-5 and V-EHS scales were verified using the Mann-Whitney test. To statistically evaluate the differences between groups, between assessments (pre, 1 month, 3 months, and 6 months), and the interaction between groups and assessments for the measurements of peak velocity of the right (r-PSV) and left (l-PSV) cavernous artery, the ANOVA technique for repeated measures was used, with a within-subject factor (repeated measure) and a between-subject factor. The within-subject factor was represented by the assessments, and the between-subject factor was represented by the groups. The significance level used as a criterion for acceptance or rejection in the statistical tests was 5% ($p < 0.05$).

The Pearson Correlation Index was used to determine the value of the correlation coefficient. The value of the correlation coefficient can range from - 1 to +1. The closer to -1, the stronger the negative correlation between the variables (negative correlation indicates that the higher the values of one variable, the lower the values of the other variable tend to be). The closer to +1, the stronger the positive correlation between the variables (positive correlation indicates that the higher the values of one variable, the higher the values of the other variable tend to be). Coefficient values close to 0 (zero) indicate an absence of correlation.

For ROC curve, area under the curve (AUCs) <0.5, between 0.5 and 0.7, between 0.7 and 0.8, and >0.8, the test was considered worthless, acceptable, good, or excellent, respectively. DeLong's empirical method was used to compare the AUC without a pairwise approach. All tests were 2-sided, and statistical significance was considered at a P value<0.05.

RESULTS

A total of 21 patients completed the protocol with 6 months of follow-up (6 patients in the sham group were excluded after initial recruitment because they missed more than one therapy session). The mean age of patients was 62.71 ± 9.38 years, and cardiovascular risk factors were common among participants in both groups (Table-1). The most frequent comorbidities were systemic arterial hypertension (57.1%), followed by type 2 diabetes mellitus (23.8%).

All data regarding IIEF-5 parameters, penile hemodynamic findings (PSV, EDF, and RI), and V-EHS pretreatment at 1, 3, and 6 months are described in Table-1. The diagnosis of arterial insufficiency was made in all cases, with 3 patients in the treated group and 3 patients in the sham group requiring a re-dose of trimix to achieve their best erection quality.

Before the sessions of shock wave therapy, the group that would undergo treatment presented IIEF-5 of 14.29 ± 3.173 points and the control group (sham) 12.57 ± 2.507 points. After 1 month, the treated group presented IIEF-5 of 17.50 ± 6,430 and the control group (sham) 13.14 ± 4.670 (p=0.149). After 3 months, the treated group

presented IIEF-5 of 18.86 ± 6.037 and the control group (sham) (12.43 ± 4.467) p-value = 0.020. Finally, at 6 months after low-intensity shock wave therapy, after 3 months of treatment, the treated group presented IIEF-5 of 19 ± 5.657 and the control group (sham) 11.57 ± 2.760 p-value = 0.006.

Before starting LI-ESWT, in the case group, there was a strong positive correlation between IIEF-5 and V-EHS (r =0.816, p<0.001), indicating that even before the procedure, erectile function was strongly associated with the new visual erectile function score. In this same period, the correlations between IIEF-5 and the systolic velocities of the right (r =0.415, p=0.140) and left (r =0.217, p=0.455) cavernous arteries were not statistically significant.

After 1 month of LI-ESWT, in the treatment group, the correlation between IIEF-5 and V-EHS increased to very strong (r=0.945, p<0.001). The correlation between IIEF-5 and the right cavernous artery was weak (r=0.436, p=0.119), and between IIEF-5 and the left cavernous artery was weak (r=0.354, p=0.215), both of which were not statistically significant. In the control group, the correlation between IIEF-5 and V-EHS was also strong and significant (r=0.872, p=0.011), but the correlations with the right (r=0.348, p=0.445) and left (r=0.116, p=0.805) cavernous arteries were not significant.

At 3 months, in the treatment group, the correlation between IIEF-5 and V-EHS remained very strong (r=0.970, p<0.001). The correlations between IIEF-5 and the systolic velocities of the right (r=0.307, p=0.285) and left (r=0.476, p=0.085) cavernous arteries were again not statistically significant. In the control group, the correlation between IIEF-5 and V-EHS remained strong (r=0.868, p=0.011), and the correlations with the right (r=-0.295, p=0.521) and left (r=-0.228, p=0.623) cavernous arteries remained non-significant.

At 6-month final follow-up, in the treatment group, the correlation between IIEF-5 and V-EHS remained very strong (r =0.928, p<0.001). The correlation between IIEF-5 and the right cavernous artery was moderate (r =0.510, p =0.062), whereas the correlation between IIEF-5 and the left cavernous artery was weak (r=0.404, p=0.152). In the control (sham) group, the correlation between IIEF-5 and EHS remained strong and significant (r=0.825, p=0.022), but the correlations with the right (r =0.124, p=0.791) and left (r=-0.331, p=0.468) cavernous arteries were not significant.

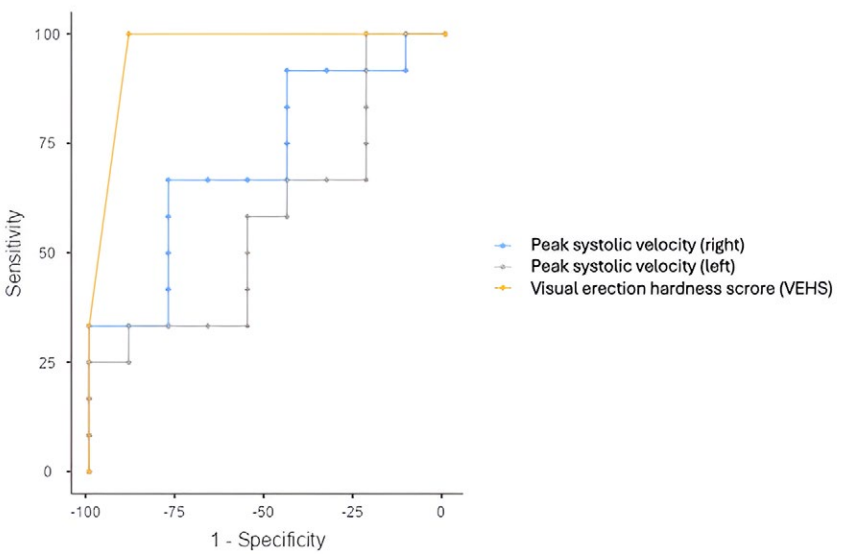
The ROC curves for V-EHS and PSV based on clinical improvement in erectile function are shown in Figure-3. The AUCs for right and left PSV and V-EHS to discriminate clinical improvement from ED (4 or more points improvement in IIEF-5) were 0.713 (p=0.035), 0.574 (p=0.290), and 0.963 (p=0.001), respectively. V-EHS was rated as excellent, right PSV as good, and left PSV as acceptable in discriminating clinical improvement. Pairwise comparison of ROC curves showed a statistically significant difference between V-EHS and Doppler PSV (p=0.0301), with V-EHS showing a sensitivity of 100% and a specificity of 88.89% vs. 66.67% sensitivity and 77% specificity for penile Doppler USG.

