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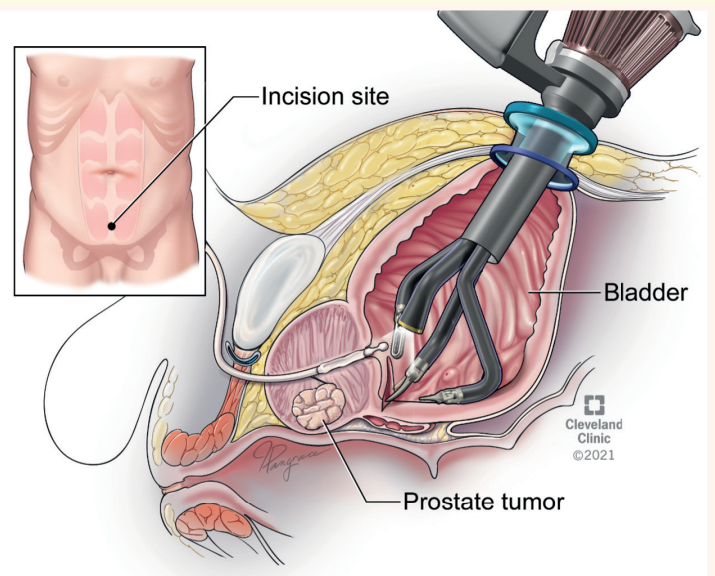

Single-port transvesical robot-assisted radical prostatectomy. The patient is kept in a supine position. The camera and instruments are introduced directly into the urinary bladder. (page 704)

XXXIX Brazilian Congress of Urology
November 18 - 21, 2023 - Salvador - BA - Brazil

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LETTER TO THE EDITOR

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EDITORIAL
IN THIS ISSUE

Vesical imaging reporting and data system (VI-RADS) in bladder cancer diagnosis in review in this number of International Brazilian Journal of Urology

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The July-August number of *Int Braz J Urol*, the 17th under my supervision, presents original contributions with a lot of interesting papers in different fields: Robotic Surgery, Prostate Cancer, Overactive Bladder, Bladder Cancer, renal cancer, myelomeningocele, renal stones, congenital adrenal hyperplasia, Testicular torsion, penile cancer, BPH, Urinary incontinence and reconstructive urology. The papers came from many different countries such as Brazil, USA, Turkey, China, Belgium, Qatar and Colombia and as usual the editor´s comment highlights some of them.

In the present issue we present a important reviews about Vesical Imaging Reporting and Data System (VI-RADS) in bladder cancer diagnosis. The paper about the group of Dr.Nicola and colleagues from USA and Brazil in page 609 shows a very complete narrative review about the topic (1). The authors shows that. the technological innovation of MR imaging has advanced the assessment of bladder cancer. MR findings can be incorporated to increase the accuracy of the traditional prediction models as the EORTC, CUETO, and EAU risk stratification. The authors conclude that the use and implication of VI-RADS will improve the communication in the diagnosis, staging and surveillance of patients with bladder cancer. The editor in chief would like to highlight the following works too:

Dr. Bai and colleagues from China, presented in page 625 (2) a nice systematic review about the trifecta achievement in patients undergoing partial nephrectomy and conclude that the larger tumor size, medium and high PADUA score are associated with decreased probability of trifecta achievement.

Dr. Qin and colleagues from China performed in page 637 (3) a interesting systematic review about the Comparison of mini percutaneous nephrolithotomy and standard percutaneous nephrolithotomy for renal stones >2cm and concluded that in the treatment of >2cm renal stones, mini-PCNL should be considered an effective and reliable alternative to standard-PCNL (30FR) with less blood loss, lower transfusion rate, and shorter hospitalization. However, the mini-PCNL does not show a significant advantage over the 24F standard-PCNL. On the contrary, this procedure takes a longer operation time.

Dr. Terziotti and colleagues from Brazil performed in page 649 (4) an interesting retrospective study about the incontinence outcomes in women undergoing retropubic mid-urethral sling and conclude that both hand-made synthetic sling (HMS) and SafyreTM have similar satisfaction and subjective cure rates, with marked International Consultation on Incontinence Modular Questionnaire

for Urinary Incontinence Short Form (ICIQ-UI SF) score improvement. Higher rates of intraoperative bladder injury were seen in patients who received SafyreTM retropubic sling.

Dr. Macedo Jr. and colleagues from Brazil performed in page 672 (5) a prospective study about in utero myelomeningocele repair and high-risk bladder pattern and concluded that early urological treatment of high-risk bladder pattern was effective in approximately 60% of the patients.

Dr. Diao and colleagues from USA performed in page 679 (6) a nice study about the signs and symptoms of artificial urinary sphincter cuff erosion and concluded that artificial urinary sphincther cuff erosion most commonly presents as localized scrotal inflamation symptoms. Obstructive voiding symptoms and worsening incontinence are also common. Any of these symptoms should prompt further investigation of cuff erosion.

Dr. Moschovas and colleagues from USA performed in page 696 the cover paper of this number (7). The authors eport a multicentric opinion of referral centers on different techniques to approach the Vinci single port robotic-assisted radical prostatectomy (SP-RARP) and concluded that several techniques of SP-RARP have been reported in the literature. The authors performed a multicentric collaboration describing and illustrating the most challenging steps of this surgery. We believe that the details provided in this article are useful teaching material for new centers willing to adopt the SP technology.

Dr. Elifranji and colleagues from Doha – Qatar performed in page 706 (8) the description of a interesting surgical technique to cover and fix detorsed testis undergoing fasciotomy of tunica albuginea and concluded that the orchio-septopexy after testicular fasciotomy is a simple and fast technique that can be utilized in cases of prolonged testicular ischemia and questionable viability. More than half of the testes recovered, encouraging us to propose its utilization as well as its validation by other surgeons.

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

REFERENCES

1. Nicola R, Pecoraro M, Lucciola S, Dos Reis RB, Narumi Y, Panebianco V, et al. VI-RADS score system - A primer for urologists. Int Braz J Urol. 2022;48: 609-22.
2. Bai N, Qi M, Shan D, Liu S, Na T, Chen L. Trifecta achievement in patients undergoing partial nephrectomy: a systematic review and meta-analysis of predictive factors. Int Braz J Urol. 2022;48: 625-36.
3. Qin P, Zhang D, Huang T, Fang L, Cheng Y. Comparison of mini percutaneous nephrolithotomy and standard percutaneous nephrolithoto-my for renal stones >2cm: a systematic review and meta-analysis. Int Braz J Urol. 2022;48: 637-48.
4. Terziotti F, Gregório EP, Averbeck MA, Almeida SHM. Incontinence outcomes in women undergoing retropubic mid-urethral sling: a retrospective cohort study comparing Safyre™ and handmade sling. Int Braz J Urol. 2022;48: 649-59.
5. Macedo A Jr, Ottoni SL, Moron A, Cavalheiro S, da Cruz ML. In utero myelomeningocele repair and high-risk bladder pattern. a prospective study. Int Braz J Urol. 2022;48: 672-78.
6. Diao L, Nealon SW, Carpinito GP, Badkhshan S, Wolfe AR, Dropkin BM, et al. Presenting signs and symptoms of artificial urinary sphincter cuff erosion. Int Braz J Urol. 2022;48: 679-85.
7. Moschovas MC, Brady I, Noel J, Zeinab MA, Kaviani A, Kaouk J, et al. Contemporary techniques of da Vinci SP radical prostatectomy: multicentric collaboration and expert opinion. Int Braz J Urol. 2022;48: 696-705.
8. Elifranji M, Abbas T, Leslie B, Vallasciani S, El Kadhi A, Pippi-Salle JL. Orchio-Septopexy: A new technique to cover and fix detorsed testis undergoing fasciotomy of tunica albuginea. Int Braz J Urol. 2022;48: 706-11.

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REVIEW ARTICLE

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VI-RADS score system – A primer for urologists

Refky Nicola [1], Martina Pecoraro [2], Sara Lucciola [2], Rodolfo Borges dos Reis [3], Yoshifumi Narumi [4], Valeria Panebianco [2], Valdair Francisco Muglia [5]

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ABSTRACT

Bladder cancer (BCa) is one of the most common cancers worldwide and is also considered to be one of the most relapsing and aggressive neoplasms. About 30% of patients will present with muscle invasive disease, which is associated with a higher risk for metastatic disease.

The aim of this article is to review the state of art imaging in Radiology, while providing a complete guide to urologists, with case examples, for the rationale of the development of the Vesical Imaging Reporting and Data System (VI-RADS), a scoring system emphasizing a standardized approach to multiparametric Magnetic Resonance Imaging (mpMRI) acquisition, interpretation, and reporting for BCa.

Also, we examine relevant external validation studies and the consolidated literature of mpMRI for bladder cancer. In addition, this article discusses some of the potential clinical implications of this scoring system for disease management and follow-up.

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INTRODUCTION

Bladder cancer (BC) is the second common cancer within the genitourinary tract and the ninth most common malignancy in the World. It is even more prevalent within Western Europe (1). As of 2018, the number of global new cases and deaths from bladder cancers were estimated at approximately 550.000 and 200.000, respectively (2).

Smoking is the primary risk factor for bladder cancer and has been associated with over 55% of all cases in the United States (3). In addition, occupational exposure to polycyclic aromatic hydrocarbons and chlorinated hydrocarbons among paint and dye plant workers is the second

most common risk factor (4). Also, the chronic irritation of the bladder mucosa, caused either by chronic urinary tract infections or stones is associated with an increased incidence of squamous cell cancers (5). With bladder cancer, there is a slight male predominance, ranging from 1.3/1.0 in Central Africa up to 4.0/1.0 in Southern Europe (1, 5).

The staging of bladder cancer is of utmost importance. Usually, BC is staged as either non-muscle invasive BC (NMIBC) or muscle invasive BC (MIBC), based on the extension of the tumor invading the bladder wall. The proportion of MIBC, at initial diagnosis, is estimated between 25-30%. The invasion of the muscularis layer of the bladder has tremendous implications in the management and prognosis of the disease.

Despite all advances in the detection of small bladder lesions and carcinoma in situ (CIS), including narrow band imaging, fluorescence cystoscopy, and optical coherence, and the great interest about molecular assays, the chances of progression and recurrence in NMIBC patients are still very high and comparable to those seen at the end of 1990 (6, 7). Some studies have showed that 10-20% of NMIBC patients at one time will eventually progress to MIBC, but roughly 50-70% will recur over time (8). Even when more aggressive management is chosen, the prognosis of BC is poor, with 5-year overall survive of 50% only, and with systemic (metastatic) disease up to 15% (1, 9).

The relevance of BC, however, cannot be estimated only by those numbers. Not only is the mortality rate a significant concern in BC, but also the high rate of recurrence has a great impact on quality of life of a significant portion of patients with BC (8) and the high lifetime treatment-associated costs (10, 11).

The case for an Imaging Stratification Risk Score

Once the diagnosis of BC is made, the status of the bladder wall, according to major International Guidelines (12-14) is defined after tissue sampling performed at transurethral resection of bladder tumor (TURBT).

The need for appropriate staging tool could be scaled when Dutta et al. (15) demonstrated that for the patients who were under staged at initial diagnosis, the 5-year mortality rate was up to 30% higher compared to those correctly staged. One of the main limitations of TURBT for the diagnosis and staging of BC is its low sensitivity for assessment of MIBC (16). As showed, these clinically under staged patients are at higher risk for advance disease progression.

The clinical staging errors, at TURBT procedure, considering only T1 BC lesions, has been described and varies from 24 to 62%. In the series of Fristche et al. (17) and Ark et al. (18), the rate of incorrect staging at first TURBT was quite similar, 49.7% and 48.0%, respectively. In the study of Ark et al., multiple lesions and a history of prior TURBT were considered independent predictors of understaging at radical cystectomy (RC). Currently, en bloc TURBT has been proposed and advocated to reduce recurrence rates and the need for a second TURBT (19).

Besides these relevant implications for patient's management, TURBT is a quite invasive procedure, although performed on an outpatient basis (12). The risk of bladder perforation is estimated by Herkommer et al. (20) in 1.1 to 5.3% patients. However, this could be underestimated, as demonstrated in a study by Balbay et al. (21), that found bladder perforations occurring in up to 58% of the cases, when using cystograms as the standard of reference.

Based on the lack of reliable molecular assays and the known limitations of TURBT as staging tool, there would be room for a staging technique that could accurately define the status of muscular layer, sparing patients from additional invasive procedures and, at the limit, potentially unnecessary surgery. For a long time, the use of imaging for local staging of BC has been limited to both Computed Tomography, and secondarily to Magnetic Resonance Imaging (MRI) (22-24).

However, based upon enhancement in soft tissue characterization with diffusion-weighted imaging (DWI) and dynamic-contrast enhancement (DCE), the accuracy of the multiparametric MRI for staging BC has significantly increased to greater than 90% (25-27).

Standardization of imaging approach to BC - The VI-RADS initiative

In 2018, a multidisciplinary group of radiologists, urologists, pathologists and radiation oncologist, with an interest in bladder cancer, developed a scoring system (28) aimed to: 1) standardize the protocols for MR imaging of BC; 2) provide a structured reporting system to improve communication between referring physicians and radiologists, and; 3) provide a risk score for muscle layer invasion in BC. This initiative was named VI-RADS (Vesical Imaging-Reporting and Data System), which followed the precursors of "RADS", the BI-RADS (Breast Imaging-Reporting and Data System) and the PI-RADS (Prostate Imaging-Reporting and Data System).

Briefly, the VI-RADS score system could be divided in three distinct, interconnected steps: patient preparation; exam acquisition protocol and images interpretation.

Patient preparation. Some important details are required in the preparation of patients undergoing a pelvic MRI for BC staging. These steps are all essentials to obtain the best results from the examination (28).

Antispasmodic agents are administered in order to minimize motion and inherent susceptibility artifacts (29). Patients are usually advised to void one to two hours before imaging and, depending on individual tolerance, to drink 0.5 to 1L of water before the examination. Indeed, adequate bladder distension is the major requirement. Ideally, the bladder should not be under or overdistended and a volume of 250 to 300mL is an ideal range for a good examination (30). Rapid sequences or real-time MRI can be used to monitor bladder distension. A good guide is to ensure proper visualization of the vesical dome on sagittal plane: an outward convex contour of the dome usually indicates an adequate distention. Without distention, the bladder wall can appear falsely thicker than usual, which, occasionally, could be misinterpreted as a lesion which can result in over staging (31).

MRI protocol

The VI-RADS is largely based on multiparametric MRI, this multimodal approach was chosen to reduce the risk of error when staging a BC from one single sequence.

The evidence in literature suggests that high-field scanners, 1.5 and 3.0T, can be used indistinctively, as both generate high spatial resolution and signal-to-noise ratio (28, 32). Here, the main recommendation is the use of a phased-array external, surface coil also with at least 16-channels.

The T2-weighted images were named structural category as these images, due to high contrast-resolution and excellent spatial resolution, are well suited for assessing the anatomy of the whole pelvis, including bladder and surrounding structures. These images can be acquired as 2D sequences in three planes (axial, coronal and sagittal) or can be acquired in a single volumetric (3D) acquisition. The choice will be specific for every scanner, as the spatial and contrast resolution may show large variation depending on the vendor and generation of the scanner. The slice thickness should be kept thin, 3.0 to 4.0mm, maximum (33). T2WI is used to assess tumor detection, localization, evaluation of the size and morphology.

Diffusion-weighted images (DWI) is a functional technique based on the movements of water molecules in a given tissue or material (34). DWI has been used in virtually all abdominal examinations due to the significant provided information, particularly in oncological imaging, regardless of the site. It plays a critical role in prostate, liver and bladder cancer imaging (35-37). Although, at first glance, the T2 sequence provides better spatial resolution for assessing the depth of tumor extension, DWI has been proved more accurate for defining muscle layer status. Dynamic contrast enhanced (DCE) MRI is considered the dominant (defining) sequences, when disparities between sequences are found (25, 38). A high B value (800-1000s/mm2) is usually required to visualize BC. Images are obtained in at least the axial plane; however, an additional plane (such as sagittal) is helpful for staging, especially for small lesions (39).

The DCE is the third key component of the VI-RADS and bladder MRI protocol (28). Its acquisition strongly relies on well-defined time points, which improves the differentiation between the inner layer (mucosa + lamina propria) from the muscularis propria (also referred to as detrusor muscle) (40). Although, anatomical evaluation is the major

goal, it can be considered a functional technique, as it reflects vascularity and microvessel permeability and semi-quantitative analysis can be performed from this sequence. The best option is the use of an axial 3D T1-weigthed, gradient echo (GRE) sequence with fat-suppression that can be reformatted in other planes, due to high spatial resolution (41). Recently, a prospective study reported similar accuracy of a protocol without intravenous contrast media compared to multiparametric one, for the detection of muscle invasion (42). However, further studies are required for better evaluation of a biparametric approach for BC staging.

The original VI-RADS manuscript provides details of the technical requirements and the acquisition protocol of MRI, along with specific references (28).

Interpretation and Reporting

The VI-RADS score has five categories (28), based upon degrees of invasion of the muscularis layer from highly unlikely, category 1, to very likely, category 5 (Table-1).

The initial approach is usually done using T2-weigthed images, where the lesions present with intermediate signal, contrasting to the low

Table 1 - VI-RADS original description for SC-Structured Category (T2 images), Dynamic Contrast-Enhanced (DCE) and Diffusion-Weighted Imaging (DWI). Adapted from reference #27.