DISCUSSION

The present study demonstrated a significant improvement in erectile function in patients treated with LI-ESWT for mild to moderate vasculogenic erectile dysfunction. This improvement was evidenced by a mean increase of 4.71 points in IIEF-5 six months after treatment, compared to a decrease of -1.0 points in the placebo group, as shown in previous literature demonstrating the short-term clinical efficacy of low-intensity shock waves in cases of mild to moderate vasculogenic erectile dysfunction (11, 12). A previous review shows that LI-ESWT has the potential to promote tissue remodeling through neovascularization and partial recovery of erectile function (13). Although the efficacy of LI-ESWT is promising, the review also highlights a lack of standardization in terms of treatment protocols, including the applied energy, number of sessions, and application sites, factors that can influence the observed outcomes. Despite being an innovative therapy, LI-ESWT still lacks robust and higher-quality studies to consolidate its clinical indication (14-20). The present study employed a standardized protocol with 12 treatment sessions over six weeks, which may explain the consistency of the short-term results.

We observed a strong correlation between V-EHS and IIEF-5 in the shockwave group. On the

Figure 3 - The figure shows the ROC Curves for Visual Erection Hardness Score (V-EHS) and peak systolic velocity (PSV) based on clinical improvement in erectile function with V-EHS showing a sensitivity of 100% and a specificity of 88.89% vs. 66.67% sensitivity and 77% specificity for penile Doppler USG.



other hand, penile Doppler only showed a moderate correlation with IIEF-5 over the same period, suggesting that V-EHS may be a more reliable predictor of erectile function in the context of ED therapies. Considering the findings described, the V-EHS presented greater accuracy (sensitivity and specificity) when compared to penile Doppler (PSV, EDF, and RI) in predicting the degree of erectile dysfunction and the presence of clinical improvement (or refractory ED) after low-intensity shock wave therapy.

These findings are consistent with a previous analysis (21-24), which compared EHS with penile Doppler in a study of patients treated with non-surgical therapy for ED. The study showed that EHS has predictive value similar to or even greater than Doppler in identifying patients with refractory ED, defined as failure to respond to non-invasive treatments such as sildenafil or alprostadil therapy. In our study, the AUCs for predicting clinical improvement in ED was higher for V-EHS (AUC=0.963) compared to Doppler, which corroborates previous findings (24).

We know that Penile Doppler ultrasound is widely regarded as a valuable tool for assessing penile hemodynamics, but its clinical utility has been questioned in some contexts. Our study demonstrated that penile Doppler did not show a high correlation with clinical outcomes, as indicated by the low correlation coefficients with IIEF-5 after six months of treatment. This raises questions about the practical applicability of penile Doppler in certain therapeutic contexts, particularly in non-invasive treatments such as LI-ESWT, promoting the healthy question of whether the assessment of erection rigidity is not a more accurate form of assessment because, in addition to inferring the vascular factor, it also assesses the expansion of the tunica albuginea and possible geometric alterations that cause penile instability, such as EHS and now the new V-EHS (25, 26).

This debate is highlighted by studies like that of Morgado et al., which point to the lack of additional prognostic value provided by Doppler compared to the simpler intracavernosal injection test (27). While Doppler can provide detailed information about penile blood flow, it is often seen as overly complex and time-consuming, with little added value over a pharmaco-induced erection test in predicting treatment response to sildenafil or other oral therapies for ED. Additionally, the

variability in Doppler protocols, such as the use of different vasoactive agents, doses, and time intervals, can result in false diagnoses, as observed in other studies, which report false-positive diagnosis rates of up to 47% for venous-occlusive dysfunction.

In contrast to penile Doppler, V-EHS is a simple and practical tool that can be easily applied by clinicians during a pharmacologically induced erection assessment. As the EHS has been validated in several studies, such as that of Mulhall et al. (5), which demonstrated that it is highly responsive and correlates well with other measures of erectile function, such as IIEF, we think that V-EHS may assume a very important practical parameter. Mulhall's study also highlights the ease of use of EHS in clinical trials, being a direct and reliable measure of penile rigidity without the need for specialized equipment or advanced technical skills exactly as the new V-EHS (5). Furthermore, unlike even the subjective evaluation by the patient through EHS, the new V-EHS is carried out entirely by the examiner himself, during the erection test, without the need for the patient's own perception.

The results presented here further reinforce the utility of V-EHS, suggesting that it may be an adequate substitute for penile Doppler in many clinical situations, particularly in the evaluation of patients undergoing therapies for erectile dysfunction, not only LI-ESWT. The simplicity and reproducibility of V-EHS, combined with its strong correlation with IIEF-5, make it a valuable tool for clinical practice, especially in resource-limited settings.

Although our results are encouraging, both regarding the efficacy of LI-ESWT and the use of V-EHS as an assessment tool, the lack of standardization across studies is a recurring issue. As highlighted before, there is an urgent need for greater standardization in terms of treatment protocols and evaluation methods so that clinical outcomes can be comparable and replicable. Future studies should focus on expanding sample sizes and standardizing treatment parameters, such as the LI-ESWT energy dose, number of sessions, and the intervals between them, as well as defining consistent protocols for evaluating outcomes with V-EHS. With the implementation of these measures and through the use of penile rigidometers, it will be possible to obtain more accurate results and further validate the preliminary results of this study, in addition to consolidating LI-ESWT as first-line therapy for moderate vasculogenic ED.

The present paper has some limitations: The small sample size limits the generalizability of the findings, as acceptance of LI-ESWT and the relatively short follow-up.

CONCLUSIONS

In the present study, low-intensity shockwave therapy was effective in the treatment of mild to moderate vasculogenic erectile dysfunction, with results observed from 1 month and optimized up to 6 months. The use of the new visual erection hardness score provides a simple, reliable, and reproducible assessment of erectile function and is therefore also a practical tool that allows the standardization of drug-induced erection testing.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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V-EHS needs more studies to consolidate its use in clinical practice

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COMMENT

The current literature shows that low-intensity extracorporeal shock wave therapy (LI-EWST) appears to be effective and safe for treatment of erectile dysfunction (ED) (1). In this manuscript, the authors report that LI-ESWT is effective for the treatment of moderate vasculogenic ED, with optimal results after 6 months. However, care is needed regarding these findings, especially due to the limitations of the study, including the small sample size and short follow-up. Moreover, since the first publication about LI-EWST by Vardi in 2010, there have been no high-quality studies that allow establishing the patient profile, type of energy, and ideal application protocol needed to achieve clinically satisfactory results (2).

In addition, the study tries to define the best tool for routine clinical assessment of ED using the International Index of Erectile Function (IIEF-5), V-EHS (a new visual scale), and standardized penile Doppler ultrasound before and after LI-EWST. The authors observed a strong correlation between V-EHS and IIEF-5 in the shock wave group. The V-EHS is derived from the original EHS (Erection Hardness Score) (3), but incorporates some modifications. The EHS is a single-item ("How would you rate the hardness of your erection?") patient-reported outcome for scoring erection hardness. Although the EHS is a simple, valid and reliable tool, it is a patient's subjective measurement of his own erection hardness. In V-EHS, the patient does not assign the score subjectively and the erection hardness assessment is made by the examiner. Furthermore, the score is obtained according to the axial resistance that the penis supports after a force applied by the examiner to its tip during a drug-induced erection. Therefore, the V-EHS is not exclusively visual; instead, it is a modified EHS in which the examiner evaluates the axial rigidity mechanically.

Erection hardness is a reflection of axial penile rigidity and characterizes the ability to penetrate and achieve successful intercourse without penile bending (4). Therefore, V-EHS is a very interesting score which is directly related to the penetration capacity and has a strong correlation with the IIEF-5. Thus, it is a valuable tool for clinical practice, especially when an ultrasound device is not available. It can be an adequate substitute for penile Doppler in the evaluation of ED. Despite this, the V-EHS needs more studies with better quality and larger samples to consolidate its use in clinical practice.