	Structured Category (T2)	DCE	DWI
1	Uninterrupted low SI line representing the integrity of muscularis propria (lesion <1.0 cm; e.g., exophytic tumor with or without stalk or thickened inner layer	No early enhancement of the muscularis propria (lesions corresponding to SC 1 findings)	Muscularis propria with intermediate continuous SI on DWI (lesion <1cm, hyperintense on DWI and hypointense on ADC, with or without stalk and/or low SI thickened inner layer on DWI)
2	Uninterrupted low SI line representing the integrity of muscularis propria (lesion >1cm; exophytic tumor with stalk and/or high SI thickened inner layer, when present, or sessile/broad-based tumor with high SI thickened inner layer, when present)	No early enhancement of muscularis propria with early enhancement of inner layer (lesions corresponding to SC 2 findings)	Muscularis propria with continuous intermediate SI on DWI (lesion >1cm, hyperintense on DWI and hypointense on ADC, with low SI stalk and/or low SI thickened inner layer on DWI, or broad-based/sessile tumor with low/intermediate SI thickened inner layer on DWI).
3	Lack of category 2 findings with associated presence of an exophytic tumor without stalk, or sessile/broad-based tumor without high SI thickened inner layer but with no clear disruption of low SI muscularis propria	Lack of category 2 findings (lesions corresponding to SC category 3 findings) but with no clear disruption of low SI muscularis propria.	Lack of category 2 findings (lesions corresponding to T2 category 3 findings) but with no clear disruption of low SI muscularis propria.
4	Interruption of low SI line suggesting extension of the intermediate SI tumor tissue to muscularis propria	Tumor early enhancement extends focally to muscularis propria	High SI tumor on DWI and low SI tumor on ADC extending focally to muscularis propria.
5	Extension of intermediate SI tumor to extravesical fat, representing the invasion of the entire bladder wall and extravesical tissues	Tumor early enhancement extends to the entire bladder wall and to extravesical fat	High SI tumor on DWI and low SI tumor on ADC extending to the entire bladder wall and extravesical fat.

signal of the muscle layer and the high signal of urine (43). This differentiation will be pursued in all sequences of a mpMRI of the bladder (Figure-1). An uninterrupted low signal will be the hallmark of categories 1 and 2, highly predictive of NMIBC, with category 2 reserved for lesions larger than 1.0cm (Figure-2). On the other side, an unequivocally interrupted low signal is the typical finding indicating muscle invasion, reserved for categories 4 and 5 (Figure-3). The latter is assigned when perivesical fat extension and involvement of adjacent structures are present. The category 3 is used when there is absence of category 2 findings, but when no obvious discontinuity of the muscle layer is observed.

The same approach is performed for DWI and DCE images. However, these two categories are the dominant sequences, therefore, in cases where there is discrepancy of findings between structural category (T2 images) and functional sequences (DWI and DCE), these two sequences will prevail, either for downgrading or upgrading the lesion (28). Accordingly, the final classification may be originated from several different combinations of T2, DWI and DCE categories as showed in Figure-4.

The report of any vesical lesion should be done in a semi-structured model (44), following these steps: clinical indication; a brief description of the MRI protocol; findings description including lesion location, morphology, measurements, and signal characteristics, when scoring at T2, DWI and DCE is assigned. The evaluation for transmural extension, adjacent organ invasion (when present), and pelvic lymph nodes and bone status are also performed. Finally, the final category and comments should be provided to summarize the report.

Validation Studies

The VI-RADS score system has been tested in several studies, from all over the World (45-56), either prospective or retrospective in nature. Two major points have been assessed in these initial studies: its reproducibility and its diagnostic accuracy for determining muscle layer invasion (Table-2).

The interobserver agreement for VI-RADS can be considered a major strength for the system. It has been reported in the range of optimal to almost perfect, varying from 0.73 up to 0.92, regardless of the experience of the readers. In a recent meta-analysis of Del Giudice et al. (57), focusing on the reproducibility of VI-RADS, the pooled weighted mean kappa score (κ) was 0.83

Figure 1 - These pictures illustrate how structural categories (T2 images) of VI-RADS are assigned. The muscularis propria is presented as a thick black layer. The inner layer (urothelium + lamina propria) is a thin white layer. The tumors are shown in grey and the stalk, when present, in black, in continuity with the muscular layer. The inner layer is preserved in categories 1 and 2. In category 3, the inner layer is not seen, but there is no clear sign of muscle invasion. In categories 4 and 5, the tumors have extended to the muscular layer, and in VI-RADS 5, they go beyond, until perivesical fat.

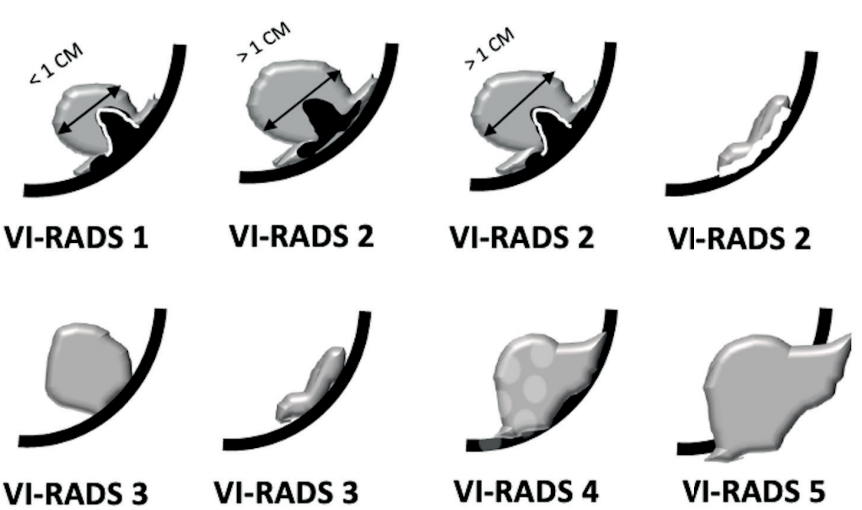
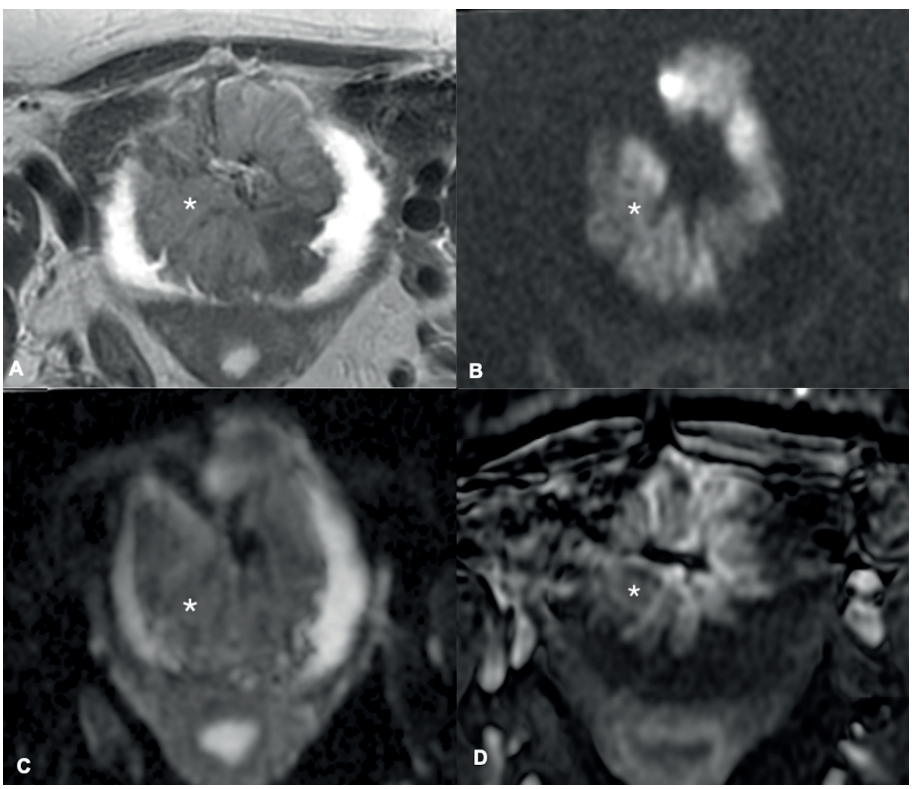


Figure 2 - A 72-year-old woman presented with macroscopic hematuria. A) T2W image (axial plane) shows a large stalked mass at the anterior bladder wall. B and C) DWI (b=2000) and ADC maps show significantly restricted diffusion, not extending through the muscularis propria; the "inchworm" sign can be appreciated. D) DCE imaging shows early and heterogeneous enhancement of the lesions, not extending through the muscularis propria. The final VI-RADS score was 2. T2W, T2 weighted; DCE, dynamic contrast-enhanced; DWI, diffusion-weighted image; ADC, apparent diffusion coefficient.

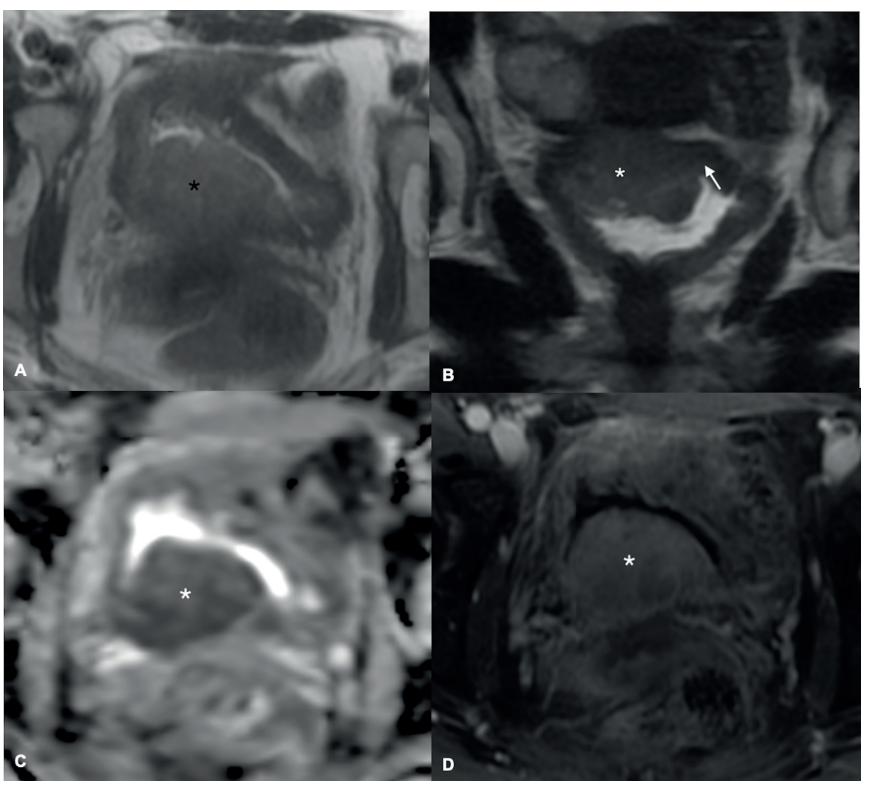


(95% Confidence Interval: 0.78-0.88), in spite of a significant heterogeneity in the studies included in the systematic review. Of importance here is to remember that reproducibility, in a broad sense, may encompass the variations across different scanners and centers, with different levels of experience, which may influence the adoption of a new classification system.

The diagnostic accuracy of VI-RADS has been evaluated in two recent meta-analysis. In the study of Woo et al. (58), six studies, two prospective, were included and the pooled sensitivity was 0.83 (95% confidence interval, 0.70-0.90) and pooled specificity was 0.90 (0.83-0.95), and the accuracy, measured by the area under the ROC curve, was 0.94 (0.91-0.95). Luo et al. (59) also included six studies (five were the same as in the study of Woo et al.), including the same two prospective studies, and pooled sensitivity, specificity, and diagnostic accuracy (again by AUC) were, respectively, 0.90 (0.86-0.94), 0.86 (0.71-0.94), and 0.93 (0.91-0.95) using VI-RADS 3 as the cutoff value for muscle invasion and, 0.77 (0.65-0.86), 0.97 (0.88-0.99), and 0.92 (0.89-0.94) when VI-RADS 4 was the cut off for invasion. In both meta-analysis, there was a significant study heterogeneity. Woo et al. (58) indicated the number of patients in the study, the magnetic field strength of the scanners (3.0 vs. 1.5T), image slice thickness (3 vs. 4mm) in T2 images, and VI-RADS cutoff score, from 3 or 4 as the major source of heterogeneity. In the study of Luo et al. (59), study design (retrospective or prospective) and surgical pattern of standard of reference were the main source of the heterogeneity.

The definition of which score should assumed as indicative of invasion of muscle layer varies, as different scores can be chosen according to

Figure 3 - A 46-year-old, female, complains of frequency, urgency, and severe incontinence. A pelvic sonogram showed moderate to marked left hydronephrosis and asymmetric bladder wall thickening on the top portion of her bladder. A and B) Axial and Coronal T2-weighted MRI of the pelvis demonstrates a 4.4 x 3.6cm mass extending to muscle layer. C) ADC map in the axial plane, and D) T1 post-contrast, also in the axial plane, confirming that mass shows extension into the muscular layer. This was consistent with VI-RADS 4, confirmed after surgery.



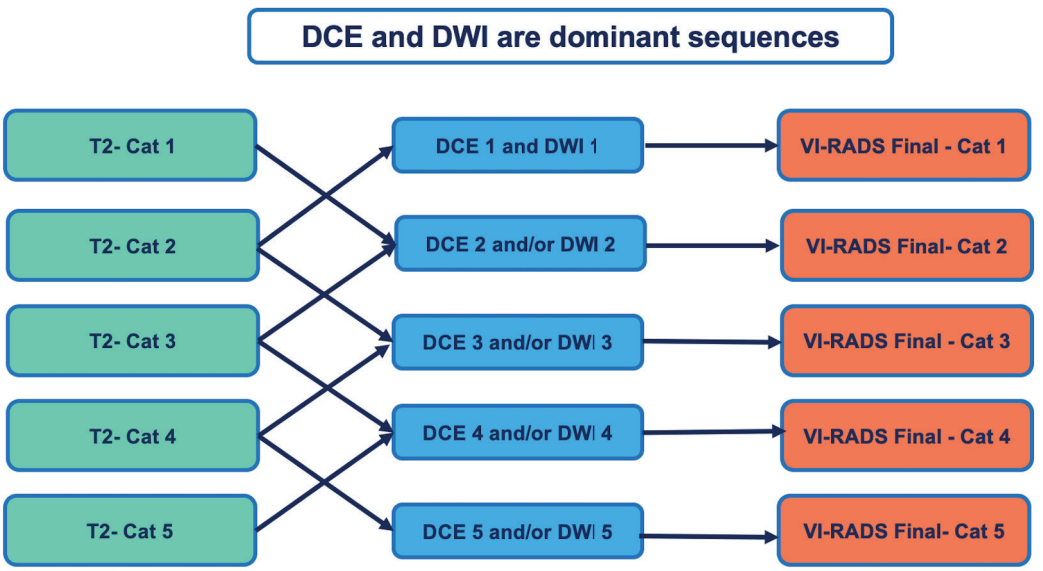
different clinical scenarios. For instance, VI-RADS 3 could be used as the cutoff value when dealing with patients with high pre-test probability of muscle invasion, including, but not limited to, patients with high-grade, recurrent, multiple and or larger lesions (>3.0cm). On the other side, VI--RADS 4 could be defined as the cut off, in clinical settings requiring higher specificity, e.g., more aggressive treatment options are being considered.

Both studies showed similar results of a previous meta-analysis, carried out in 2017, before VI-RADS release, including 24 studies, showing pooled sensitivity of 0.92 (95% CI 0.88-0.95) and specificity of 0.87 (95% CI 0.78-0.93). Here, the appeal for the use of VI-RADS relies on the future gains of using a standardized approach for image acquisition and for reporting BC lesions assessed by mpMRI. The potential gain in the reproducibility, as the performance of less skilled readers tend to increase when an established system is used, as demonstrated by the comparison of PI-RADS and Likert scale (60).

Of note, Del Giudice et al. (61) investigated the role of VI-RADS score 5 in predicting time-to--cystectomy (TTC) outcomes. Authors showed, not only that VI-RADS is valid and reliable in differentiating patients with extravesical disease, but also that the identification of a VI-RADS score of 5 implies in a significant delay in TTC, independently from other clinicopathological features.

VI-RADS also provided possible alternatives and decision aids in the treatment of BCa during the COVID-19 emergency setting, to minimize potential exposure to the infection by avoiding hospital admissions: patients with NMIBC and preoperative VI-RADS score of 1-2 were directed to appropriate adjuvant intravesical therapy for follow-up, rather than a secondary resection of

Figure 4 - The decision algorithm for VI-RADS. When all categories are coincident, the final score is directly assigned. When classification in different sequences is discordant, DCE, and DWI are the dominant sequences and will prevail for the final classification. As seen in figure 4, DCE and DWI can upgrade or downgrade the initial classification found on T2 images.



the tumor, considering the low risk of understaging (62).

Recently, the first multi-institutional, multi-reader study, authored by Ueno et al. (63), who observed moderate to substantial interobserver agreement and a pooled AUC of 0.87 among radiologists of different levels of expertise using VI-RADS, again confirming the existing high reproducibility of score in the "real life" clinical practice (different scans and different reader's experience).

Perspectives for the use of mpMRI and VI-RADS in Bladder Cancer

The original suitability of VI-RADS system was limited to patients not previously surgically manipulated, to avoid post-procedures changes influencing the final classification (28). This requirement limits the applicability of the score system, as frequently, patients have already submitted to TURBT. Considering the relevance of expanding the use of VI-RADS, new data on this topic is expected to be coming in the near future, with emphasis on the accuracy of MRI and VI-RADS scoring in differentiating inflammatory changes secondary to the surgical procedure from malignant findings (64-67).

A second issue for potential VI-RADS updating is the incorporation of associated findings. Currently, there is no place for citing these features, some of them with a potential to change management of the lesion, for instance, hydronephrosis (68).

Another potential use of mpMRI and VI-RADS is to stratify patients diagnosed with high-risk NMIBC at first TURBT (69, 70). The risk of muscle layer invasion at radical cystectomy, in these patients is estimated in about 30% (71, 72). In this setting, the use of VI-RADS for risk stratification and discrimination of those who should undergo secondary tumor resection and those who can be spared might be assessed in the near future. A trial assessing the value of mpMRI in this clinical setting was initiated in the United Kingdom (73), where the "Bladder-Path" study was designed to divide patients with confirmed BC after first TURBT, into a group with probable NMIBC, receiving current standard approach, from another group composed of patients with risk factors for MIBC, who will proceed to mpMR imaging for differentiation between MIBC and NMIBC.

With regards to the high rate of recurrence for BC, the post-treatment surveillance is another

Table 2 - Main validation studies published until March 2021.

Study/year	Country	Study type	Nature	#of patients	Interreader agreement	Sensitivity	Specificity	Accuracy	Standard of Reference
Ueno et al. 2019 (44)*	Japan	Original Research	Retrospective	74	ICC=0.85	0.76 (Cat. ≥4) 0.88 (Cat. ≥3)	0.93 (Cat. ≥4) 0.77 (Cat. ≥3)	90	TURB
Barchetti et al. 2019 (45)	Italy	Original Research	Retrospective	75	K=0.73	0.82 - 91 (Cat. ≥3)	0.85 - 0.89 (Cat. ≥3)	0.87 - 0.93	TURB
Wang et al. 2019 (46)	China	Original Research	Retrospective	340	K=0.92	0.87 (Cat. ≥3)	0.97 (Cat. ≥4)	0.94	TURB, Cystectomy
Makboul et al 2019 (47)	Egypt	Original Research	Prospective	50	K=0.87	0.78 (Cat. ≥3)	0.88 (Cat. ≥3)	0.83	TURB
Kim et al. 2019 (48)	South Korea	Original Research	Retrospective	297	K=0.89 (T2) K=0.82 (DWI) K=0.85 (DCE)	0.91 (Cat. ≥4) 0.95 (Cat. ≥3)	0.76 (Cat. ≥4) 9.44 (Cat. ≥3)	N/A	TURB, Cystectomy
Del Giudice et al. 2019 (49)	Italy	Original Research	Prospective	231	K=0.92	0.92 (Cat. ≥3)	0.91 (Cat. ≥3)	0.94	TURB, Cystectomy
Hong et al. 2020 (50)	South Korea	Original Research	Retrospective	66	K=0.97	0.90 (Cat. ≥3)	1.0 (Cat. ≥3)	0.95	TURB, Cystectomy
Marchioni et al. 2020 (51)	Italy	Original Research	Prospective	38	K=0.76	0.86 (Cat. ≥4)	0.87 (Cat. ≥4)	0.90	TURB
Liu et al. 2020 (52)	China	Original Research	Retrospective	126	N/A	0.94 (Cat. ≥4)	0.92 (Cat. ≥4)	0.90	TURB, Cystectomy
Wang et al. 2020 (53)	China	Original Research	Retrospective	220	N/A	0.92 (Cat. ≥4) 0.97 (Cat. ≥3)	0.95 (Cat. ≥4) 0.77 (Cat. ≥3)	0.96	TURB, Cystectomy
Sakamoto et al. 2020 (54)	Japan	Original Research	Retrospective	176	K=0.43	0.63 (Cat. ≥4) 0.78 (Cat. ≥3)	0.96 (Cat. ≥4) 0.70 (Cat. ≥3)	0.86	TURB
Metwally et al. 2021 (55)	Egypt	Original Research	Prospective	331	K=0.93	0.84 (Cat. ≥4)	0.90 (Cat. ≥4)	0.94	TURB
Woo et al. 2020 (57)	USA	Meta-analysis		1770 (6 studies)	K=0.81 - 0.92 ICC=0.85	0.83	0.90	0.94	TURB, Cystectomy
Luo et al. 2020 (58)	China	Meta-analysis		1064 (6 studies)	N/A	0.90	0.86	0.93	TURB, Cystectomy

*number of citation in the text.
N/A = not available.
TURB = Transurethral resection of bladder.

potential use of mpMRI (72). Although, cystoscopy is the gold-standard in the follow-up of these patients, a non-invasive tool could be helpful, especially when a local recurrence is suspected. In follow-up period, inflammatory changes after a TURBT may persist for up to 24 months (66) and could be misinterpreted, mostly within 2 weeks from the procedure, as residual or recurrent disease especially on T2-weighted images. Nonetheless, DCE and especially DWI are crucial for the correct interpretation.

The medical treatment for NMIBC and MIBC includes chemotherapy, immune checkpoint inhibitors and Bacillus Calmette-Guerin (BCG) intravesical instillations (74). However, considering the limitations of applying solid tumors response criteria in the bladder to evaluate tumor burden before and after medical treatment, mpMRI has been useful in the assessment of these patients as demonstrated by a marked increase in the ADC values with complete response after neoadjuvant chemotherapy (75-77). Also, considering the response to immunotherapy, Necchi et al. (78) demonstrated the promising role of MRI in the evaluation of response to therapy before and after immunotherapy. However, it did so apply a dichotomic method, which implied fewer promising outcomes from the combined complete/partial responder's assessment (i.e., pT≤1). Instead, the use of a five-scale assessment score for response to system therapy might provide a model to define the complete spectrum of pathological treatment response among MIBC patients ultimately undergoing RC.

CONCLUSIONS

The technological innovation of MR imaging has advanced the assessment of bladder cancer. These ongoing developments have yet to be better defined but arguably have the potential to change how BC is staged and monitored. In the future, MR findings can be incorporated to increase the accuracy of the traditional prediction models as the EORTC, CUETO, and EAU risk stratification. The use and implication of VI-RADS will improve the communication in the diagnosis, staging and surveillance of patients with bladder cancer.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Zang Y, Li X, Cheng Y, Qi F, Yang N. An overview of patients with urothelial bladder cancer over the past two decades: a Surveillance, Epidemiology, and End Results (SEER) study. Ann Transl Med. 2020; 8:1587.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68:394-424. Erratum in: CA Cancer J Clin. 2020; 70:313.
3. Mallin K, David KA, Carroll PR, Milowsky MI, Nanus DM. Transitional cell carcinoma of the bladder: racial and gender disparities in survival (1993 to 2002), stage and grade (1993 to 2007). J Urol. 2011; 185:1631-6.
4. Al-Husseini MJ, Kunbaz A, Saad AM, Santos JV, Salahia S, Iqbal M, et al. Trends in the incidence and mortality of transitional cell carcinoma of the bladder for the last four decades in the USA: a SEER-based analysis. BMC Cancer. 2019; 19:46.
5. Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013; 63:234-41.
6. Soukup V, Čapoun O, Cohen D, Hernández V, Babjuk M, Burger M, et al. Prognostic Performance and Reproducibility of the 1973 and 2004/2016 World Health Organization Grading Classification Systems in Non-muscle-invasive Bladder Cancer: A European Association of Urology Non-muscle Invasive Bladder Cancer Guidelines Panel Systematic Review. Eur Urol. 2017; 72:801-13.
7. Chang SS, Bochner BH, Chou R, Dreicer R, Kamat AM, Lerner SP, et al. Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/ASTRO/SUO Guideline. J Urol. 2017; 198:552-9. Erratum in: J Urol. 2017; 198:1175.
8. Canter DJ, Revenig LM, Smith ZL, Dobbs RW, Malkowicz SB, Issa MM, et al. Re-examination of the natural history of high-grade T1 bladder cancer using a large contemporary cohort. Int Braz J Urol. 2014; 40:172-8.
9. Maisch P, Lunger L, Düwel C, Schmid SC, Horn T, Gschwend JE, et al. Outcomes of palliative cystectomy in patients with locally advanced pT4 bladder cancer. Urol Oncol. 2021; 39:368.e11-368.e17.

10. Mossanen M, Wang Y, Szymaniak J, Tan WS, Huynh MJ, Preston MA, et al. Evaluating the cost of surveillance for non-muscle-invasive bladder cancer: an analysis based on risk categories. World J Urol. 2019; 37:2059-65.
11. Korkes F, Maluf F. Increasing costs from bladder cancer in the Brazilian Health System: the role of establishing public health policies. Int Braz J Urol. 2021; 47:443-7.
12. Alfred Witjes J, Lebret T, Compérat EM, Cowan NC, De Santis M, Bruins HM, et al. Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. Eur Urol. 2017; 71:462-75.
13. Chang SS, Boorjian SA, Chou R, Clark PE, Daneshmand S, Konety BR, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. J Urol. 2016; 196:1021-9.
14. https://auau.auanet.org/sites/default/files/US2018%20Lesson%2029.pdf. From www.aua.net. Acessed Jan 4th, 2021.
15. Dutta SC, Smith JA Jr, Shappell SB, Coffey CS, Chang SS, Cookson MS. Clinical under staging of high risk nonmuscle invasive urothelial carcinoma treated with radical cystectomy. J Urol. 2001; 166:490-3.
16. Matulewicz RS, Frainey BT, Oberlin DT, Meeks JJ. High-Risk of Adverse Pathologic Features in Patients With Clinical T1 High-Grade Bladder Cancer Undergoing Radical Cystectomy. J Natl Compr Canc Netw. 2016; 14:1403-11.
17. Fritsche HM, Burger M, Svatek RS, Jeldres C, Karakiewicz PI, Novara G, et al. Characteristics and outcomes of patients with clinical T1 grade 3 urothelial carcinoma treated with radical cystectomy: results from an international cohort. Eur Urol. 2010; 57:300-9. Erratum in: Eur Urol. 2015; 68:171.
18. Ark JT, Keegan KA, Barocas DA, Morgan TM, Resnick MJ, You C, et al. Incidence and predictors of understaging in patients with clinical T1 urothelial carcinoma undergoing radical cystectomy. BJU Int. 2014; 113:894-9.
19. Bangash M, Ather MH, Khan N, Mohammad S, Uddin Z. Comparison Of Recurrence Rate Between "EN BLOC" Resection Of Bladder Tumour And Conventional Technique For Non-Muscle Invasive Bladder Cancer. J Ayub Med Coll Abbottabad. 2020; 32:435-40.
20. Herkommer K, Hofer C, Gschwend JE, Kron M, Treiber U. Gender and body mass index as risk factors for bladder perforation during primary transurethral resection of bladder tumors. J Urol. 2012; 187:1566-70.
21. Balbay MD, Cimentepe E, Unsal A, Bayrak O, Koç A, Akbulut Z. The actual incidence of bladder perforation following transurethral bladder surgery. J Urol. 2005; 174:2260-2.
22. Persad R, Kabala J, Gillatt D, Penry B, Gingell JC, Smith PJ. Magnetic resonance imaging in the staging of bladder cancer. Br J Urol. 1993; 71:566-73.
23. Kim JK, Park SY, Ahn HJ, Kim CS, Cho KS. Bladder cancer: analysis of multi-detector row helical CT enhancement pattern and accuracy in tumor detection and perivesical staging. Radiology. 2004; 231:725-31.
24. Kim B, Semelka RC, Ascher SM, Chalpin DB, Carroll PR, Hricak H. Bladder tumor staging: comparison of contrast-enhanced CT, T1- and T2-weighted MR imaging, dynamic gadolinium-enhanced imaging, and late gadolinium-enhanced imaging. Radiology. 1994; 193:239-45.
25. Takeuchi M, Sasaki S, Ito M, Okada S, Takahashi S, Kawai T, et al. Urinary bladder cancer: diffusion-weighted MR imaging--accuracy for diagnosing T stage and estimating histologic grade. Radiology. 2009; 251:112-21.
26. Donaldson SB, Bonington SC, Kershaw LE, Cowan R, Lyons J, Elliott T, et al. Dynamic contrast-enhanced MRI in patients with muscle-invasive transitional cell carcinoma of the bladder can distinguish between residual tumour and post-chemotherapy effect. Eur J Radiol. 2013; 82:2161-8.
27. Panebianco V, De Berardinis E, Barchetti G, Simone G, Leonardo C, Grompone MD, et al. An evaluation of morphological and functional multi-parametric MRI sequences in classifying non-muscle and muscle invasive bladder cancer. Eur Radiol. 2017; 27:3759-66.
28. Panebianco V, Narumi Y, Altun E, Bochner BH, Efstathiou JA, Hafeez S, et al. Multiparametric Magnetic Resonance Imaging for Bladder Cancer: Development of VI-RADS (Vesical Imaging-Reporting And Data System). Eur Urol. 2018; 74:294-306.
29. Johnson W, Taylor MB, Carrington BM, Bonington SC, Swindell R. The value of hyoscine butylbromide in pelvic MRI. Clin Radiol. 2007; 62:1087-93.
30. Giannarini G, Petralia G, Thoeny HC. Potential and limitations of diffusion-weighted magnetic resonance imaging in kidney, prostate, and bladder cancer including pelvic lymph node staging: a critical analysis of the literature. Eur Urol. 2012; 61:326-40.
31. Pecoraro M, Takeuchi M, Vargas HA, Muglia VF, Cipollari S, Catalano C, et al. Overview of VI-RADS in Bladder Cancer. AJR Am J Roentgenol. 2020; 214:1259-68.

32. Zhou G, Chen X, Zhang J, Zhu J, Zong G, Wang Z. Contrast-enhanced dynamic and diffusion-weighted MR imaging at 3.0T to assess aggressiveness of bladder cancer. Eur J Radiol. 2014; 83:2013-8.
33. Panebianco V, Barchetti F, de Haas RJ, Pearson RA, Kennish SJ, Giannarini G, et al. Improving Staging in Bladder Cancer: The Increasing Role of Multiparametric Magnetic Resonance Imaging. Eur Urol Focus. 2016; 2:113-21.
34. Baliyan V, Das CJ, Sharma S, Gupta AK. Diffusion-weighted imaging in urinary tract lesions. Clin Radiol. 2014; 69:773-82.
35. Padhani AR, Barentsz J, Villeirs G, Rosenkrantz AB, Margolis DJ, Turkbey B, et al. PI-RADS Steering Committee: The PI-RADS Multiparametric MRI and MRI-directed Biopsy Pathway. Radiology. 2019; 292:464-74.
36. [No Authors]. Liver Reporting & Data System (LI-RADS). [Internet]. Available at. <https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS> Acessed on Jan 4th, 2021.
37. El-Assmy A, Abou-El-Ghar ME, Refaie HF, Mosbah A, El-Diasty T. Diffusion-weighted magnetic resonance imaging in follow-up of superficial urinary bladder carcinoma after transurethral resection: initial experience. BJU Int. 2012; 110(11 Pt B):E622-7.
38. Panebianco V, De Berardinis E, Barchetti G, Simone G, Leonardo C, Grompone MD, et al. An evaluation of morphological and functional multi-parametric MRI sequences in classifying non-muscle and muscle invasive bladder cancer. Eur Radiol. 2017; 27:3759-66.
39. Takeuchi M, Sasaki S, Naiki T, Kawai N, Kohri K, Hara M, et al. MR imaging of urinary bladder cancer for T-staging: a review and a pictorial essay of diffusion-weighted imaging. J Magn Reson Imaging. 2013; 38:1299-309.
40. Barentsz JO, Berger-Hartog O, Witjes JA, Hulsbergen-van der Kaa C, Oosterhof GO, VanderLaak JA, et al. Evaluation of chemotherapy in advanced urinary bladder cancer with fast dynamic contrast-enhanced MR imaging. Radiology. 1998; 207:791-7.
41. Panebianco V, Pecoraro M, Del Giudice F, Takeuchi M, Muglia VF, Messina E, et al. VI-RADS for Bladder Cancer: Current Applications and Future Developments. J Magn Reson Imaging. 2022;55:23-36.
42. Delli Pizzi A, Mastrodicasa D, Marchioni M, Primiceri G, Di Fabio F, Cianci R, et al. Bladder cancer: do we need contrast injection for MRI assessment of muscle invasion? A prospective multi-reader VI-RADS approach. Eur Radiol. 2021; 31:3874-83.
43. Caglic I, Panebianco V, Vargas HA, Bura V, Woo S, Pecoraro M, et al. MRI of Bladder Cancer: Local and Nodal Staging. J Magn Reson Imaging. 2020; 52:649-67.
44. Buckley BW, Daly L, Allen GN, Ridge CA. Recall of structured radiology reports is significantly superior to that of unstructured reports. Br J Radiol. 2018; 91:20170670.
45. Ueno Y, Takeuchi M, Tamada T, Sofue K, Takahashi S, Kamishima Y, et al. Diagnostic Accuracy and Interobserver Agreement for the Vesical Imaging-Reporting and Data System for Muscle-invasive Bladder Cancer: A Multireader Validation Study. Eur Urol. 2019; 76:54-6.
46. Barchetti G, Simone G, Ceravolo I, Salvo V, Campa R, Del Giudice F, et al. Multiparametric MRI of the bladder: inter-observer agreement and accuracy with the Vesical Imaging-Reporting and Data System (VI-RADS) at a single reference center. Eur Radiol. 2019; 29:5498-506.
47. Wang H, Luo C, Zhang F, Guan J, Li S, Yao H, et al. Multiparametric MRI for Bladder Cancer: Validation of VI-RADS for the Detection of Detrusor Muscle Invasion. Radiology. 2019; 291:668-74.
48. Makboul M, Farghaly S, Abdelkawi IF. Multiparametric MRI in differentiation between muscle invasive and non-muscle invasive urinary bladder cancer with vesical imaging reporting and data system (VI-RADS) application. Br J Radiol. 2019; 92:20190401.
49. Kim SH. Validation of vesical imaging reporting and data system for assessing muscle invasion in bladder tumor. Abdom Radiol (NY). 2020; 45:491-8.
50. Del Giudice F, Barchetti G, De Berardinis E, Pecoraro M, Salvo V, Simone G, et al. Prospective Assessment of Vesical Imaging Reporting and Data System (VI-RADS) and Its Clinical Impact on the Management of High-risk Non-muscle-invasive Bladder Cancer Patients Candidate for Repeated Transurethral Resection. Eur Urol. 2020; 77:101-9.
51. Hong SB, Lee NK, Kim S, Son IW, Ha HK, Ku JY, et al. Vesical Imaging-Reporting and Data System for Multiparametric MRI to Predict the Presence of Muscle Invasion for Bladder Cancer. J Magn Reson Imaging. 2020; 52:1249-56.
52. Marchioni M, Primiceri G, Delli Pizzi A, Basilico R, Berardinelli F, Mincuzzi E, et al. Could Bladder Multiparametric MRI Be Introduced in Routine Clinical Practice? Role of the New VI-RADS Score: Results From a Prospective Study. Clin Genitourin Cancer. 2020; 18:409-415.e1.