CONFLICT OF INTEREST

None declared.

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Is the Effectiveness of Self-Visualization During Flexible Cystoscopy Gender-Dependent in Patients with no Previous Cystoscopy History? A Prospective Randomized Study

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ABSTRACT

Purpose: To evaluate the effect of real-time self-visualisation (SV) of the procedure during flexible cystoscopy (FC) on pain and anxiety in male and female patients with no prior cystoscopy history.

Patients and Methods: Between Dec 2022-May 2024, 400 patients who underwent office-based FC were enrolled into prospective randomized study in accordance with CONSORT. Patients were randomised into two groups (SV and no-SV) using sequential (1:1 ratio) randomisation. To ensure equal numbers of male and female patients in each group, one consecutive male patient was assigned to the SV group, while the next male patient was assigned to the non-SV group; the same randomization was done for females. The primary endpoint was to evaluate the pain during FC (during urethral insertion of the cystoscope and bladder examination stages) of both groups. The secondary endpoint was to evaluate anxiety, patient satisfaction, and willingness to undergo the procedure of both groups.

Results: In males, significant lower pain scores were detected in SV group during urethral insertion of the cystoscope (1.4 vs. 4.8, p<0.001) and during bladder examination (0.9 vs. 3.1, p<0.001). However, pain scores during urethral insertion of the cystoscope (1.9 vs. 2, p=0.38) and during bladder examination (1.2 vs. 1.3, p=0.63) were statistically similar between two groups in female patients. In both genders, significant lower anxiety levels, higher patient satisfaction and higher willingness to undergo repeat cystoscopy were detected in SV group.

Conclusion: SV during FC may be beneficial in reducing pain in male patients but not in female patients. SV during FC has a positive effect on anxiety, patients' satisfaction, and willingness to undergo repeat procedures, regardless of gender.

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INTRODUCTION

Cystoscopy is a procedure frequently performed by urologists in daily practice to diagnose various urological conditions such as bladder tumour (BT), benign prostatic hyperplasia, recurrent cystitis, and urethral stenosis. Cystoscopy can be performed in an operating room (under sedation, spinal block, or general anaesthesia) or as an office procedure (under local anaesthesia).

Office-based cystoscopies are important for reducing the workload in the operating room, especially for BT patients who require multiple cystoscopy procedures during follow-up each year. The procedure is usually well tolerated; however, it may cause mild to moderate pain, discomfort, and anxiety in some patients, even when a flexible cystoscope is used (1).

Experiencing pain during the procedure not only impacts the patient's quality of life but also affects the completion of the procedure. Patients may sometimes need to interrupt the procedure due to pain and postpone it to be performed under general anaesthesia. This can be particularly distressing for BT patients who require multiple cystoscopies throughout the year for follow-up. Pain and anxiety may even lead patients to consider skipping follow-up visits altogether.

Although pain relief methods such as intraurethral lidocaine-based lubricant application or distraction techniques like listening to music or watching relaxing videos during the procedure are used to alleviate pain and anxiety, an optimal solution has not yet been achieved (2, 3). In recent years, randomized controlled studies (RCSs) have also been published with conflicting results regarding the impact of patients watching their own cystoscopy video during the procedure as another distraction method (4-10). However, these studies evaluate mixed patient groups (male or female patients, first or repeat cystoscopy, cystoscopy alone or with additional procedures such as JJ stent removal) and have relatively small sample sizes. In some studies, most patients had a history of BT and thus had undergone at least one previous cystoscopy (4, 7, 9). It is well known that pain levels during the first cystoscopy are higher compared to repeated cystoscopies in BT patients undergoing surveillance (1).

We planned a randomised prospective study to evaluate the effect of real-time self-visualisation (SV) during flexible cystoscopy (FC) on pain and anxiety in male and female patients with no prior cystoscopy history. The rationale for selecting patients with no previous cystoscopy experience was to reveal the impact of real-time SV more clearly on pain and anxiety. Another distinction of our study from previous research is that we designed and managed it according to the Consolidated Standards of Reporting Trials (CONSORT) statement.

MATERIAL AND METHODS

This prospective RCS was conducted at the outpatient clinic of our hospital after institutional ethical approval (Date:07.04.2021, Decision no:2021-04/1099). This trial was designed and managed based on the CONSORT guidelines (11, 12).

Determination of sample size

A power analysis was conducted using the G*Power (v3.1.9.6) software to determine the sample size. The sample size for the study was calculated to achieve a power of 95%, with a significance level set at 0.05. Estimated pain scores were based on the mean pain values [mean VAS (Visual analogue scale) scores were 1.66±1.4 and 4.39±2.4 in SV and no-SV groups] reported in Soomro et al.'s study (8). Consequently, a total of 210 volunteers were required, comprising 105 volunteers in each group. We aimed to recruit 200 volunteers in each group to avoid potential volunteer dropouts and statistical errors.

Patients, inclusion, and exclusion criteria

Four hundred patients (aged 18 or older) who underwent office-based FC were included in the study between Dec 2022 and May 2024. Indications for cystoscopy were haematuria (suspicious of BT), lower urinary tract symptoms (LUTS), and incontinence. Patients with

a history of cystoscopy, active urinary tract infection, those who could not communicate, understand written material, or complete forms independently were excluded from the study. Additionally, patients with psychiatric disorders, language barriers, or a history of urethral stenosis (detected during the procedure) were not included. Patients requiring other procedures during FC, such as biopsy, fulguration for superficial BT, urethral dilation, or removal of foreign bodies or JJ stents, were also excluded from the study. The study design is summarized in the CONSORT flow chart (Figure-1).

Randomization

Patients were randomized into two groups using sequential (1:1 ratio) randomization. To ensure an equal number of male and female patients in each group, one consecutive male patient was assigned to the SV group, while the next male patient was assigned to the no-SV group. Similarly, one consecutive female patient was assigned to the SV group, and the next female patient was assigned to the no-SV group.