53. Liu S, Xu F, Xu T, Yan Y, Yao X, Tang G. Evaluation of Vesical Imaging-Reporting and Data System (VI-RADS) scoring system in predicting muscle invasion of bladder cancer. Transl Androl Urol. 2020; 9:445-51.
54. Wang Z, Shang Y, Luan T, Duan Y, Wang J, Wang H, et al. Evaluation of the value of the VI-RADS scoring system in assessing muscle infiltration by bladder cancer. Cancer Imaging. 2020; 20:26.
55. Sakamoto k, Ito M, Nakanishi Y, Kataoka M. Prediction of muscle invasive bladder cancer using the Vesical Imaging-Reporting and Data System and apparent diffusion coefficient values (VI-RADS/ADC). European Urology Supplements 2019, 18:e242-e243.
56. Metwally MI, Zeed NA, Hamed EM, Elshetry ASF, Elfwakhry RM, Alaa Eldin AM, et al. The validity, reliability, and reviewer acceptance of VI-RADS in assessing muscle invasion by bladder cancer: a multicenter prospective study. Eur Radiol. 2021; 31:6949-61.
57. Del Giudice F, Pecoraro M, Vargas HA, Cipollari S, De Berardinis E, Bicchetti M, et al. Systematic Review and Meta-Analysis of Vesical Imaging-Reporting and Data System (VI-RADS) Inter-Observer Reliability: An Added Value for Muscle Invasive Bladder Cancer Detection. Cancers (Basel). 2020; 12:2994.
58. Woo S, Panebianco V, Narumi Y, Del Giudice F, Muglia VF, Takeuchi M, et al. Diagnostic Performance of Vesical Imaging Reporting and Data System for the Prediction of Muscle-invasive Bladder Cancer: A Systematic Review and Meta-analysis. Eur Urol Oncol. 2020; 3:306-315. Erratum in: Eur Urol Oncol. 2020; 3:811.
59. Luo C, Huang B, Wu Y, Chen J, Chen L. Use of Vesical Imaging-Reporting and Data System (VI-RADS) for detecting the muscle invasion of bladder cancer: a diagnostic meta-analysis. Eur Radiol. 2020; 30:4606-14.
60. Catala V, Barcina MJM, Mayordomo O, et al. Characterization of prostate lesions as benign or malignant by multiparametric 3 T MR imaging: comparison of Likert score to the Prostate Imaging Reporting and Data System 2 version Cancer Imaging. 2020;20:26.
61. Del Giudice F, Leonardo C, Simone G, Pecoraro M, De Berardinis E, Cipollari S, et al. Preoperative detection of Vesical Imaging-Reporting and Data System (VI-RADS) score 5 reliably identifies extravesical extension of urothelial carcinoma of the urinary bladder and predicts significant delayed time to cystectomy: time to reconsider the need for primary deep transurethral resection of bladder tumour in cases of locally advanced disease? BJU Int. 2020; 126:610-9.
62. Panebianco V, Del Giudice F, Leonardo C, Sciarra A, Catalano C, Catto JWF. VI-RADS Scoring Criteria for Alternative Risk-adapted Strategies in the Management of Bladder Cancer During the COVID-19 Pandemic. Eur Urol. 2020; 78:e18-e20.
63. Ueno Y, Tamada T, Takeuchi M, Sofue K, Takahashi S, Kamishima Y, et al. Murakami T. VI-RADS: Multiinstitutional Multireader Diagnostic Accuracy and Interobserver Agreement Study. AJR Am J Roentgenol. 2021; 216:1257-66.
64. El-Assmy A, Abou-El-Ghar ME, Refaie HF, Mosbah A, El-Diasty T. Diffusion-weighted magnetic resonance imaging in follow-up of superficial urinary bladder carcinoma after transurethral resection: initial experience. BJU Int. 2012; 110(11 Pt B):E622-7.
65. Barentsz JO, Jager GJ, van Vierzen PB, Witjes JA, Strijk SP, Peters H, et al. Staging urinary bladder cancer after transurethral biopsy: value of fast dynamic contrast-enhanced MR imaging. Radiology. 1996; 201:185-93.
66. Johnson RJ, Carrington BM, Jenkins JP, Barnard RJ, Read G, Isherwood I. Accuracy in staging carcinoma of the bladder by magnetic resonance imaging. Clin Radiol. 1990; 41:258-63.
67. Wang HJ, Pui MH, Guo Y, Yang D, Pan BT, Zhou XH. Diffusion-weighted MRI in bladder carcinoma: the differentiation between tumor recurrence and benign changes after resection. Abdom Imaging. 2014; 39:135-41.
68. Xiao GQ, Rashid H. Bladder Neck Urothelial Carcinoma: A Urinary Bladder Subsite Carcinoma With Distinct Clinicopathology. Int J Surg Pathol. 2015; 23:517-23.
69. van der Heijden AG, Witjes JA. Vesical Imaging-Reporting and Data System (VI-RADS) for Bladder Cancer Diagnostics: The Replacement for Surgery? Eur Urol Oncol. 2020; 3:316-7.
70. Hamad J, McCloskey H, Milowsky MI, Royce T, Smith A. Bladder preservation in muscle-invasive bladder cancer: a comprehensive review. Int Braz J Urol. 2020; 46:169-84.
71. Herr HW, Donat SM. Quality control in transurethral resection of bladder tumours. BJU Int. 2008; 102(9 Pt B):1242-6.
72. Sim KC, Sung DJ. Role of magnetic resonance imaging in tumor staging and follow-up for bladder cancer. Transl Androl Urol. 2020; 9:2890-907.
73. [No Authors]. BladderPath:Image Directed Redesign of Bladder Cancer Treatment Pathway. [Internet]. Available at. <https://www.birmingham.ac.uk/research/crctu/trials/Bladder-Path/index.aspx>. Acessed Jan 5th, 2021.

74. Grisay G, Pierrard J, Confente C, Seront E. Future Strategies Involving Immune Checkpoint Inhibitors in Advanced Urothelial Carcinoma. Curr Treat Options Oncol. 2020; 22:7.
75. Yoshida S, Koga F, Kobayashi S, Tanaka H, Satoh S, Fujii Y, et al. Diffusion-weighted magnetic resonance imaging in management of bladder cancer, particularly with multimodal bladder-sparing strategy. World J Radiol. 2014; 6:344-54.
76. Nguyen HT, Mortazavi A, Pohar KS, Zynger DL, Wei L, Shah ZK, et al. Quantitative Assessment of Heterogeneity in Bladder Tumor MRI Diffusivity: Can Response be Predicted Prior to Neoadjuvant Chemotherapy? Bladder Cancer. 2017; 3:237-44.
77. Yoshida S, Koga F, Kobayashi S, Ishii C, Tanaka H, Tanaka H, et al. Role of diffusion-weighted magnetic resonance imaging in predicting sensitivity to chemoradiotherapy in muscle-invasive bladder cancer. Int J Radiat Oncol Biol Phys. 2012; 83:e21-7.
78. Necchi A, Bandini M, Calareso G, Raggi D, Pederzoli F, Farè E, et al. Multiparametric Magnetic Resonance Imaging as a Noninvasive Assessment of Tumor Response to Neoadjuvant Pembrolizumab in Muscle-invasive Bladder Cancer: Preliminary Findings from the PURE-01 Study. Eur Urol. 2020; 77:636-43.

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EDITORIAL COMMENT

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A brief review of the VI-RADS classification for bladder tumors on MRI (and a call for increased interface, consistent communication and more joined studies by the radiological and urological communities)

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COMMENT

In 1993 the American College of Radiology (ACR) proposed a new classification for breast tumor evaluation and reporting on mammography, called BI-RADS (Breast Imaging Reporting and Data System), a standardized lexicon, which was developed on the back of the established 5-tier ACR system (a Likert scale) (1). The aim of BI-RADS was to improve distinction between benign and malignant diseases, to remove ambiguity from radiology reports, permit automated auditing of data and improve clinical interface with the referring physicians. Nowadays, there are more than twenty RADS available for the radiological evaluation of many diseases and organs, nine of then developed under the ACR criteria and supervision, including two that are more widely used and well know: LI-RADS (liver cancer) and PI-RADS (prostate cancer) (2).

In 2018, a multidisciplinary group of radiologists, urologists, pathologists and radiation oncologists developed and published a new scoring system called VI-RADS (Vesical Imaging-Reporting and Data System), focused on the local staging of bladder cancer on MRI, including the standardization of MRI protocols and the proposal of a structured reporting system to improve communication between referring physicians and radiologists (3). The main goal of the proposed system was to overcome, through a non-invasive imaging method, the risks and limitations of transurethral resection of bladder tumor (TURBT), such as bladder perforation and under/overstaging. The system relies on a 5-point scale (VI-RADS 1 to VI-RADS 5), using multiparametric MRI (that includes high-resolution T2-weighted, diffusion-weighted, and dynamic contrast-enhanced imaging), to stratify the risk of invasion of the muscular layer of the bladder wall in a previously detected lesion. VI-RADS rapidly gained acceptance by the radiological and urological communities, and many multicentric studies were published since then confirming that the system has excellent interobserver agreement and accuracy for local staging. Those studies include two systematic reviews and meta-analysis, published in 2020 by Woo et al (4) and Luo et al (5), that found similar AUC accuracies for local staging of bladder cancer using VI-RADS (between 0,92 and 0,94) Another systematic review and meta-analysis, published in 2022 by Del Giudice et al. (6), focused on inter-reader reproducibility and found a Cohen's Kappa of 0,83.

The article from Nicola et al (7), gives a very comprehensive and step-by-step review of the many aspects of VI-RADS, targeting the urological community. It is of utmost importance that urologists (as well as clinical oncologists and radiation oncologists) become familiar with the applications,

limitations and basis of imaging interpretation of the system. Being a relatively young classification (as compared to BI-RADS, LI-RADS and PI-RADS), VI-RADS demands more prospective and multicentric studies to further validate its already excellent results.

I believe that one of the major strengths of VI-RADS relies on the fact that it was developed from the very beginning with the inputs of all involved "stakeholders" (radiologists, urologists, pathologists and radiation oncologists). This should be a must for all studies that intend to standardize how we perform, read and report an imaging exam. The PI-RADS steering committee consider the PI-RADS classification (now in version 2.1) as a "living document", since continuous improvements will certainly occur and be incorporated in the newer versions. I am positive that the same idea is valid for VI-RADS. Let's work together to make it even better and more widely used.

REFERENCES

1. [No Authors]. Breast Imaging Reporting and Data System (BI-RADS). Reston, VA: American College of Radiology, 1993. [Internet]. Available at. <https://www.acr.org/>
2. [No Authors]. Reporting and Data Systems (RADS). American College of Radiology. [Internet]. Available at. <https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems>
3. Panebianco V, Narumi Y, Altun E, Bochner BH, Efstathiou JA, Hafeez S, et al. Multiparametric Magnetic Resonance Imaging for Bladder Cancer: Development of VI-RADS (Vesical Imaging-Reporting And Data System). Eur Urol. 2018;74:294-306.
4. Woo S, Panebianco V, Narumi Y, Del Giudice F, Muglia VF, Takeuchi M, et al. Corrigendum to 'Diagnostic Performance of Vesical Imaging Reporting and Data System for the Prediction of Muscle-invasive Bladder Cancer: A Systematic Review and Meta-analysis' [European Urology Oncology 3 (2020) 306-315]. Eur Urol Oncol. 2020;3:811.
5. Luo C, Huang B, Wu Y, Chen J, Chen L. Use of Vesical Imaging-Reporting and Data System (VI-RADS) for detecting the muscle invasion of bladder cancer: a diagnostic meta-analysis. Eur Radiol. 2020;30:4606-14.
6. Del Giudice F, Flammia RS, Pecoraro M, Moschini M, D'Andrea D, Messina E, et al. The accuracy of Vesical Imaging-Reporting and Data System (VI-RADS): an updated comprehensive multi-institutional, multi-readers systematic review and meta-analysis from diagnostic evidence into future clinical recommendations. World J Urol. 2022;16. Epub ahead of print.
7. Nicola R, Pecoraro M, Lucciola S, Dos Reis RB, Narumi Y, Panebianco V, et al. VI-RADS score system - A primer for urologists. Int Braz J Urol. 2022;48: 609-22.

CONFLICT OF INTEREST

None declared.

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Trifecta achievement in patients undergoing partial nephrectomy: a systematic review and meta-analysis of predictive factors

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ABSTRACT

Purpose: The predictors of trifecta achievement in partial nephrectomy (PN) were poorly inquired and remained a controversial area of discovery. To evaluate predictive factors of trifecta achievement in patients undergoing PN.

Materials and Methods: A systematic literature search was performed to identify relevant articles. Only studies focusing on postoperative trifecta achievement and exploring its predictor with multivariable analyses were included. The trifecta achievement was defined as negative surgical margins, warm ischemia time <25 minutes, and no complications. Merged odds ratio (OR) and 95% confidence interval (CI) were used to evaluate the predictive effect.

Results: Thirteen studies with 7066 patients meeting the inclusion criteria were included. The rate of trifecta achievement ranged from 43.3% to 78.6%. Merged results showed that preoperative eGFR (OR: 1.01, 95% CI: 1.00, 1.02, P=0.02), operative time (OR: 0.99, 95% CI: 0.99, 1.00, P=0.02), estimated blood loss (OR: 1.00, 95% CI: 1.00, 1.00, P <0.001), tumor size (OR: 0.70, 95% CI: 0.58, 0.84, P <0.001), medium (OR: 0.39, 95% CI: 0.18, 0.84, P=0.02) and high PADUA score (OR: 0.23, 95% CI: 0.08, 0.64, P=0.005) were independently associated with trifecta achievement. A publication bias was identified for tumor size. Sensitivity analysis confirmed the stability of result for tumor size.

Conclusions: Larger tumor size, medium and high PADUA score are associated with decreased probability of trifecta achievement. After verifying by further high-quality studies, these variables can be incorporated into tools to predict probability of trifecta achievement during clinical practice.

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INTRODUCTION

In 2020, kidney and renal pelvis cancer was estimated to be associated with nearly 73.750 newly diagnosed patients and 14.830 cancer-related deaths in the United States (1). Renal cell carcinoma accounts for the vast majority of these cases. Compared with radical nephrectomy, partial nephrectomy (PN) is more effective for cT1a renal masses in terms of surgically related mortality, overall survival, and renal function, and has become a standard treatment regimen (2, 3). In addition, for larger renal masses

(cT1b and cT2), a recent study has shown that PN can offer the same cancer control, better preserved renal function, acceptable surgical morbidity, and potential better long-term survival compared to radical surgery (4). With the development of medical instruments, PN has evolved from open surgery to laparoscopic and robot-assisted surgery, and became widely applied in managing highly complex kidney cancer (5, 6).

As a novel concept from radical prostatectomy, the trifecta outcome was initially proposed by Hung et al. to describe the outcome of partial nephrectomy (7). It provides a definition of an ideal surgical outcome that includes the following three criteria: negative surgical margins, maximum renal function retention and patient recovery without complications. The use of trifecta rate as a key indicator of partial nephrectomy success has been widely reported (8-11). Recently, some researchers have proposed several anatomic classification scoring systems to classify and stratify patients into different anatomic complexity groups, and allow doctors to evaluate perioperative outcomes (12-15). In addition to these anatomic scoring systems, some other perioperative variables such as age, gender, BMI, tumor size, operative time, estimated blood loss have been studied as predictive factors for trifecta achievement in patients undergoing partial nephrectomy (16-20). However, inconsistent results reported by different studies confuse our understanding and interpretation. Hence, based on studies reporting predictive factors for trifecta achievement, we merged the results using the method of systematic review and meta-analysis.

MATERIALS AND METHODS

The protocol of the present study was registered on PROSPERO (ID: CRD42020220307). The PRISMA checklist was presented in supplementary data.

Literature researching

After establishing a prior study protocol, two authors independently used PubMed, Embase and Cochrane Library, respectively, to conduct a literature search for post-PN trifecta achievement until September 2020. The free-text strategy was considered best suited to this purpose: "post-PN trifecta achievement". The key words included "partial nephrectomy", "nephron sparing surgery", "trifecta", "trifecta achievement". The language was restricted to English, non-English articles were filtrated. Publication type was restricted to original article, reviews, congress abstracts, letters to editor, editorials, erratum, and short communications were filtrated.

Study selection

The studies focused on patients with renal tumor who had undergone partial nephrectomy and achieved trifecta or not. The trifecta achievement was defined as negative surgical margins, warm ischemia time <25 minutes, and no complications. Predictive factors of post-PN trifecta achievement were studied with multivariable logistic analyses and reported in included studies. The abstract of each study was evaluated to assess the eligibility of the study. Those studies that provided relevant data were chosen for detailed checking.

The studies were excluded due to the following reasons: (1) didn't reported relevant outcomes, (2) without results from multivariable analysis, (3) inconsistent definition of trifecta achievement, (4) duplicated publication.

Data extraction

Based on the included studies, the following data were extracted: (1) study features (first author's name, publication year, study design, patient resource, study period, country, sample size); (2) patient characteristics (age, surgical procedure, T stage, rate of trifecta, variables included in multivariable analysis); (3) predictors of trifecta achievement (multivariable odds ratio [OR] and 95% confidence interval [CI] of age, body mass index (BMI), Charlson comorbidity index, preoperative estimated glomerular filtration rate (eGFR), operative time, estimated blood loss, tumor size, N score component, RENAL score, PADUA score (medium or high vs. low)).

Study quality assessment

For non-randomized controlled studies, the Newcastle-Ottawa Assessment Scale was considered appropriate for the assessment of study quality (21) and established a value ladder, with a

score of 5 for low-quality studies, 6-7 for medium--quality studies, and 8-9 for high-quality studies.

Data analysis

Multivariable ORs and 95% CIs from each study were merged to assess the predictive effect of factors for post-PN trifecta achievement. Only the factors reported by more than two studies were included in the meta-analyses. The Cochrane Q p value and I2 statistic were used to determine the heterogeneity between reports. This was deemed to be significant when p <0.05 or I2> was 50%, and a random-effect model was used to combine the results. Or else, a fixed-effect model was used. To assess publication bias (only for comparisons that include most studies), we examined funnel plots and performed sensitivity analyses of these comparisons. P <0.05 was considered statistically significant. All statistical analyses were conducted using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) and Stata 12.0 software (StatCorp, College Station, TX, USA).