Cystoscopy procedure

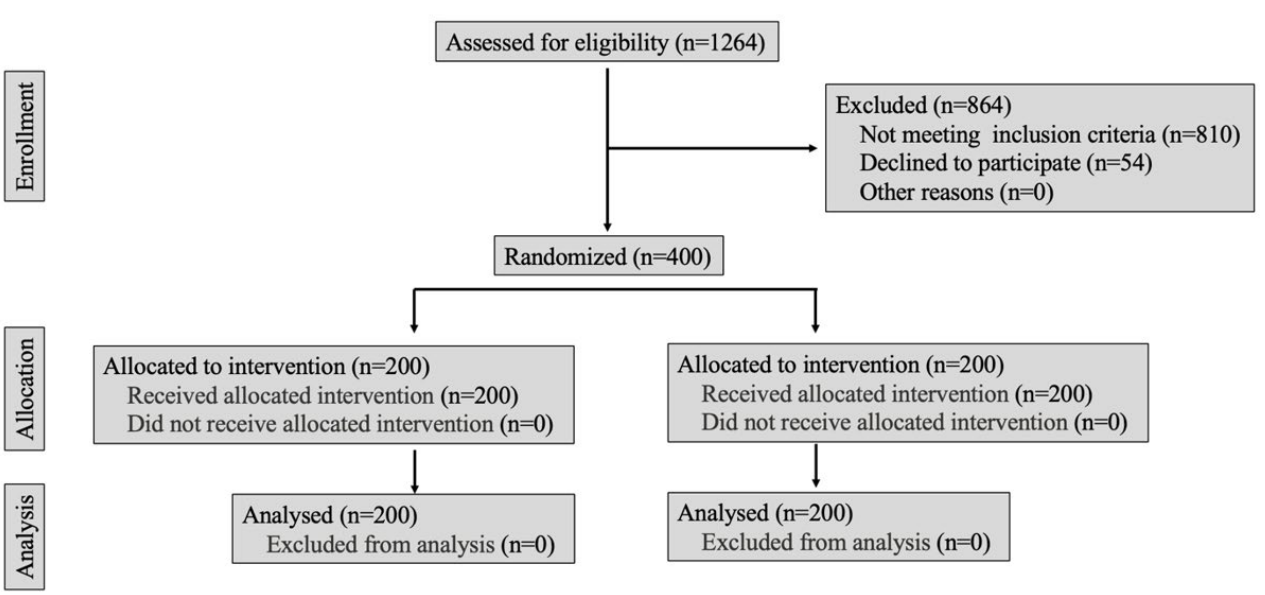
Before the procedure, patients were positioned in the lithotomy position. After scrubbing with an iodine-based solution and standard draping, local anesthesia consisting of 2% lidocaine gel was applied to the urethra. A 15F flexible cystoscope (Fiber-Cystoscope WL40, Richard-Wolf) was then inserted through the urethral meatus. All procedures were performed by final-year residents (MD, OC). For patients in the SV group, a monitor was positioned for both the urologist and the patient. For patients in the no-SV group, the monitor was positioned only for the urologist.

The primary endpoint was to evaluate the pain during FC in both groups. The secondary endpoint was to evaluate anxiety, patient satisfaction, and willingness to undergo the procedure in both groups.

Pain, satisfaction, and willingness to undergo the procedure evaluations

The pain was assessed during the passage of the cystoscope through the urethra and during the bladder examination. Pain levels were quantified using a VAS ranging from 0 to 10, with higher scores indicating greater pain. Additionally, patient satisfaction and willingness to undergo repeat cystoscopy (if needed) were evaluated using the VAS by a nurse

Figure 1 - Flowchart of the study.



who was blinded to the study protocol after the patient had dressed.

Anxiety evaluations

Before (after the patient was informed about the procedure and possible complications) and immediately after the cystoscopy, anxiety levels were evaluated using the State Trait Anxiety Inventory (STAI) by a nurse who was blinded to the study protocol. A self-reported anxiety inventory comprised 20 questions. STAI scores range from 20 to 80, with higher scores indicating greater anxiety levels.

Statistical Analysis

Statistical analysis was performed using SPSS version 25 (IBM, Chicago, IL, USA). The normality of the data was assessed using the Shapiro-Wilk (W) Test. Qualitative variables such as gender and indications for cystoscopy were considered categorical. The Chi-square test was used to compare categorical variables, which were expressed as counts and percentages. Quantitative variables, such as age, VAS scores, STAI scores, heart rates, and systolic blood pressure values, were expressed as mean and standard deviation. Student t-test was employed to compare independent groups of quantitative variables. The p-value of < 0.05 was considered statistically significant.

RESULTS

General data and comparison of all patients according to SV status without gender distribution

Four hundred patients (136 female and 264 male) were randomized into two groups (no-SV and SV groups), taking into account gender distribution. The mean age of the patients was 57.4±13.6 years. Indications for cystoscopy were haematuria, LUTS and incontinence in 292(73%), 67(16.7%), and 41(10.3%) patients, respectively. BT was revealed during FC in 76 (19 %) patients. The mean pain scores on VAS during urethral insertion of the cystoscope and during bladder examination were 2.76±2 and 1.79±1.5, respectively. Pre-cystoscopy and post-cystoscopy anxiety levels on STAI were 50.4±17.6 and 35.2±13.5, respectively. Post-cystoscopy patients' satisfaction and willingness to undergo repeat cystoscopy levels on VAS were 6.2±1.8 and 6.1±2, respectively (Table-1).

There were no significant differences between no-SV and SV groups in terms of patient age, indications, presence of BT, pre-cystoscopy heart rate, pre-cystoscopy systolic blood pressure, post-cystoscopy systolic blood pressure, pre-cystoscopy anxiety levels. Post-cystoscopy heart rate, pain during urethral insertion of the cystoscope, pain during bladder examination and post-cystoscopy anxiety levels were significantly lower in SV group compared with those in no-SV group (for all comparisons $p<0.001$). Patients' satisfaction and willingness to undergo repeat cystoscopy were statistically significant higher in SV group than no-SV group (for all comparisons $p<0.001$). Comparisons between no-SV and SV groups are detailed in Table-1.

Comparison of female patients according to SV status

Post-cystoscopy heart rate was significantly lower in SV group than no-SV group ($p<0.001$). No statistically significant effect of SV on pain levels in both stages (during urethral insertion of the cystoscope and bladder examination) of FC was detected in female patients ($p>0.05$). However, post-cystoscopy anxiety levels were statistically significant lower in female patients who underwent SV($p<0.001$). Post-cystoscopy patients' satisfaction and willingness to undergo repeat cystoscopy were statistically significant higher in SV group than no-SV group (for all comparisons $p<0.001$). Other variables were comparable in SV and no-SV groups. Comparisons of female patients are detailed in Table-2.

Comparison of male patients according to self-visualization status

Post-cystoscopy heart rate was significantly lower in SV group than no-SV group ($p<0.001$). SV was determined to have a statistically significant positive effect on pain during urethral insertion of the cystoscope, bladder examination stages and post-cystoscopy anxiety levels in male patients (for

Table 1 - Comparison of patients according to self-visualization status in all patients without gender distribution.

Variables	All patients (n=400)	no-SV (n=200)	SV (n=200)	p value
Age (Years), Mean ± SD	57.4±13.6	57.9±13.3	57±14	0.48
Gender, n (%)				-
Female	136 (34)	68 (34)	68 (34)	
Male	264 (66)	132 (66)	132 (66)	
Indication for cystoscopy, n (%)				0.49
Haematuria	292 (73)	150 (75)	142 (71)	
LUTS	67 (16.7)	29 (14.5)	38 (19)	
Incontinence	41 (10.3)	21 (10.5)	20 (10)	
Presence of BT at cystoscopy, n (%)	76 (19)	37 (18.5)	39 (19.5)	0.8
Pre-cystoscopy heart rate (beats/min), Mean ± SD	69.2±11.3	69±11.2	69.3±11.4	0.75
Post-cystoscopy heart rate (beats/min), Mean ± SD	78.9±13.9	82.3±13.7	75.5±13.3	<0.001*
Pre-cystoscopy systolic blood pressure (mmHg), Mean ± SD	119±12.5	118.3±12.7	119.8±12.3	0.24
Post-cystoscopy systolic blood pressure (mmHg), Mean ± SD	124.3±19.2	124.2±19.1	124.3±19.4	0.95
Pain during urethral insertion of the cystoscope (VAS), Mean ± SD	2.76±2	3.9±2.1	1.6±1.1	<0.001*
Pain during bladder examination (VAS), Mean ± SD	1.79±1.5	2.53±1.8	1.04±0.7	<0.001*
Pre-cystoscopy anxiety (STAI), Mean ± SD	50.4±17.6	49.6±17.3	51.1±17.9	0.38
Post-cystoscopy anxiety (STAI), Mean ± SD	35.2±13.5	41.9±14.5	28.4±7.7	<0.001*
Patients' satisfaction (VAS), Mean ± SD	6.2±1.8	4.9±1.3	7.6±1.03	<0.001*
Willingness to undergo repeat cystoscopy (VAS), Mean ± SD	6.1±2	4.5±1.6	7.6±1.05	<0.001*

BT = Bladder tumour; LUTS = Lower urinary tract symptoms; SD = Standard Deviation; STAI = State Trait Anxiety Inventory; SV = Self-visualization; VAS = Visual analog scale

*Statistically significant

all comparisons p<0.001). Moreover, post-cystoscopy patients' satisfaction and willingness to undergo repeat cystoscopy were statistically significant higher in SV group than no-SV group (for all comparisons p<0.001). Other variables were comparable in SV and no-SV groups. Comparisons of male patients are detailed in Table-3.