RESULTS

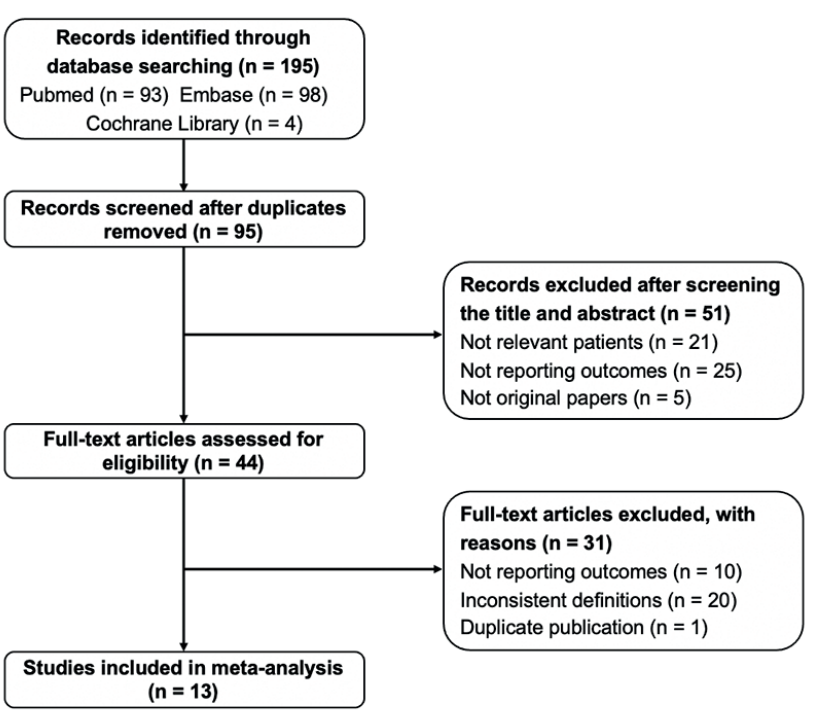
Included studies

According to the flowchart of literature searching (Figure-1), 44 studies were selected for detailed evaluation. Of them, 10 were excluded due to not reporting outcomes, 20 describing inconsistent definitions of trifecta were excluded, and 1 was a duplicate publication. Finally, 13 studies meeting the inclusion criteria were included (16-20, 22-29).

Baseline characteristics of studies

Eight studies relied on data from multi-institutional database, five studies analyzed patients in single center. Two studies prospectively collected data, and the rest studied retrospectively collected data. In terms of country, 3 were from Japan, 3 from Italy, 2 from France, 2 from Germany, 2 from USA, 1 from Korea. The median sample size was 285 (60-2392). The median or mean age ranged from 49.5 to 63.2 years. Most PN were performed in minimally invasive approach (laparoscopic or robot-assisted). The

Figure 1 - Flow diagram detailing the search strategy and identification of studies included in data synthesis.



rate of trifecta achievement ranged from 43.3% to 78.6% (Table-1A). The detailed variables in multivariable analysis are presented in Table-2, most of them were patients features, tumor characteristics, and surgical variables. Six were medium-quality (score 6-7) studies, seven were high-quality (score 8) studies, the detailed risk of bias for each study is presented in supplementary Table-S1. The other characteristics and perioperative outcomes are detailed in supplementary Table-1B.

Predictors of trifecta achievement

Most predictive factors were patients features, surgical variables, and tumor characteristics. Patients features were analyzed as continuous variables. Since no significant heterogeneity was identified (I2=0%-12%, P=0.30-0.85), the fixed-effect model was used. A pooled analysis of ORs proved age (OR: 1.00, 95% CI: 0.98, 1.02, P=0.79), body mass index (OR: 0.96, 95% CI: 0.91, 1.02, P=0.17), Charlson comorbidity index (OR: 0.98, 95% CI: 0.84, 1.13, P=0.74) weren't independent predictive factors for trifecta achievement (Figures 2 A-C). The merged results showed that preoperative eGFR (OR: 1.01, 95% CI: 1.00, 1.02, P=0.02) was independently associated with trifecta achievement, but the predictive effect was minor (Figure-2D).

Since significant heterogeneity was identified (I2=74%, P=0.008), the random-effect model was used for operative time. Since no significant hetero-

Table 1A - Baseline characteristics of included studies.

First author	Year	Design	Patient population	Study period	Country	Sample size	Age (years)	Procedure	T stage	Trifecta (%)
Furukawa et al. (22)	2020	Retro	Multi-institution	2011-2016	Japan	804	63 (55-70)	RAPN	pT1a-T3a	62.1
Takeda et al. (23)	2020	Retro	Single institution	2006-2016	Japan	66	54.5 Mean	LPN	cT1a	55
Peyronnet et al. (16)	2018	Retro	Multi-institution	2009-2015	France	1099	60.3 Mean	RAPN	-	75.2
Khene et al. (17)	2018	Retro	Multi-institution	2010-2016	France	500	59 (51-67)	RAPN	pT1-T3a	70.4
Harke et al. (18)	2018	Retro	Multi-institution	2008-2016	Germany	140	-	OPN/ RAPN	-	OPN: 68.4; RAPN: 75.0
Castellucci et al. (19)	2018	Retro	Single institution	2013-2016	Italy	123	63.2±13.6	RAPN	-	64.2
Paulucci et al. (24)	2017	Retro	Multi-institution	2008-2016	USA	960	61 (51-69)	RAPN	-	72.2
Lebentrau et al. (25)	2017	Retro	Single institution	2006-2013	Germany	124	-	OPN	cT1	69.4
Porpiglia et al. (26)	2016	Pro	Multi-institution	2009-2012	Italy	285	60.3±14.3	OPN/LPN/ RAPN	cT1b	OPN: 62.4; LPN: 63.2; RAPN: 69.5
Kim et al. (27)	2016	Retro	Single institution	2006-2015	Korea	60	49.5 (39.8-62)	RAPN	cT1b	43.3
Zargar et al. (20)	2015	Retro	Multi-institution	2004-2013	USA	1831	-	LPN/RAPN	cT1a	LPN: 33.0; RAPN: 70.0
Osaka et al. (28)	2015	Retro	Single institution	2007-2012	Japan	63	57.9±10.2	LPN	cT1a	61.9
Minervini et al. (29)	2014	Pro	Multi-institution	2009-2011	Italy	450	62.7 Mean	OPN/LPN	cT1a	OPN: 78.6; LPN: 74.3

Retro = retrospective; **Pro** = prospective; **RAPN** = robot-assisted partial nephrectomy; **LPN** = laparoscopic partial nephrectomy; **OPN** = open partial nephrectomy.

Table 1B. The other characteristics and perioperative outcomes for included studies.

First author	Year	Gender (male/female)	Median BMI (kg/m2)	Median tumor size (cm)	Median nephrometry score	Total complication (n)	Median OT (min)	Median WIT (min)	Median EBL (mL)	Median LOS (d)	PSM (n)
Furukawa et al. (22)	2020	584/220	-	2.6	7 R	132 (Clavien≥III: 74)	234	21	30	9	8
Takeda et al. (23)	2020	55/11	-	-	-	8 (I: 0, II: 3, III: 5)	-	-	-	-	0
Peyronnet et al. (16)	2018	712/387	-	-	-	162 (Clavien≥III: 60)	-	-	-	-	56
Khene et al. (17)	2018	297/203	27	3.3	7 R	125 (Clavien≥III: 49)	160	15	250	3	19
Harke et al. (18)	2018	90/50	-	-	11 P	30 (Clavien≥III: 16)	-	-	-	-	2
Castellucci et al. (19)	2018	70/53	27	-	-	23 (II: 15, III: 7, IV:1)	115	-	205	-	14
Paulucci et al. (24)	2017	568/392	29.3	3	7 R	115 (Clavien≥III: 33)	179	16	100	1	38
Lebentrau et al. (25)	2017		-	-	-	-	-	-	-	-	8
Porpiglia et al. (26)	2016	171/114	25.9	5	-	31 (II: 17, III: 8)	135	16	200	-	9
Kim et al. (27)	2016	33/27	24.7	5	9 R	9 (II: 7, III: 2, IV:0)	165.5	-	425	-	4
Zargar et al. (20)	2015	1097/734	30	-	-	359	-	-	-	-	100
Osaka et al. (89)	2015	50/13	24.7	24	6 R	4	177	21	87	-	4
Minervini et al. (29)	2014	179/101	-	2.5	-	46	-	-	-	-	-

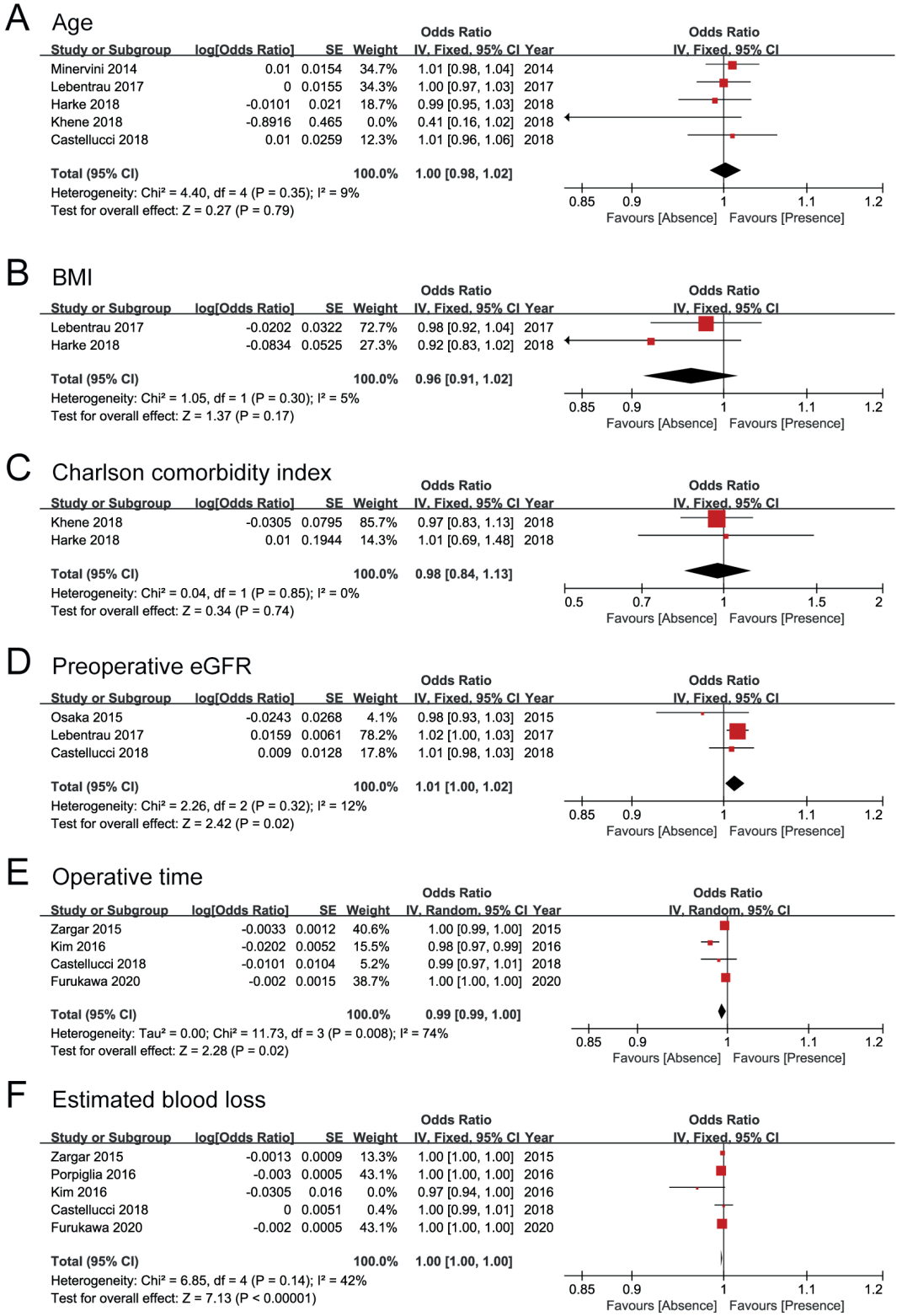
BMI = body mass index; **OT** = operative time; **WIT** = warm ischemia time; **EBL** = estimated blood loss; **LOS** = length of hospital stay; **PSM** = positive surgical margin; **R** = RENAL; P = PADUA.

Table 2 - Included variables in multivariable analysis and study quality.

Author	Year	Variables included in multivariable analysis	NOS score
Furukawa et al. (22)	2020	tumor size, OT, EBL, RENAL score, N score component, hilar location	8
Takeda et al. (23)	2020	tumor size	6
Peyronnet et al. (16)	2018	tumor size, RENAL score, surgeon experience, surgeon volume, hospital volume	8
Khene et al. (17)	2018	age, CCI, ECOG, tumor size, RENAL score, MAP score	8
Harke et al. (18)	2018	age, BMI, CCI, tumor size, solitary kidney, PADUA score, OPN vs RAPN, experience	8
Castellucci et al. (19)	2018	age, symptoms, tumor size, PADUA score, preoperative eGFR, EBL, OT	7
Paulucci et al. (24)	2017	surgeon experience, tumor size	7
Lebentrau et al. (25)	2017	age, sex, BMI, eGFR, ASA, PADUA score, surgical experience	7
Porpiglia et al. (26)	2016	tumor growth pattern, EBL, centers	8
Kim et al. (27)	2016	tumor size, OT, EBL	7
Zargar et al. (20)	2015	RAPN vs LPN, tumor size, RENAL score, EBL, OT	8
Osaka et al. (28)	2015	preoperative eGFR, tumor size, nearness of UCS, Surgeon's learning curve	7
Minervini et al. (29)	2014	age, tumor size, indication	8

OT = operative time; **EBL** = estimated blood loss; **CCI** = charlson's comorbidity index; **ECOG** = Eastern Cooperative Oncology Group; **BMI** = body mass index; **OPN** = open partial nephrectomy; **RAPN** = robot-assisted partial nephrectomy; **eGFR** = estimated glomerular filtration rate; **ASA** = American Society of Anesthesiologists; **LPN** = laparoscopic partial nephrectomy; **UCS** = urinary collecting system.

Figure 2 - Forest plots for predictors of trifecta achievement. The predictors included (A) age, (B) body mass index, (C) Charlson comorbidity index, (D) preoperative estimated glomerular filtration rate, (E) operative time, (F) estimated blood loss.



geneity was identified (I2=42%, P=0.14), the fixed--effect model was used for estimated blood loss. A pooled analysis of ORs demonstrated operative time (OR: 0.99, 95% CI: 0.99, 1.00, P=0.02) and estimated blood loss (OR: 1.00, 95% CI: 1.00, 1.00, P <0.001) were independently associated with trifecta achievement, but the predictive effect was minor (Figures 2E and F).

Tumor characteristics included tumor size, N score component, RENAL score, and PADUA score. Due to significant heterogeneity, the random-effect model was used for tumor size and RENAL score, the fixed-effect model was used for other meta-analyses. Pooled analysis of ORs demonstrated tumor size (OR: 0.70, 95% CI: 0.58, 0.84, P <0.001), medium (OR: 0.39, 95% CI: 0.18, 0.84, P=0.02) and high PADUA score (OR: 0.23, 95% CI: 0.08, 0.64, P=0.005) were independently associated with trifecta achievement (Figures 3A, D and E). N score component (OR: 0.83, 95% CI: 0.65, 1.05, P=0.12) and RENAL score (OR: 0.68, 95% CI: 0.35, 1.34, P=0.27) weren't independent predictive factors for trifecta achievement (Figures 3 B and C).

Bias assessment

Given the inadequate studies, publication bias checking and sensitivity analysis were only performed for tumor size. The funnel plot seemed to be asymmetric (Figure-4A), and Egger's test identified significant difference (P=0.001). Sensitivity analysis confirmed the stability of results (Figure-4B).

DISCUSSION

A comprehensive outcome measure, the trifecta achievement (i.e., negative surgical margins, warm ischemia time <25 minutes, no complications), has been recommended as a measure of postoperative surgical quality for PN (24, 26, 28, 29). Some perioperative parameters including patient features, tumor characteristics, and surgical variables were hypothesized to be associated with the trifecta achievement of PN. We firstly assessed the predictive factors of trifecta achievement for patients undergoing PN with the method of systematic review and meta-analysis. The present study included 7.066 patients, and the rate of trifecta achievement ranged from 43.3% to 78.6%. High variability was found regarding the rate of trifecta achievement may due to the differences in patient condition, tumor size and stage, surgical approach, and so on.

More than thirty studies have reported predictive factors for trifecta achievement, however, different definitions of trifecta achievement were described. Trifecta achievement was consisted of three aspects, namely surgical margin, renal function preservation, and perioperative complication. The inconsistency lies mainly in the latter two aspects. The most common definition was adopted, specifically negative surgical margins, warm ischemia time <25 minutes, and no complications. Finally, 13 studies meeting the inclusion criteria were included (16-20, 22-29). The detailed variables in multivariable analysis are presented in Table-2, most of them were patients features, tumor characteristics, and surgical variables. For the same variables, different forms of data were used in different studies, and the most common data type was chosen. Based on the results from multivariable analyses, several independent predictors have been identified.

Patients features including age, body mass index, Charlson comorbidity index, and preoperative eGFR were analyzed as continuous variables. Only preoperative eGFR was found to be independently associated with trifecta achievement. However, the predictive effect was minor, the odd ratio was 1.01 (1.00-1.02). Moreover, a recent study based on 790 patients treated with laparoscopic PN found that preoperative eGFR (OR: 1.01, 95% CI: 1.00, 1.02) was associated with an increased probability of pentafecta achievement (30). These results indicated that preoperative eGFR had a limited effect on postoperative outcomes. Surgical variables including operative time and estimated blood loss were analyzed as continuous variables. Though they were found to be independently associated with trifecta achievement, the predictive effect was minor, the odd ratios were 0.99 (0.99-1.00) and 1.00 (1.00-1.00). Moreover, these two variables were related to surgery, and only can be obtained after surgery, their predictive value was limited.

Tumor characteristics including tumor size, N score component, RENAL score, and PADUA score were analyzed. The variable tumor size has been most

Figure 3 - Forest plots for predictors of trifecta achievement. The predictors included (A) tumor size, (B) N score component, (C) RENAL score, (D) PADUA score (medium vs. low), (E) PADUA score (high vs. low).

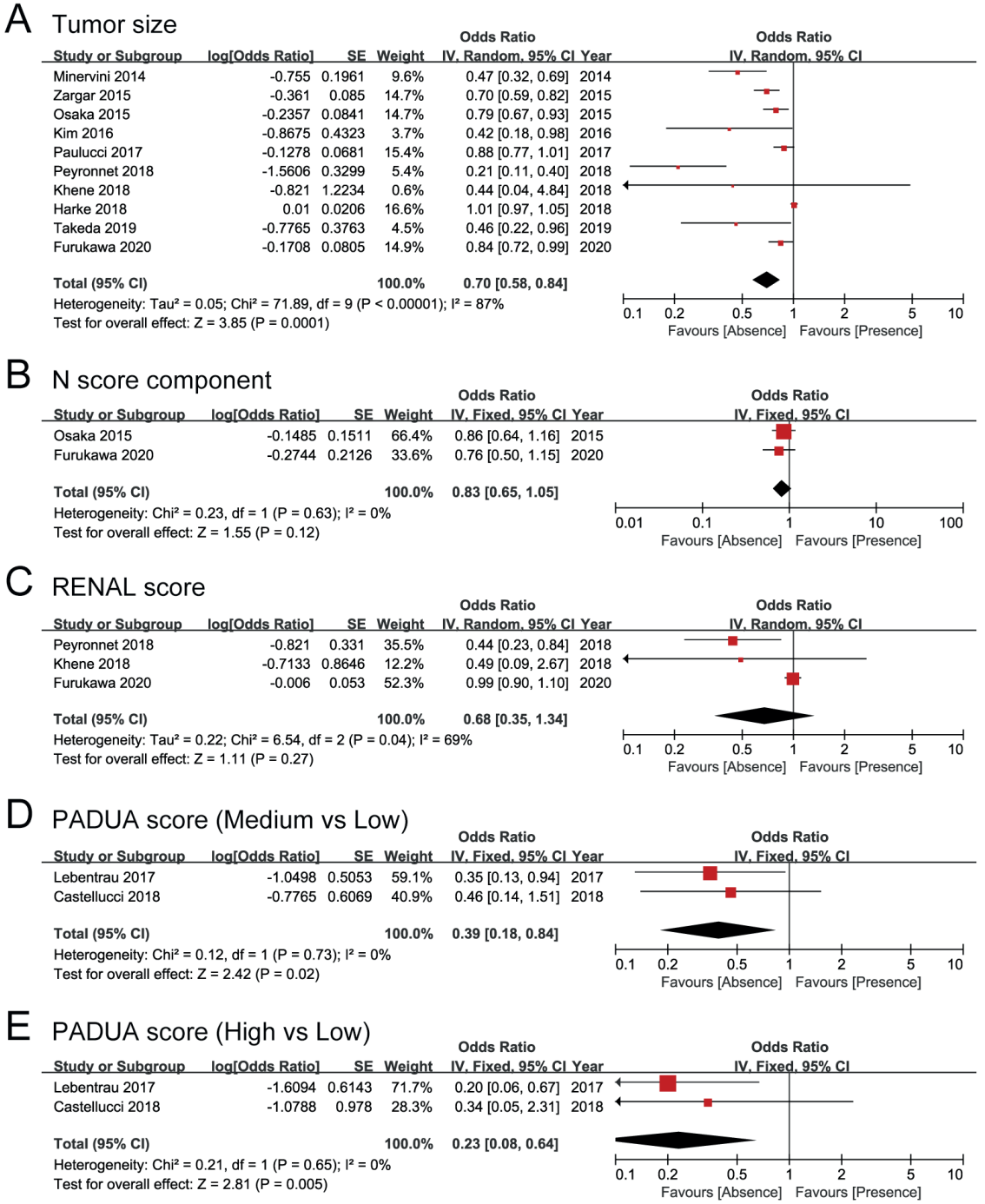
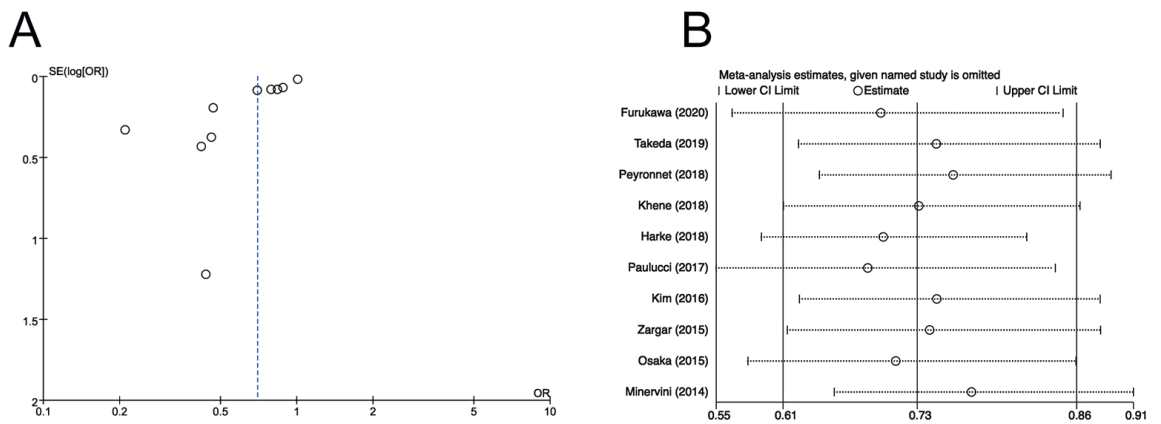


Figure 4 - (A) Funnel plot to assess publication bias for tumor size, (B) sensitivity analysis for tumor size.



studied and reported in the included literatures. Merged data showed that tumor size (OR: 0.70, 95% CI: 0.58, 0.84) was associated with a decreased probability of trifecta achievement. This result is reasonable because tumor size obviously affects the two components (renal function, perioperative complication) of trifecta achievement. Reynolds et al. (31) have compared perioperative and functional outcomes for patients with clinical T1a and T1b renal tumors undergoing robot-assisted PN. They found that clinical T1a tumors were correlated with shorter warm ischemia time, lower rate of perioperative complications. Similarly, in the setting of robot-assisted PN, Delto et al. (32) have compared perioperative outcomes for patients with clinical T1a, T1b, and T2a renal tumors. They found that clinical T2a renal tumors were associated with a 7% increase in warm ischemia time, a 3.93 higher odds of acute kidney injury compared to T1a renal tumors. Both the two studies didn't identify significant difference in surgical margins among different clinical stage renal tumors. Due to the significant effect of tumor size on ischemia time and perioperative complication, Castellucci et al. (33) have reported that patients with renal masses ≥4cm achieved an obviously lower rate of trifecta achievement (44.7% vs. 72.9%) than those with renal masses <4cm.

In terms of anatomic scoring systems, renal tumors with medium (OR: 0.39, 95% CI: 0.18, 0.84) and high PADUA score (OR: 0.23, 95% CI: 0.08, 0.64) were associated with decreased probability of trifecta achievement when compared with those with low PADUA score. These results seemed to be reasonable, more complex tumors may experience more unfavorable perioperative outcomes. However, no significant difference was identified for N score component and RENAL score. The possible reasons included limited studies have reported these results, and these two variables were analyzed in continuous variable which underestimate the differences.

Though the present study stands for the first systematic review and meta-analysis about the predictive factors for trifecta achievement in patients undergoing partial nephrectomy, several limitations need to be addressed. First, all included studies were retrospectively designed or database based, and therefore inherent biases were included. Some studies were of moderate quality and cannot be comparable for each related variable. Hence, we just analyzed the results from multivariable analyses which adjusted the confounding factors. Second, more than thirty studies have reported predictive factors for trifecta achievement, however, different definitions of trifecta achievement were described. The most common definition was adopted, then 13 studies were included. Some endpoints were reported by limited studies and analyzed in different data type, the pooled results for theses endpoints should been verified by further studies. Moreover, due to the inadequate studies, some important variables such as surgical approach have not been analyzed in our study. Third, the-

re were significant heterogeneity among studies for some endpoints, such as tumor size, operative time. The publication bias checking identified a potential publication bias for tumor size. Hence, these results might be interpreted with caution.

CONCLUSIONS

Trifecta achievement provides a definition of an ideal surgical outcome for patients undergoing partial nephrectomy. Larger tumor size, medium and high PADUA score are associated with decreased probability of trifecta achievement. After verifying by further high-quality studies, these variables can be incorporated into tools to predict probability of trifecta achievement during clinical practice.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020; 70:7-30.
2. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol. 2015; 67:913-24.
3. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, et al. Renal Mass and Localized Renal Cancer: AUA Guideline. J Urol. 2017; 198:520-9.
4. Mir MC, Derweesh I, Porpiglia F, Zargar H, Mottrie A, Autorino R. Partial Nephrectomy Versus Radical Nephrectomy for Clinical T1b and T2 Renal Tumors: A Systematic Review and Meta-analysis of Comparative Studies. Eur Urol. 2017; 71:606-17.
5. Minervini A, Grosso AA, Di Maida F, Mari A, Vittori G, Muto G, et al. How far is too far? Exploring the indications for robotic partial nephrectomy in a highly complex kidney tumor. Int Braz J Urol. 2020; 46:871-2.
6. Kartal I, Karakoyunlu N, Çakici MÇ, Karabacak O, Sağnak L, Ersoy H. Oncological and functional outcomes of open versus laparoscopic partial nephrectomy in T1b tumors: A single-center analysis. Int Braz J Urol. 2020; 46:341-50.
7. Hung AJ, Cai J, Simmons MN, Gill IS. "Trifecta" in partial nephrectomy. J Urol. 2013; 189:36-42.
8. Castilho TML, Lemos GC, Cha JD, Colombo JR, Claros OR, Lemos MB, et al. Transition from open partial nephrectomy directly to robotic surgery: experience of a single surgeon to achieve "TRIFECTA". Int Braz J Urol. 2020; 46:814-21.
9. Bindayi A, Autorino R, Capitanio U, Pavan N, Mir MC, Antonelli A, et al. Trifecta Outcomes of Partial Nephrectomy in Patients Over 75 Years Old: Analysis of the REnal SURGery in Elderly (RESURGE) Group. Eur Urol Focus. 2020; 6:982-90.
10. Bianchi L, Schiavina R, Borghesi M, Chessa F, Casablanca C, Angiolini A, et al. Which patients with clinical localized renal mass would achieve the trifecta after partial nephrectomy? The impact of surgical technique. Minerva Urol Nefrol. 2020; 72:339-49.
11. Basatac C, Akpinar H. 'Trifecta' outcomes of robot-assisted partial nephrectomy: Results of the 'low volume' surgeon. Int Braz J Urol. 2020; 46:943-9.
12. Ficarra V, Novara G, Secco S, Macchi V, Porzionato A, De Caro R, et al. Preoperative aspects and dimensions used for an anatomical (PADUA) classification of renal tumours in patients who are candidates for nephron-sparing surgery. Eur Urol. 2009; 56:786-93.
13. Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. J Urol. 2009; 182:844-53.
14. Spaliviero M, Poon BY, Karlo CA, Guglielmetti GB, Di Paolo PL, Beluco Corradi R, et al. An Arterial Based Complexity (ABC) Scoring System to Assess the Morbidity Profile of Partial Nephrectomy. Eur Urol. 2016; 69:72-9.
15. Gu L, Ma X, Li H, Yao Y, Xie Y, Chen L, et al. External validation of the Arterial Based Complexity (ABC) scoring system in renal tumors treated by minimally invasive partial nephrectomy. J Surg Oncol. 2017; 116:507-14.
16. Peyronnet B, Tondut L, Bernhard JC, Vaessen C, Doumerc N, Sebe P, et al. Impact of hospital volume and surgeon volume on robot-assisted partial nephrectomy outcomes: a multicentre study. BJU Int. 2018; 121:916-22.
17. Khene ZE, Peyronnet B, Kocher NJ, Robyak H, Robert C, Pradere B, et al. Predicting morbidity after robotic partial nephrectomy: The effect of tumor, environment, and patient-related factors. Urol Oncol. 2018; 36:338.e19-338.e26.
18. Harke NN, Mandel P, Witt JH, Wagner C, Panic A, Boy A, et al. Are there limits of robotic partial nephrectomy? TRIFECTA outcomes of open and robotic partial nephrectomy for completely endophytic renal tumors. J Surg Oncol. 2018; 118:206-11.

19. Castellucci R, Primiceri G, Castellan P, Marchioni M, D'Orta C, Berardinelli F, et al. Trifecta and Pentafecta Rates After Robotic Assisted Partial Nephrectomy: Comparative Study of Patients with Renal Masses <4 and ≥4 cm. J Laparoendosc Adv Surg Tech A. 2018; 28:799-803.
20. Zargar H, Allaf ME, Bhayani S, Stifelman M, Rogers C, Ball MW, et al. Trifecta and optimal perioperative outcomes of robotic and laparoscopic partial nephrectomy in surgical treatment of small renal masses: a multi-institutional study. BJU Int. 2015; 116:407-14.
21. Lo CK, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. BMC Med Res Methodol. 2014; 14:45.
22. Furukawa J, Kanayama H, Azuma H, Inoue K, Kobayashi Y, Kashiwagi A, et al. Trifecta' outcomes of robot-assisted partial nephrectomy: a large Japanese multicenter study. Int J Clin Oncol. 2020; 25:347-53.
23. Takeda T, Komatsuda A, Yanai Y, Tanaka N, Matsumoto K, Morita S, et al. Factors affecting renal function preservation among patients not achieving trifecta after laparoscopic partial nephrectomy for clinical T1a renal masses. Asian J Endosc Surg. 2020; 13:526-31.
24. Paulucci DJ, Abaza R, Eun DD, Hemal AK, Badani KK. Robot-assisted partial nephrectomy: continued refinement of outcomes beyond the initial learning curve. BJU Int. 2017; 119:748-54.
25. Lebentrau S, Rauter S, Baumunk D, Christoph F, König F, May M, et al. Nephron sparing surgery for renal cell carcinoma up to 7 cm in the context of guideline development: a contribution of healthcare research. World J Urol. 2017; 35:753-9.
26. Porpiglia F, Mari A, Bertolo R, Antonelli A, Bianchi G, Fidanza F, et al. Partial Nephrectomy in Clinical T1b Renal Tumors: Multicenter Comparative Study of Open, Laparoscopic and Robot-assisted Approach (the RECORd Project). Urology. 2016; 89:45-51.
27. Kim DK, Kim LH, Raheem AA, Shin TY, Alabdulaali I, Yoon YE, et al. Comparison of Trifecta and Pentafecta Outcomes between T1a and T1b Renal Masses following Robot-Assisted Partial Nephrectomy (RAPN) with Minimum One Year Follow Up: Can RAPN for T1b Renal Masses Be Feasible? PLoS One. 2016; 11:e0151738.
28. Osaka K, Makiyama K, Nakaigawa N, Yao M. Predictors of trifecta outcomes in laparoscopic partial nephrectomy for clinical T1a renal masses. Int J Urol. 2015; 22:1000-5.
29. Minervini A, Siena G, Antonelli A, Bianchi G, Bocciardi AM, Cosciani Cunico S, et al. Open versus laparoscopic partial nephrectomy for clinical T1a renal masses: a matched-pair comparison of 280 patients with TRIFECTA outcomes (RECORd Project). World J Urol. 2014; 32:257-63.
30. Gu L, Liu K, Du S, Li H, Ma X, Huang Q, et al. Prediction of pentafecta achievement following laparoscopic partial nephrectomy: Implications for robot-assisted surgery candidates. Surg Oncol. 2020; 33:32-7.
31. Reynolds CR, Delto JC, Paulucci DJ, Weinstein C, Badani K, Eun D, et al. Comparison of perioperative and functional outcomes of robotic partial nephrectomy for cT1a vs cT1b renal masses. BJU Int. 2017; 120:842-7.
32. Delto JC, Paulucci D, Helbig MW, Badani KK, Eun D, Porter J, et al. Robot-assisted partial nephrectomy for large renal masses: a multi-institutional series. BJU Int. 2018; 121:908-15.
33. Castellucci R, Primiceri G, Castellan P, Marchioni M, D'Orta C, Berardinelli F, et al. Trifecta and Pentafecta Rates After Robotic Assisted Partial Nephrectomy: Comparative Study of Patients with Renal Masses <4 and ≥4 cm. J Laparoendosc Adv Surg Tech A. 2018; 28:799-803.

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APPENDIX 1

Table S1 - Risk of bias for each included study.

Study	Year	Selection				Comparability	Outcome			Overall
		Representativeness of exposed cohort	Selection of nonexposed	Ascertainment of exposure	Outcome not present at start		Assessment of outcome	Adequate follow-up length	Adequacy of follow-up	
Furukawa et al. (22)	2020	1	1	1	1	1	1	1	1	8
Takeda et al. (23)	2020	0	1	1	1	1	0	1	1	6
Peyronnet et al. (16)	2018	1	1	1	1	1	1	1	1	8
Khene et al. (17)	2018	1	1	1	1	1	1	1	1	8
Harke et al. (18)	2018	1	1	1	1	1	1	1	1	8
Castellucci et al. (19)	2018	0	1	1	1	1	1	1	1	7
Paulucci et al. (24)	2017	1	1	1	1	1	0	1	1	7
Lebentrau et al. (25)	2017	0	1	1	1	1	1	1	1	7
Porpiglia et al. (26)	2016	1	1	1	1	1	1	1	1	8
Kim et al. (27)	2016	0	1	1	1	1	1	1	1	7
Zargar et al. (20)	2015	1	1	1	1	1	1	1	1	8
Osaka et al. (28)	2015	0	1	1	1	1	1	1	1	7
Minervini et al. (29)	2014	1	1	1	1	1	1	1	1	8

REVIEW ARTICLE

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Comparison of mini percutaneous nephrolithotomy and standard percutaneous nephrolithotomy for renal stones >2cm: a systematic review and meta-analysis

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ABSTRACT

Background: The purpose is to compare the efficacy and safety of mini percutaneous nephrolithotomy (mini-PCNL) versus standard percutaneous nephrolithotomy (standard-PCNL) in patients with renal stones >2cm.

Materials and Methods: A systematic literature search was conducted in PubMed, Web of Science, Scopus, and the Cochrane Library databases to identify relevant studies before March 8, 2021. Stone-free rate (SFR), operation time, fever rate, hemoglobin drop, blood transfusion rate, and hospitalization time were used as outcomes to compare mini-PCNL and standard-PCNL. The meta-analysis was performed using the Review Manager version 5.4.