DISCUSSION

In this RCS, we observed that SV during FC significantly reduced pain in male patients, although this effect was not observed in female patients. Additionally, SV during FC was found to have a positive impact on anxiety in both genders. A key difference between our

Table 2 - Comparison of female patients according to self-visualization status.

Variables	Female patients (n=136)	no-SV (n=68)	SV (n=68)	p value
Age (Years), Mean ± SD	55 ± 13.6	56.6 ± 13.3	53.4 ± 13.7	0.17
Indication for cystoscopy, n (%)				0.6
Haematuria	94 (69.1)	47 (69.1)	47 (69.1)	
LUTS	13 (9.6)	5 (7.4)	8 (11.8)	
Incontinence	29 (21.3)	16 (23.5)	13 (19.1)	
Presence of BT at cystoscopy, n (%)	20 (14.7)	12 (17.6)	8 (11.8)	0.33
Pre-cystoscopy heart rate (beats/min), Mean ± SD	68.5±11.5	68.7±11.2	68.3±11.9	0.87
Post-cystoscopy heart rate (beats/min), Mean ± SD	80.1±14.5	84.2±14	76±13.8	0.001*
Pre-cystoscopy systolic blood pressure (mmHg), Mean ± SD	118.7±11.6	117.6±12	119.8±11.1	0.26
Post-cystoscopy systolic blood pressure (mmHg), Mean ± SD	124.5±18.6	122.1±19.3	126.9±17.7	0.13
Pain during urethral insertion of the cystoscope (VAS), Mean±SD	1.95±0.9	2±0.9	1.9±0.8	0.38
Pain during bladder examination (VAS), Mean± SD	1.29±0.7	1.32±0.7	1.26±0.7	0.63
Pre-cystoscopy anxiety (STAI), Mean ± SD	52.3±16.7	51.8±16.3	52.8±17.2	0.72
Post-cystoscopy anxiety (STAI), Mean ± SD	36.4±13.3	43.9±13.4	28.7±7.7	<0.001*
Patients' satisfaction (VAS), Mean ± SD	6.2±1.8	4.7±1.2	7.6±1	<0.001*
Willingness (VAS), Mean ± SD	6±2.1	4.4±1.7	7.5±1	<0.001*

BT = Bladder tumour; LUTS = Lower urinary tract symptoms; SD = Standard Deviation; STAI = State Trait Anxiety Inventory; SV = Self-visualization; VAS = Visual analog scale
*Statistically significant

study and previous studies is the exclusion of patients with prior cystoscopy experience, allowing us to more accurately assess the effect of SV on pain and anxiety. Another distinguishing feature of our study is that it was designed and conducted in accordance with the CONSORT statement. We also found that SV has a clear positive effect on patient satisfaction and their willingness to undergo repeat procedures. Importantly, our study is the first to address these specific outcomes, as no prior data exists on the impact of SV on patient satisfaction or willingness to repeat procedures.

To date, several RCSs (4–10) have been published on the effect of SV of pain during FC, with varying outcomes. Firstly, Clements et al. reported an RCS involving 129 patients (4). They evaluated pain at the different stages of the procedure (during insertion of the scope and bladder examination). Pain levels were classified as none (VAS score 1), mild (VAS score 2-3), moderate (VAS score 4-6) and severe (VAS score 7-10) degrees. They reported that video viewing had an effect on pain during bladder examination (p=0.028) whereas it had no effect during scope

Table 3 - Comparison of male patients according to self-visualization status.

Variables	Male patients (n=264)	no-SV (n=132)	SV (n=132)	p value
Age (Years), Mean ± SD	58.6 ± 13.6	58.5 ± 13.2	58.7 ± 14	0.9
Indication for cystoscopy, n (%)				0.51
Haematuria	198 (75)	103 (78)	95 (72)	
LUTS	54 (20.5)	24 (18.2)	30 (22.7)	
Incontinence	12 (4.5)	5 (3.8)	7 (5.3)	
Presence of BT at cystoscopy, n (%)	56 (21.2)	25 (18.9)	31 (23.5)	0.45
Pre-cystoscopy heart rate (beats/min), Mean ± SD	69.5±11.2	69.2±11.2	69.9±11.1	0.61
Post-cystoscopy heart rate (beats/min), Mean ± SD	78.3±13.6	81.3±13.5	75.3±13	<0.001*
Pre-cystoscopy systolic blood pressure (mmHg), Mean ± SD	119.2±13	118.7±13.1	119.8±13	0.51
Post-cystoscopy systolic blood pressure (mmHg), Mean ± SD	124.1±19.5	125.3±19	123±20	0.34
Pain during urethral insertion of the cystoscope (VAS), Mean ± SD	3.2±2.2	4.8±1.8	1.4±1.1	<0.001*
Pain during bladder examination (VAS), Mean ± SD	2.1±1.8	3.1±1.8	0.9±0.7	<0.001*
Pre-cystoscopy anxiety (STAI), Mean ± SD	49.3±18	48.4±17.8	50.2±18.2	0.42
Post-cystoscopy anxiety (STAI), Mean ± SD	34.5±13.5	41±15.1	28.1±7.6	<0.001*
Patients' satisfaction (VAS), Mean ± SD	6.3±1.7	4.9±1.3	7.6±1	<0.001*
Willingness (VAS), Mean ± SD	6.1±2	4.6±1.6	7.6±1	<0.001*

BT = Bladder tumour; LUTS = Lower urinary tract symptoms; SD = Standard Deviation; STAI = State Trait Anxiety Inventory; SV = Self-visualization; VAS = Visual analog scale
*Statistically significant

insertion (p=0.79). They also evaluated anxiety levels using a four-point descriptive scale (none, mild, moderate, and severe) and found no significant difference between groups (p=0.189). There were some methodological concerns. Firstly, no data on the gender distribution of the participants was provided. Secondly, instead of comparing mean VAS scores for pain, pain levels were categorized by severity, with a percentage comparison made. Additionally, the objectivity of anxiety levels using a four points scale is questionable. Nowadays, anxiety levels can be measured more objectively with scales such as STAI or Beck Anxiety Inventory scores.

Patel et al. published their outcomes for both genders in two different RCSs (5, 6). First, they evaluated the effect of SV on pain in 100 male patients who underwent FC and determined that the mean VAS (evaluated with a 100 mm unmarked horizontal line)

score was statistically lower in the SV group than no-SV group (14 vs. 23, p=0.02) (5). One year later, the effect of SV on pain was evaluated in a 100 female population who underwent rigid cystoscopy (6). However, they could not demonstrate the positive effect of SV on reducing pain in the female population (6).

In another study, 114 patients were randomized to SV and no-SV groups (7). They detected statistically similar pain levels into two groups (p=0.18) (7). In the same study, they also subdivided all patients according to their cystoscopy history and compared pain levels. They revealed that there was no statistically significant effect of SV on pain in patients who had first cystoscopy (p=0.23), who had 2-5 cystoscopies (p=0.58), and who had > 5 cystoscopies (p=0.37) (7).

Two low-sample size RCS have been published showing that SV during FC is effective in reducing pain in male patients (8,9). Somro et al. evaluated 76 patients and they found patients who viewed their FC had lower VAS scores (1.66 vs. 4.39, p<0.001) (8). Somro et al. highlighted that the different results obtained compared to previous studies (the positive effect of SV on pain) might be attributed to differences in the patient's position and geographical location (8). They conducted all procedures in supine position, unlike previous studies. The supine position may make patients feel more comfortable than the lithotomy position, which could help prevent pain. However, we attribute this difference to the characteristics of the patients, as in Somro et al. study (8), 42% of the patients underwent additional invasive and potentially painful procedures (like JJ stent removal).

In the second RCS analysed, Zhang et al. (9) included only male patients and excluded patients who underwent additional procedures during FC, like our study. However, they included patients undergoing first or repeated cystoscopy. Pain levels were lower in patients who watched their procedure (1.12 vs. 3.33, p<0.001) (9). They also divided the patients into subgroups (first cystoscopy, previous cystoscopy history, diagnostic cystoscopy, surveillance cystoscopy for BT). It was shown that watching the procedure is statistically significantly beneficial in reducing pain across all patient subgroups (9).

In the present study, we revealed that SV of the FC significantly reduced pain in male patients, though this effect was not reached in female patients. Additionally, we found that men experienced more pain than women during both stages of the cystoscopy procedure. We believe this difference between genders is due to anatomical differences. Urethral length is short in females, making them less likely to experience pain during insertion of the cystoscope. Moreover, elongation in the craniocaudal diameter due to prostate enlargement, particularly in older men, and narrowing at the membranous urethra level may cause increased pain. Taghizadeh et al. (13) and Chen et al. (14) noted that the most painful part of the procedure occurs when the tip of the flexible cystoscope passes through the membranous urethra in men. For these reasons, it is expected that females experience less pain and discomfort during FC procedures compared to males.

More recently, González-Padilla et al. (10) evaluated the impact of SV of the procedure on pain in 318 male and 86 female patients. In this quasi-randomized study, they found a beneficial effect of SV on pain (VAS scores) in female patients (1.64 vs. 2.78, p=0.008) but not in male patients (2.5 vs. 2.6, p=0.276) (10). This difference between genders can be attributed to some reasons. González-Padilla et al. (10) used flexible and rigid cystoscopes during cystoscopy procedures in male and female patients, respectively. The effect of the flexible cystoscope on pain and patient comfort is well known (15). Therefore, SV may not make much difference on pain in patients who are undergoing FC. However, SV may have made a difference in patients who were undergoing rigid cystoscopy. To avoid this controversy, we used flexible cystoscopes for both genders in our study.

Moreover, González-Padilla et al. (10) stated that conducting their study using a quasi-randomized method due to logistical constraints may have introduced some theoretical weaknesses. There is another detail in this study despite existing theoretical weaknesses and the conclusion that the SV of the procedure only reduces pain in females. They emphasized that the number of previous cystoscopies has an in-

fluence, diminishing the perception of pain, regardless of whether the patient visualizes the procedure or not. They reported a higher mean VAS score in patients who have no cystoscopy history than patients who have three or more cystoscopy histories in males (3.1 vs. 2.1, p=0.001) and in females (2.89 vs. 1.56, p=0.02) (10). These findings have been also supported by data from 1320 consecutive cystoscopies showing that pain level during the first cystoscopy is higher than for repeated cystoscopies (1). Therefore, while planning our study, we excluded patients with a previous history of cystoscopy to evaluate the effect of SV on pain more clearly. Patients who have had cystoscopy more than once usually feel less pain as they become accustomed to the procedure. Additionally, we excluded from the study patients who would require additional procedures such as JJ stent removal, biopsy, and stenosis dilation, which would prolong the procedure time and therefore probably make the patient feel more pain.

Anxiety levels can vary between individuals, regardless of SV. Waiting for the results of a diagnostic procedure can be a significant source of anxiety. Real-time information about a "normal" examination may help reduce this anxiety. However, the bias towards potential malignancy could be related to the absence or presence of abnormal findings during the diagnostic procedure, rather than the SV. Therefore, we also analysed the cystoscopy findings of the patients included in the study. We found no differences in the rates of malignancy detected during cystoscopy between the SV and no-SV groups for both genders.

Although our sample size is large and our methodology was well-planned, there are some limitations. We performed all procedures in the lithotomy position for both genders. Literature suggests that patients may be more comfortable during cystoscopies performed in the supine position rather than lithotomy (8). FC under the supine position could be considered for female patients, but we were unable to implement this due to the specific design of the patient bed in the outpatient clinic, which is tailored for the lithotomy position.

CONCLUSIONS

In conclusion, SV during FC may be beneficial in reducing pain in male patients but not in female patients. SV during FC has a positive effect on anxiety, patients' satisfaction, and willingness to undergo repeat procedures, regardless of gender.

ABBREVIATIONS

BT - Bladder Tumour
FC - Flexible Cystoscopy
LUTS - Lower Urinary Tract Symptoms
RCS - Randomized Controlled Study
SV - Self-Visualisation
STAI - State Trait Anxiety Inventory
VAS - Visual Analogue Scale

COMPLIANCE WITH ETHICAL STANDARDS

This research followed the Declaration of Helsinki and was approved by the Dr. Abdurrahman Yurtaslan Ankara Oncology Research and Training Hospital Ethics Committee under decision number 2021-04/1099.

Data Availability Statement

Due to personal data security laws, the data sets created and/or analysed for this study are not available to the public. However, they can be obtained from the associated author upon reasonable request.

Informed consent

Written informed consent was obtained from all volunteers.

CONFLICT OF INTEREST

None declared.

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Editorial Comment: Assessment of Factors Responsible for Stone-Free Status After Retrograde Intrarenal Surgery

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COMMENT

Retrograde intrarenal surgery is a great option to treat renal stones and had low risk of complications compared to percutaneous nephrolithotomy (PCNL). The anatomic aspects are of great importance for these procedures (1). The previous paper shows the importance of pre-operative oral antibiotics to reduce the risk of infection in this surgery (2). In the paper of Raj and collegues (3) the authors evaluate the predictive factors that determined stone-free rate (SFR) after retrograding intrarenal surgery (RIRS). In this prospective study 183 patients undergoing RIRS for renal stones were studied. The authors concluded that RIRS has lately emerged as an effective and reliable modality for treating selected renal stones. Patients with large or multiple stones require follow-up due to the high risk of residual stones after a single session of RIRS. Patients who undergo RIRS in large-volume stones should be counseled for staged procedures beforehand. Lower pole stone location, stone density (HU), and abnormal renal anatomy are essential predictors for SFR after RIRS. Lower pole RIPA and RIL are significant influencing factors for SFR after RIRS. RIRS and RUSS scores show a significant association with stone-free outcomes, with higher scores predicting poorer SFR. RIRS score performed better than the RUSS score in predicting stone-free outcomes. These scoring systems can be used preoperatively to gauge treatment success and counsel patients regarding appropriate treatment modalities. We congratulate the authors for the interesting paper.