Results: Seven randomized controlled trials were included in our meta-analysis, involving 1407 mini-PCNL cases and 1436 standard-PCNL cases. Our results reveal that, for renal stones >2cm, mini-PCNL has a similar SFR (risk ratio (RR)=1.01, 95% confidence interval (CI): 0.98 to 1.04, p=0.57) and fever rate (RR=1.22, 95% CI: 0.97-1.51, p=0.08). Standard-PCNL was associated with a significantly shorter operating time (weighted mean difference (WMD)=8.23, 95% CI: 3.44 to 13.01, p <0.01) and a longer hospitalization time (WMD=-20.05, 95% CI: -29.28 to -10.81, p <0.01) than mini-PCNL. Subgroup analysis showed hemoglobin drop and blood transfusion for 30F standard-PCNL were more common than mini-PCNL (WMD=-0.95, 95% CI: -1.40 to -0.50, p <0.01; RR=0.20, 95% CI: 0.07 to 0.58, p <0.01).

Conclusion: In the treatment of >2cm renal stones, mini-PCNL should be considered an effective and reliable alternative to standard-PCNL (30F). It achieves a comparable SFR to standard-PCNL, but with less blood loss, lower transfusion rate, and shorter hospitalization. However, the mini-PCNL does not show a significant advantage over the 24F standard-PCNL. On the contrary, this procedure takes a longer operation time.

Trial registration: This meta-analysis was reported consistent with the PRISMA statement and was registered on PROSPERO, with registration number 2021CRD42021234893.

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INTRODUCTION

Percutaneous nephrolithotripsy (24-30F) remains the standard procedure for treating large renal calculi (1). While achieving high SFR, it also has many drawbacks such as bleeding, postoperative pain, and a long recovery period due to its large access tract (2), so the mini percutaneous nephrolithotripsy (14-22F)

with a smaller tract size came into being. It has been more than 20 years since Jackman et al. (3) and Helal et al. (4) first reported the application of mini-PCNL in pediatric surgery. Although numerous studies have been conducted on comparing the two types of percutaneous nephrolithotripsy, the debate on which one is better continues, and the main point of conflict is the difference in SFR and incidence of postoperative complications (5-8). In the treatment of renal stones >2cm, retrograde intrarenal surgery (RIRS) and extracorporeal shock wave lithotripsy (ESWL) seem not to be competitive enough compared with PCNL, so can mini-PCNL, which is more minimally invasive, be used as a substitute to standard-PCNL in such cases? Scholars (9-11) have systematically reviewed the comparison of percutaneous nephrolithotripsy with different tract sizes. However, the quality of the included evidence was poor, and more reliable data from randomized controlled trial (RCT) studies are needed. Furthermore, there was no meta-analysis comparing standard-PCNL and mini-PCNL in patients with large kidney stone burdens. Therefore, our focus is on comparing surgical procedures for renal stones >2cm, and updated RCT studies in recent years were added, including some high-quality large multicenter RCT studies such as Zeng et al. (12). Efficacy and safety of the two surgical procedures in renal stones >2cm were compared, and subgroup analyses were performed to derive a more optimal recommendation for clinical practice.

MATERIALS AND METHODS

Search strategy

Registration for this study was conducted on PROSPERO, with registration number 2021CRD42021234893. Two independent authors conducted separate searches in PubMed, Web of Science, Scopus, and the Cochrane Library databases to identify relevant studies before March 8, 2021. Only articles published in English were selected. The key words we used in the search were "mini percutaneous nephrolithotomy" OR "mini--PCNL" OR "miniperc" OR "MPCNL" OR "minimally invasive percutaneous nephrolithotomy" AND "standard percutaneous nephrolithotomy" OR "standard PCNL". We also searched for relevant systematic reviews and references to identify any omitted studies (13). The articles which meet our inclusion criteria were selected based on their titles and abstracts.

Selection of studies

The literature selection was performed independently by two authors according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14). Disagreement was resolved by consensus or arbitrated by a senior author. Inclusion and exclusion criteria were specified before our search. The inclusion criteria were as follows: (1) available RCT studies; (2) patients with renal stones >2cm; (3) studies that compared mini-PCNL with standard PCNL; (4) reporting at least one of the following outcomes: SFR, operation time, hospitalization time, hemoglobin drop, blood transfusion, fever. Exclusion criteria were composed of: (1) pediatric patients (<18 years old); (2) super-mini/ultra-mini/micro percutaneous nephrolithotomy (<14F); (3) case reports, conference abstracts, editorials, reviews, animal experiments, and letters.

Data extraction

All the articles included were read, and the relevant data from the articles were also extracted on a standard form by two reviewers. The primary analyzed outcome was SFR. The secondary outcomes were operation time, hospitalization time, hemoglobin drop, blood transfusion, and fever. For some continuous variable data reported using the median and the first and third quartiles, we converted them into sample mean and standard deviation according to the method improved by Luo et al. (15) and Wan et al. (16) to pool results in a consistent format.

Quality assessment

The level of evidence (LE) for included studies was assigned according to the criteria provided by Oxford Centre for Evidence-Based Medicine (17). The risk of bias assessment for these RCT studies was based on the Cochrane Systematic Reviews Manual, in which studies were evaluated in seven aspects (allocation concealment, random

sequence generation, blinding of participants and personnel, selective reporting, incomplete outcome data, blinding of outcome assessment and other bias). Any discrepancy was resolved by consensus.

Statistical analysis

The related data analysis was performed using the Review Manager version 5.4 (Cochrane Collaboration, UK). Risk ratio (RR) and weighted mean difference (WMD) were used to evaluate the dichotomous variables and continuous parameters, respectively. Both types of data were reported with 95% confidence intervals (CI). The Chi-square test and I^2 statistic were used to calculate statistical heterogeneity among included studies. When I^2 <50%, fixed-effect models were used, and random-effect models were applied for the meta-analysis when I^2 >50%. In addition, the pooled effects were assessed by the Z test. For the result of data analysis, a P <0.05 can be considered statistically significant. Subgroup analysis was performed on all outcomes by dividing the standard-PCNL group into 30F and 24F groups. Forest plots were drawn to present the results of the meta-analysis. In order to evaluate the stability of the meta-analysis results, a sensitivity analysis was performed by leave-one-out cross validation.

RESULTS

Study selection

The study search process and results are shown in Figure-1. A total of 814 studies were collected using the search strategy mentioned above, and 7 studies were finally considered eligible after the exclusion (Table-1). All 7 studies are randomized controlled trials, including 1407 mini-PCNL cases and 1436 standard-PCNL cases (5, 6, 13, 18-21). All of the included studies compared mini-PCNL with standard-PCNL for patients with kidney stones larger than 2cm.

Characteristics and quality of the included studies

The baseline characteristics of the 7 studies such as age, stone burden and tract size are shown in Table-2. Actual surgical procedures varied in terms of access sheath size, dilator, nephroscope size and type of lithotriptor. In all the studies included in this meta-analysis, the access sheath size of standard-PCNL was 30F or 24F. The level of evidence of the included literature is described in Table-1, and the quality of the studies was assessed by Cochrane's risk of bias tool in Figure-2. There is some "unclear risk of bias" in the assessment results because some literature is inadequate in some trial details.

Meta-analysis outcomes

SFR

Data on SFR were available in all seven studies, and the pooled results showed no significant difference in SFR between mini-PCNL and standard-PCNL (RR=1.01, 95% CI: 0.98 to 1.04, p=0.57, Figure-3 A). The result of subgroup analysis also showed no difference between the 30F subgroup and the 24F subgroup and the mini-PCNL group (RR=0.99, 95% CI: 0.92 to 1.08, p=0.86; RR=1.01, 95% CI: 0.98 to 1.05, p=0.49). Mild heterogeneity was detected in the 24F subgroup (I^2 =17%), while there was no heterogeneity in comparison of mini-PCNL and standard-PCNL (I^2 =0%).

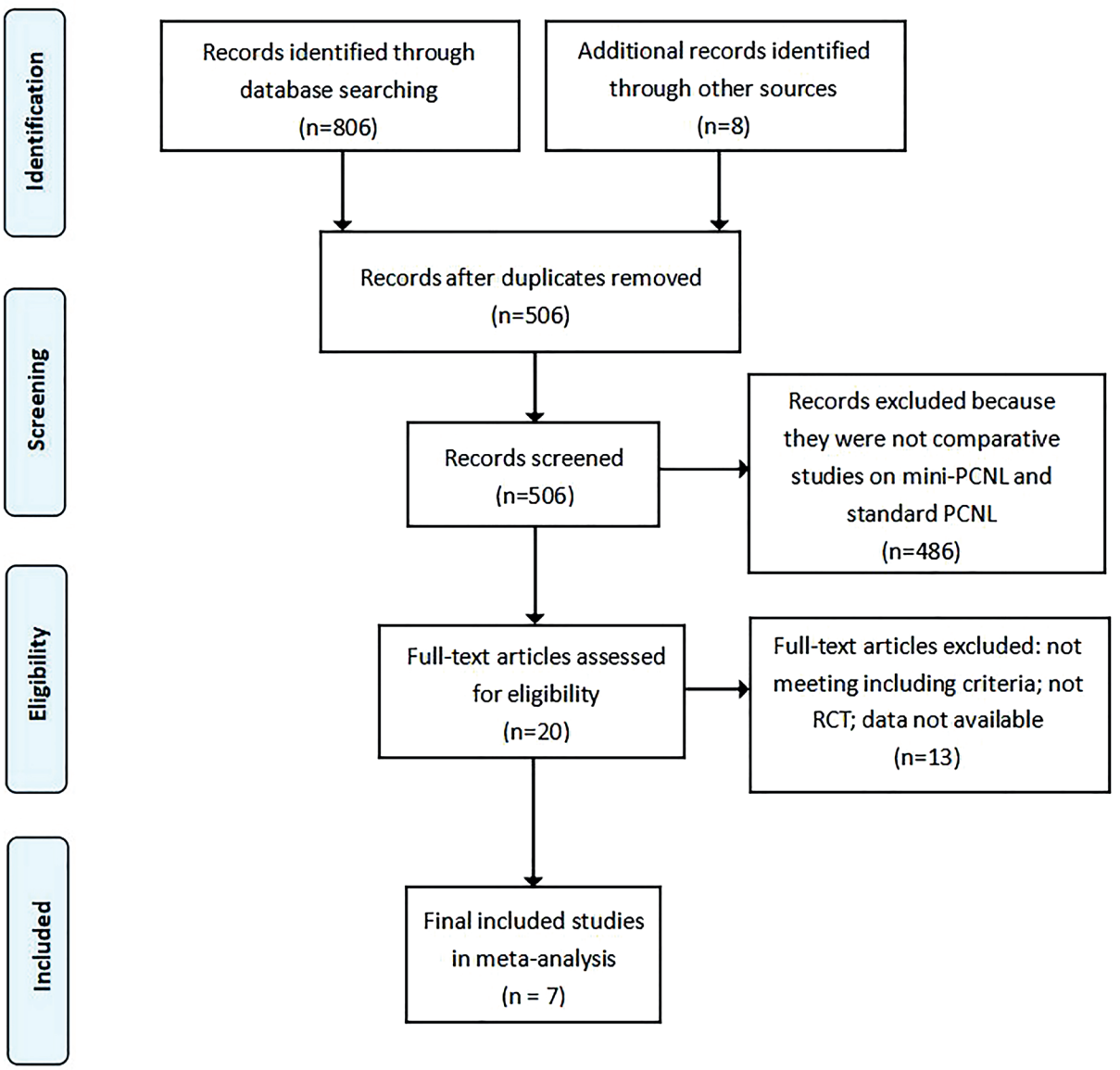
Operation time

The pooled results showed that the standard-PCNL group was associated with a significantly shorter operating time than the mini-PCNL group (WMD=8.23, 95% CI: 3.44 to 13.01, p <0.01, Figure-3 B) while high heterogeneity (I^2 =80%) was observed. The results of subgroup analysis showed that both the 30F subgroup and the 24F subgroup were superior to the mini-PCNL group in terms of operation time (WMD=9.71, 95% CI: 1.72 to 17.69, p=0.02; WMD=7.64, 95% CI: 1.80 to 13.47, p=0.01). The high heterogeneity was mainly detected in the 24F subgroup (I^2 =84%).

Fever

With data extracted from all seven studies, fever rate was higher with mini-PCNL. However, no statistical difference was found in fever rate between the mini-PCNL group and the standard-PCNL group according to this meta-analysis (RR=1.22, 95% CI: 0.97-1.51, p=0.08, Figure-3 C). The result of subgroup analysis showed no statistical difference between the 30F subgroup and the 24F subgroup versus the mi-

Figure 1 - Flow diagram of studies selection process.



ni-PCNL group (RR=1.22, 95% CI: 0.50 to 3.01, p=0.66; RR=1.21, 95% CI: 0.97 to 1.52, p=0.09), with mild heterogeneity in the 24F subgroup (I^2 =22%).

Hemoglobin drop and blood transfusion

Overall, the comparison of hemoglobin drop and blood transfusion rate between the mini--PCNL group and the standard-PCNL group showed significant differences (WMD=-1.35, 95% CI: -2.07 to -0.63, p<0.01, Figure-3 D; RR=0.40, 95% CI: 0.23 to 0.72, p <0.01, Figure-3E). Compared with the mini-PCNL group, the 30F subgroup was associated with a greater hemoglobin drop and higher blood transfusion rate (WMD=-0.95, 95% CI: -1.40 to -0.50, p <0.01; RR=0.20, 95% CI: 0.07 to 0.58, p <0.01). However, the hemoglobin drop and blood transfusion rate in the 24F subgroup was not significantly different from that in the mini--PCNL group (WMD=-2.53, 95% CI: -6.70 to 1.64,

Table 1 - Summary of comparative studies.

Study	Country	Study period	Study design	LE	Cases, n		Definition of SFR
					Mini	Standard	
Güler et al. (18)	Turkey	2016.01-2017.04	RCT	2b	51	46	complete clearance of stones
Kandemir et al. (5)	Turkey	2016.11-2018.09	RCT	2b	76	72	complete clearance of stones or with residual fragments <4 mm
Wu et al. (19)	China	2014.03-2015.07	RCT	2b	114	114	complete clearance of stones or with residual fragments <4 mm
Zeng et al. (12)	China	2016.01-2019.08	RCT	2b	978	966	complete clearance of stones or <4mm asymptomatic, noninfectious, and non-obstructive residual stones at 1 month after the removal of the J-J stent
Sakr et al. (6)	Egypt	2010.09-2013.12	RCT	2b	75	75	complete clearance of stones or with residual fragments <4 mm
Cheng et al. (20)	China	2004.05-2007.12	RCT	2b	69	111	complete clearance of stones or with residual fragments <4 mm
Song et al. (21)	China	2008.08-2009.08	RCT	2b	30	30	complete clearance of stones or with residual fragments <4 mm

p=0.23; RR=0.60, 95% CI: 0.29 to 1.24, p=0.17). In the subgroup analysis of hemoglobin drop, heterogeneity was high in both 30F and 24F subgroups (I^2 =73%; I^2 =98%) while in blood transfusion rate, only the 24F subgroup showed high heterogeneity (I^2 =72%).

HOSPITALIZATION

Data on hospitalization were available in four studies. The pooled results and subgroup analysis results indicated that the mini-PCNL group was associated with a significantly shorter hospitalization (WMD=-20.05, 95% CI: -29.28 to -10.81, p <0.01, Figure-3 F; 30F: WMD=-14.11, 95% CI: -23.03 to -5.19, p <0.01; 24F: WMD=-23.82, 95% CI: -37.92 to -9.71, p <0.01). High heterogeneity was detected in the 24F subgroup (I^2 =92%).

SENSITIVITY ANALYSIS

A sensitivity analysis was performed by leave-one-out cross validation for some outcome indicators with high statistical heterogeneity. The analysis results showed no significant decrease in heterogeneity in operation time or hemoglobin drop after articles were sequentially removed. Study reported by Wu et al. (19) were considered the

Table 2 - Baseline characteristics of included studies.

Study	Mean age		Mean stone burden		Access sheath size		Dilator		Nephroscope size		Lithotripsy	
	Mini	Standard	Mini	Standard	Mini	Standard	Mini	Standard	Mini	Standard	Mini	Standard
Güler et al. (18)	46.9 ± 13.7	47.4 ± 13.9	38.7 ± 13.1mm	42.8 ± 22.5mm	16.5/20F	30F	AD	BD/ AD	12F	26F	Laser	Pneumatic and ultrasonic
Kandemir et al. (5)	47.0 ± 13.9	46.7 ± 14.2	32.6 ± 8.1mm	33.1 ± 10.9mm	16.5/20F	30F	AD	BD/ AD	12/14F	26F	Laser	Pneumatic, ultrasonic, laser
Wu et al. (19)	47.6 ± 8.2	48.1 ± 7.9	3.4 ± 1.0cm	3.3 ± 1.1cm	16F	24F	FD	AD	8/9.8F	20.8F	Ultrasonic	Ultrasonic
Zeng et al. (12)	51.0 (43.0, 59.0)[a]	51.0 (44.0, 60.0)[a]	29.0 (23.0, 35.0)mm[a]	29.0 (25.0, 35.0)mm[a]	18F	24F	FD	FD	12F	20.8F	Pneumatic, ultrasonic, laser	Pneumatic, ultrasonic, laser
Sakr et al. (6)	43.8 ± 9.5	40.2 ± 8.3	2.7 ± 0.2cm	2.6 ± 0.6cm	16.5F	30F	TMD	TMD	12F	26F	Pneumatic	Pneumatic
Cheng et al. (20)	37.2	39.6	9.54cm^2	9.62cm^2	16F	24F	TMD	TMD	8/9.8F	20.8F	Pneumatic	Pneumatic and ultrasonic
Song et al. (21)	NA	NA	8.57 ± 2.2cm^2	8.65 ± 2.0cm^2	16F	24F	FD	FD + TMD	NA	24F	Laser	Pneumatic and ultrasonic

FD = fascial dilators; **TMD** = telescoping metal dilators; **AD** = Amplatz dilators; **BD** = balloon dilators; **NA** = not available
[a] Data are presented as median (first quartile, third quartile)

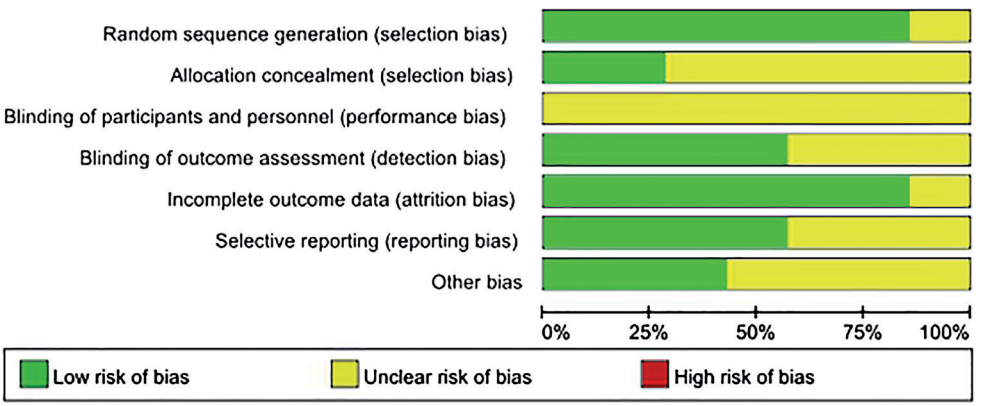
main sources of heterogeneity in hospitalization, and the result remained unchanged after its removal. Of note, in the analysis of fever rate, the results showed a significantly higher fever rate with mini-PCNL when a study reported by Cheng et al. (20) was removed.