CONFLICT OF INTEREST

None declared.

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Editorial Comment: Adverse Effects of Intravesical OnabotulinumtoxinA Injection in Patients with Idiopathic Overactive Bladder or Neurogenic Detrusor Overactivity: A Systematic Review and Meta-Analysis of Randomized Controlled Studies

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COMMENT

Intravesical injection of OnabotulinumtoxinA (BTA) is an established treatment for both neurogenic detrusor overactivity (NDO) and idiopathic overactive bladder (OAB) symptoms, but it is not devoid of risks (1). The meta-analysis conducted by Yu and Wang focused on local and systemic adverse events (AE) associated with BTA injections in the bladder.

This study included 26 randomized clinical trials, 8 of which focused on NDO and 18 on idiopathic OAB. BTA versus placebo significantly increased the incidence of urinary tract infections (UTI) in individuals with NDO (relative risk, or RR, 1.54) and idiopathic OAB (RR, 2.53). The RR of urinary retention was 6.56 in the NDO and 7.32 in the idiopathic OAB group, respectively, with similar rates of de novo clean intermittent catheterization (CIC). In patients with idiopathic OAB, BTA increased the likelihood of voiding symptoms. Systemic AEs of BTA were observed in individuals with NDO, including muscle weakness (RR, 2.79) and nausea (RR, 3.15). However, the majority of systemic AEs were rare and self-limited.

These findings highlight the need of a proper alignment of patients' expectations concerning BTA treatment, assessing the tolerability profile, as well as the stratification of risk for voiding dysfunction and urinary retention.

CONFLICT OF INTEREST

None declared.

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Editorial Comment: Nocturia and Obstructive Sleep Apnea in Spinal Cord Injured Patients - a Cohort Study

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COMMENT

This study intended to describe the prevalence of nocturia and obstructive sleep apnea (OSA) in a cohort of spinal cord injured (SCI) patients and to explore their connection. A retrospective data analysis was undertaken in a tertiary care rehabilitation hospital with specialist sleep and neuro-urology units. All adult SCI patients referred to urodynamic evaluation prior to polysomnography (PSG) between 2015 and 2023 were eligible. Subjective (nocturia) and objective data (urodynamics, polysomnography, built-in CPAP software) were evaluated. Among the 173 patients included, 57.5% had nocturia and 61.9% had OSA. However, research did not discover a statistical link between nocturia and OSA in these individuals. It also revealed significant differences between patients with and without nocturia in terms of neurogenic detrusor overactivity (NDO), volume at first detrusor contraction, and bladder functional capacity, implying that these factors may play an important role in SCI patients with nocturia (1).

The authors concluded that, while both conditions were highly prevalent in SCI patients, there was no direct statistical association between nocturia and OSA in this cohort. Some limitations should be addressed, such as the study's retrospective methodology and the significance of NDO in nocturia in SCI patients. Well-designed prospective studies are still required to better understand the influence of OSA on lower urinary tract symptoms

in SCI patients. The effect of bladder overdistension at night has been previously related to the worsening of bladder dysfunction, as well as the occurrence of recurrent urinary infections in this group of patients.

CONFLICT OF INTEREST

None declared.

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Mixed Reality Ultrasound-Guided Mini-ECIRS with Apple Vision Pro™ - First Case Report

Roberto Montoro Neto [1], Fabio C. Vicentini [2, 3], Ricardo T.S. Ugino [3], Alexandre Danilovic [3], Giovanni S. Marchini [3], Fabio C.M. Torricelli [3], Carlos A. Batagello [3], Anderson B. Pellanda [3], Alexandre Silva [4], William C. Nahas [3], Eduardo Mazzucchi [3]

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ABSTRACT

Introduction: Some endourological surgeries require multiple screens to perform combined procedures, which can present ergonomic challenges (1, 2). Apple Vision Pro (AVP) is a spatial computing device developed by Apple that incorporates virtual reality (VR) for life-like simulations, realistic medical scenarios, interactive anatomical models, and augmented reality (AR) technologies (3). In health care, VR is used for pain management, physical therapy, psychological therapy, and surgical simulations, providing a controlled and safe environment for both patients and healthcare professionals (4).

Objective: To demonstrate the step-by-step technique of the Mini-Endoscopic Combined Intra-Renal Surgery (Mini-ECIRS) procedure guided by ultrasound and using mixed reality technology with the Apple Vision Pro (multiscreen and 3D reconstruction). To the best of our knowledge, this is the first report of this procedure being performed with AVP assistance.

Patient and Methods: We present the case of a 40-year-old female with a history of right lumbar pain for one year. A CT scan revealed a proximal ureteral stone (20mm) and a lower pole stone (14mm) on the right side, with a Guys's Score grade 2 4. In this case, we opted for Ultrasound-Guided Mini-ECIRS (5, 6). This choice allowed for precise puncture and dilation, ensuring effective treatment and minimal invasiveness, assisted by the Apple Vision Pro. This device is equipped with eight external cameras that capture the real world at a resolution of 4K, enhancing the surgeon's experience with unparalleled efficiency and ease of mixed reality. This advanced imaging allows for precise visualization and integration of digital elements into the physical environment, significantly improving the accuracy and effectiveness of surgical procedures. During this procedure, the multitude of equipment in the operating room often obstructs the view of the physical monitors, including ultrasound. However, this technology addresses these challenges by offering enhanced ergonomics, efficiency, and safety to the surgeon. By providing seamless integration of digital overlays and real-world visuals, it ensures that crucial information is always within the surgeon's line of sight, thereby improving operational precision and overall outcomes. The surgeon had no previous contact with the AVP and was assisted by an AVP expert urologist throughout the procedure.

Results: The procedure was performed in the Barts flank-free position. Initially, ureterolithotomy was performed using holmium laser. After the dusting phase, an ultrasound-guided renal puncture was performed using a virtual screen, providing enhanced comfort and ergonomics for the surgeon. Throughout the procedure, the surgeon had simultaneous access to both screens (nephroscope and flexible ureteroscope), facilitating efficient location of any residual stones. The AVP functioned effectively, dis-

playing multiple screens within its own interface, improving ergonomics during surgery and maintaining safety throughout the procedure. The surgery was performed uneventfully in 2 hours, and the patient was rendered stone-free on CT and was discharged on the first postoperative day.

Conclusion: Apple Vision Pro provides multiscreen and 3D reconstruction capabilities, ensuring a comfortable, safe, and easily replicable procedure. Its advanced technology may be particularly beneficial for surgeries, such as Mini-ECIRS, which require simultaneous screens.

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Aldehyde free - Bovine Pericardium – A New Option of Graft in Urethral Stricture Treatment

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ABSTRACT

Objective: The current management for complex urethral strictures commonly uses open reconstruction with buccal mucosa urethroplasty. However, there are multiple situations whereby buccal mucosa is inadequate (pan-urethral stricture or prior buccal harvest) or inappropriate for utilization (heavy tobacco use or oral radiation). Multiple options exist for use as alternatives or adjuncts to buccal mucosa in complex urethral strictures (injectable antifibrotic agents, augmentation urethroplasty with skin flaps, lingual mucosa, bladder mucosa, colonic mucosa, and new developments in tissue engineering for urethral graft material) (1, 2). In the present video, we present a case where we used a new option of graft to treat urethral strictures: the L-Hydro® tissue treatment technology 100% aldehyde free, VIVENDI graft.

Materials and Methods: The present study was approved according to the ethical standards of the hospital's institutional committee on experimentation with human beings. A 57 year-old male patient developed a urethral stricture due to prolonged use of a urinary catheter during a previous hospitalization. A cystourethrogram was performed, which revealed a stenosis of the penile urethra measuring 2.5 cm in length. Urethroplasty was proposed for the surgical treatment in this case. We used a longitudinal penile incision with a ventral sagittal urethrotomy in the penile stricture. A free VIVENDI graft was placed into the longitudinal incision in the dorsal urethra and fixed with interrupted suture as dorsal inlay. The ventral urethrotomy was closed over a 16Fr Foley catheter and the skin incision was then closed in layers. The patient will receive post-operative follow-up for 3 months for clinical assessment through symptoms, uroflowmetry, urethroscopy and residual urine volume after urination.

Results: No intraoperative or postoperative complications occurred. The patient could achieve satisfactory voiding and no complication was seen during the three-month follow-up. Four weeks after surgery, he underwent urethroscopy, which revealed a good appearance of the urethra, with no stenosis or signs of infection.

Conclusion: In the present case the use of bovine pericardium graft for the treatment of penile urethral stricture had a good result and can be an option to repair complex urethral strictures. However, the results presented require a larger population group in addition to multicenter studies with longer follow-up time to ensure the findings obtained.

CONFLICT OF INTEREST

None declared.

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Abstract (maximum 200 words) and should contain

- **Main findings:** Report case(s) relevant aspects
- **Case(s) hypothesis:** Proposed premise substantiating case(s) description
- **Promising future implications:** Briefly delineates what might it add? Lines of research that could be addressed

Full text (maximum 2000 words):

- **Scenario**: Description of case(s) relevant preceding and existing aspects;
- **Case(s) hypothesis and rational:** precepts, clinical and basic reasoning supporting the case(s) hypothesis and the raised scenario. Why is it important and is being reported?
- **Discussion and future perspectives:** what might it add and how does it relate to the current literature. 'Take-home message' - lessons learnt;
- **Table and/or Figure limits:** 2 (plates aggregating multiple images are encouraged) each exceeding table or figure will decrease 250 words of the full text;
- **Number of references:** 10-15.

Radiology Page: Will be published upon the Section Editor decision.

Video Section: The material must be submitted in the appropriate local, in the Journal's site, whe-

re all instructions may be found (Video Section link) Letters to the Editor: The letter should be related to articles previously published in the Journal, should be useful for urological practice and must not exceed 500 words. They will be published according to the Editorial Board evaluation.

ILLUSTRATIONS:

The illustrations should not be sent merged in the text. They should be sent separately, in the final of the manuscript.

1) The number of illustrations should not exceed 10 per manuscript.
2) Check that each figure is cited in the text.
3) The legends must be sent in a separate page.
4) The legends of histological illustrations should contain the histological technique and the final magnification.
5) The International Braz J Urol encourages color reproduction of illustrations wherever appropriate.
6) All histological illustrations should be supplied in color.

ELECTRONIC SUBMISSION:

1) Do not embed the figures in the text, but supply them as separate files.
2) For Submitting Photographs Electronically, please:
Supply photographs as TIFF (preferable) or JPG files. The TIFF of JPG should be saved at a resolution of 300 dpi (dots per inch) at final size. If scanned, the photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, not embed in Word or PowerPoint.
3) For Submitting Line Artwork Electronically please note that:
Line drawings must be supplied as EPS files (give an EPS extension, e.g. Fig01.eps). Use black text over light to mid grey and white text over dark grey or black shades. Use lower case for all labeling, except for initial capitals for proper nouns and necessary mathematical notation. Centre each file on the page and save it at final size with the correct orientation. We recommend a minimum final width of 65 mm, but note that artwork may need to be resized and relabeled to fit the format of the Journal.
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TABLES: The tables should be numbered with Arabic numerals. Each table should be typed on a single page, and a legend should be provided for each table. Number tables consecutively and cites each table in text in consecutive order.
REFERENCES: The References should be numbered following the sequence that they are mentioned in the text. The references should not be alphabetized. They must be identified in the text with Arabic numerals in parenthesis. Do not include unpublished material and personal communications in the reference list. If necessary, mention these in the body of the text. For abbreviations of journal names refer to the "List of Journals Indexed in Index Medicus" (http://www.nlm.nih.gov). The authors must present the references according to the following examples; the names of all authors must be included; when exist more than six authors, list the first six authors followed by et al. The initial and the final pages of the reference should be provided:

Papers published in periodicals:

- Paterson RF, Lifshitz DA, Kuo RL, Siqueira Jr TM, Lingeman JE: Shock wave lithotripsy monotherapy for renal calculi. Int Braz J Urol. 2002; 28:291-301.

- Holm NR, Horn T, Smedts F, Nordling J, de la Rossete J: Does ultrastructural morphology of human detrusor smooth muscle cell characterize acute urinary retention? J Urol. 2002; 167:1705-9.

Books:

- Sabiston DC: Textbook of Surgery. Philadelphia, WB Saunders. 1986; vol. 1, p. 25.

Chapters in Books:

- Penn I: Neoplasias in the Allograft Recipient. In: Milford EL (ed.), Renal Transplantation. New York, Churchill Livingstone. 1989; pp. 181-95.

The Int Braz J Urol has the right of reject inappropriate manuscripts (presentation, number of copies, subjects, etc.) as well as proposes modifications in the original text, according to the Referees' and Editorial Board opinion.

THE EDITORS SUGGEST THE AUTHORS TO OBSERVE THE FOLLOWING GUIDELINES WHEN SUBMITTING A MANUSCRIPT:

The **Ideal Manuscript** may not exceed 2500 words.

The **Title** must be motivating, trying to focus on the objectives and content of the manuscript.

Introduction must exclude unnecessary information. It should briefly describe the reasons and objective of the paper.

Materials and Methods should describe how the work has been done. It must contain sufficient information to make the study reproducible. The statistical methods have to be specified.

The **Results** should be presented using Tables and Figures whenever possible. Excessive Tables and Figures must be avoided. The tables should not be repeated on the text.

The **Discussion** must comment only the results of the study, considering the recent literature.

Conclusions must be strictly based on the study findings.

References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

The Abstract must contain up to 250 words and must conform to the following style: Purpose, Materials and Methods, Results and Conclusions. Each section of the manuscript must be synthesized in short sentences, focusing on the most important aspects of the manuscript. **The authors must remember that the public firstly read only the Abstract, reading the article only when they find it interesting.**

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The authors should observe the following checklist before submitting a manuscript to the International Braz J Urol

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- The Article is restricted to about 2,500 words and 6 authors.
- Abbreviations were avoided and are defined when first used and are consistent throughout the text.
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- The staining technique and the final magnification were provided for all histological illustrations. The histological illustrations are supplied in color.
- Legends were provided for all illustrations, tables, and charts. All tables and charts were in separate pages and referred to in the text. All illustrations and tables are cited in the text.
- An Abstract was provided for all type of articles. The length of the Abstract is about 250 words.
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- A list of abbreviations is provided.