DISCUSSION

Mini-PCNL appears to be an increasingly popular procedure for the treatment of renal stones. However, whether it can be superior to standard-PCNL regarding efficacy and safety is still under debate worldwide (5-8). A study by Deng et al. (11) revealed a significantly higher SFR in standard-PCNL than the mini-PCNL in adult patients with <2cm renal stones, while no statistical difference was found between the two procedures in patients with >2cm renal stones. In their study, no other outcome was analyzed according to the stone size, nor have they been reported in the published literature (10, 11). Therefore, it is necessary to compare the safety and efficacy of these two procedures in these specific cases with renal stones >2cm. Only RCTs were included to ensure the reliability of the conclusions, especially the study by Zeng et al., which is of great significance (12). It is generally believed that the tract size of standard--PCNL is 24F-30F, and that of mini-PCNL is 14F-22F (22). Ultramini-PCNL and micro-PCNL should not be comparable with standard-PCNL in terms of operation indication (especially >2cm stone), and they are not intended to replace standard-PCNL but to compete with ESWL and RIRS. Therefore, the studies about ultramini-PCNL (11-13F) and micro-PCNL (4.8-10F) were not included in this meta-analysis.

In the present study, the SFR achieved by mini-PCNL was similar to that by standard-PCNL, although the definition of the SFR in these studies

Figure 2 - Overall quality assessment for the included articles.

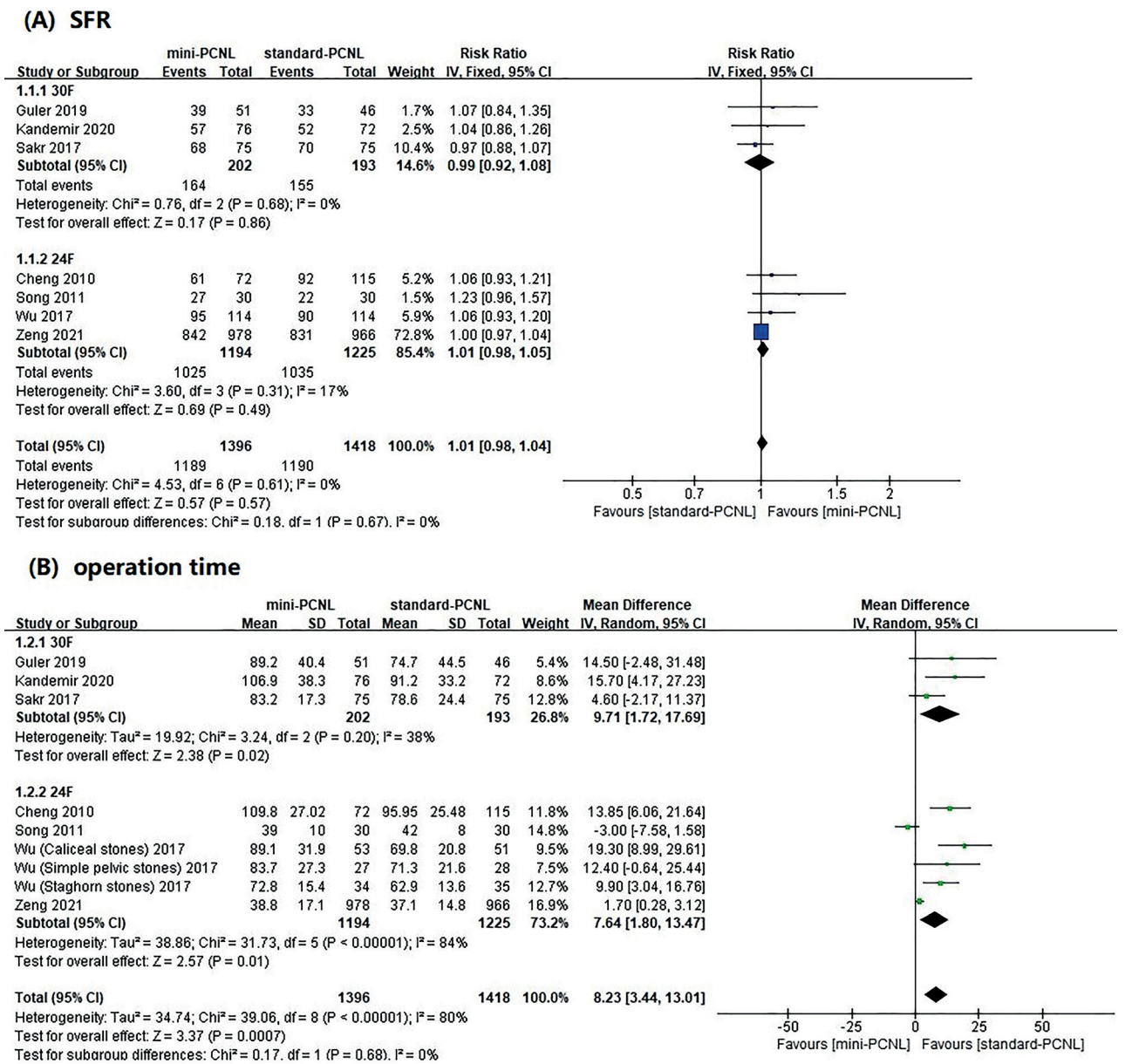


was slightly different. This result was in accordance with that of Zhu et al. (10). Notably, no significant differences in SFR between the 30F subgroup and the mini-PCNL group were found, unlike in the reviews published by Deng et al. (11), where the former has a higher SFR. This proves that mini-PCNL has been non-inferior to standard-PCNL in one-session SFR. Moreover, a study by Cheng et al. revealed that mini-PCNL even achieved a better SFR than standard-PCNL in cases with multiple calyceal stones. This can be caused by using a narrower ureteroscope which can help us reach different calyces more easily (20).

Standard-PCNL shows significant advantages regard to operation time. However, there was a high degree of heterogeneity among the included studies, which could be attributed to the differences between surgical protocols and differences in the definition of operative time. Different types of lithotripsy modalities also differ in stone fragmentation efficiency. Laser lithotripsy has become the current mainstream modality and is favored by surgeons, which is largely due to its high efficiency. Compared with pneumatic lithotripsy and ultrasonic lithotripsy, it may shorten the operation time for patients with a large stone burden. In the included studies, we found that several types of lithotripsy were often used together in standard-PCNL, whereas a single lithotripsy modality was used in mini-PCNL, which could lead to bias. Two main factors make mini-PCNL takes longer. On the one hand, the vision of mini-nephroscope surgery is worse, which makes the operation more complicated; on the other hand, in order for the stone to pass through a mini tract, surgeons have to break the stones into smaller pieces, which also significantly prolongs the operation time. Moreover, recent studies have shown that supine position was associated with lower operative time in standard-PCNL and mini-PCNL than other positions (23, 24). However, there is still no consensus on its efficacy and the incidence of complications. Xu et al. found that the trend towards metabolic acidosis was more evident as the irrigation time went by during mini-PCNL compared with standard-PCNL (25). Surgeons should keep in mind that the longer a patient spends under general anesthesia, the more postoperative complications and the slower recovery (26).

Mini-PCNL resulted in a higher rate of postoperative fever, though not statistically significant. Still, the potential fever risk is worth noting. The interspace between scope and access sheath is very important. As the diameter of the access sheath is decreased, the absolute space for irrigation outflow will also be reduced, which may lead to a higher renal pelvic pressure (RPP) and absorption of irrigation fluid (27). Infection can also result from broken stones containing endotoxins and bacteria, and thus even if the urine culture is negative before surgery, patients may still get a fever after surgery. In addition, Wu et al. found that cumulative time >60s with RPP >30mmHg will significantly increase the incidence of fever. Therefore, prevention of sepsis may be achieved by ensuring RRP remains <30mmHg during ope-

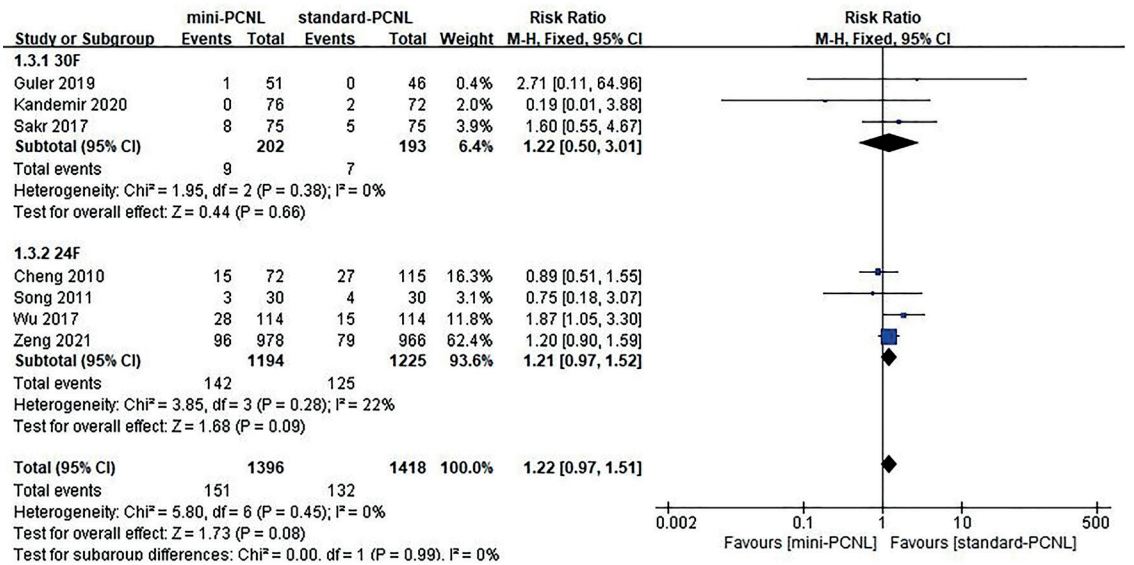
Figure 3 - Forest plots and meta-analysis. (a) SFR, (b) operation time, (c) fever rate, (d) hemoglobin drop, (e) blood transfusion, (f) hospitalization.



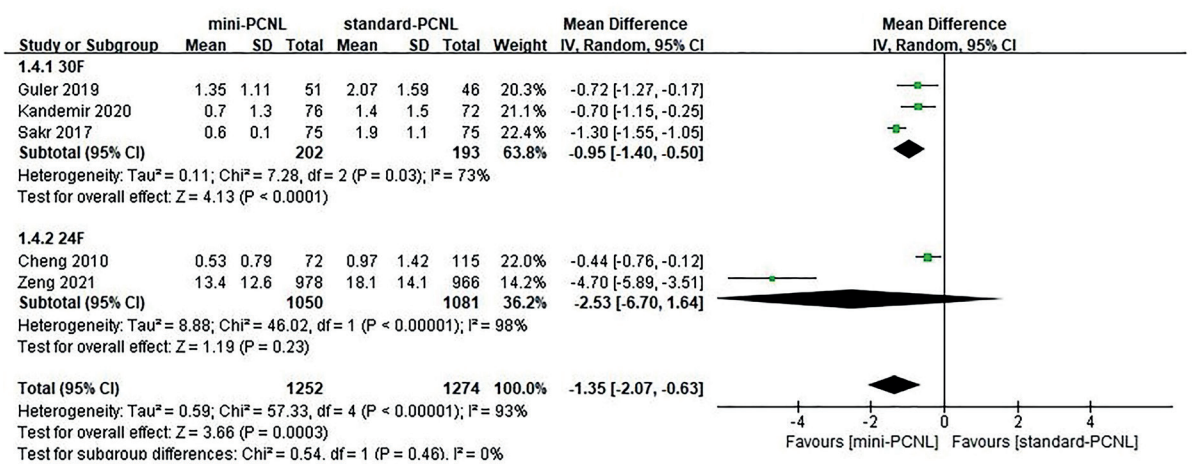
ration and indwelling the drainage tube after the operation (19).

The establishment of the access tract is considered the leading cause of PCNL blood loss, in which the size of the tract is a crucial factor (10). Both hemoglobin drop and transfusion rate were found lower in mini-PCNL compared to the 30F PCNL. Unlike the previous study (11), mini-PCNL showed a similar blood transfusion rate as standard-PCNL (24F) in this meta-analysis, which is an impressive result. This may be attributed to the large kidney stone burden, and the bleeding was more severe when dealing with large stones, even if using a mini tract. The nephroscope and access sheath are often prized by the

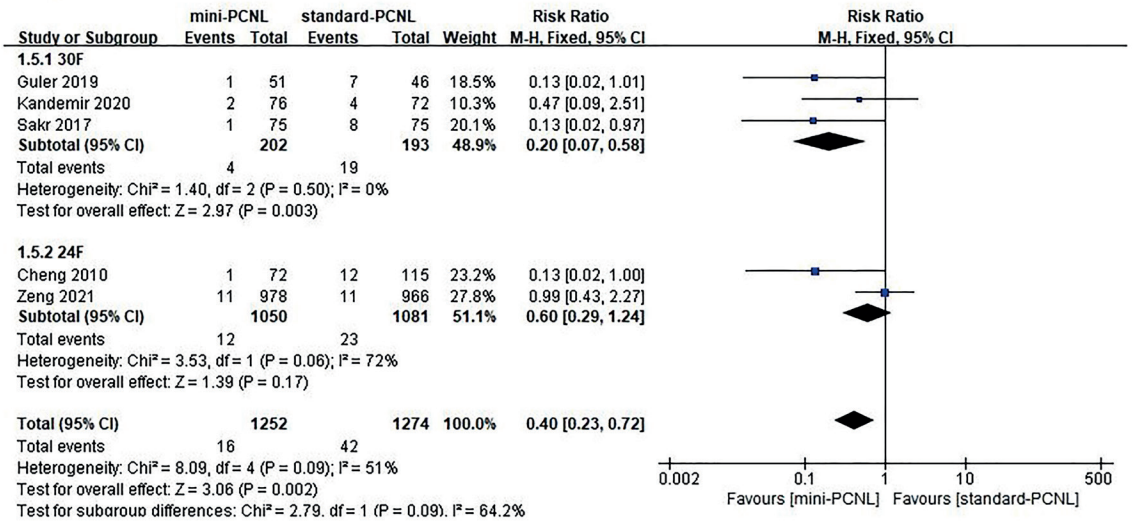
(C) fever rate



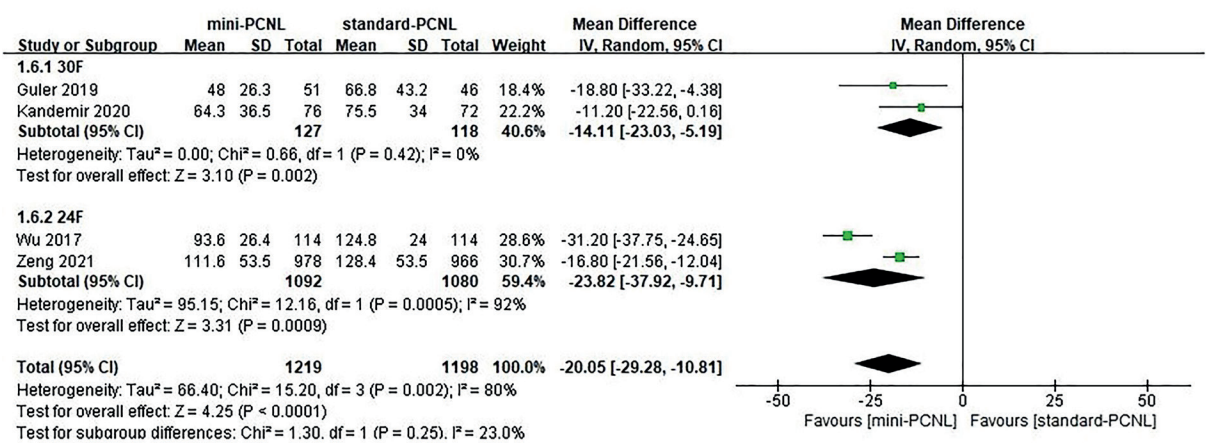
(D) hemoglobin drop



(E) blood transfusion



(F) hospitalization



surgeon to reach different calyces, resulting in severe renal damage and bleeding. Despite using a smaller tract, PCNL is still a procedure performed through a non-natural orifice, meaning that the risk of bleeding can only be minimized but not eliminated.

Only four studies evaluated hospitalization time, which can increase the risk of bias. Published studies seem to have concluded that patients undergoing mini-PCNL have significantly shorter hospitalization (5, 13, 18, 19). This may be explained by the higher tubeless rate, more minimal renal trauma and less postoperative pain in mini-PCNL.

According to the results of this meta-analysis, 24F standard-PCNL has the same SFR as mini--PCNL, with similar blood loss, but with a shorter operation time than mini-PCNL. It seems that 24F standard-PCNL is a better choice for the treatment of >2cm kidney stones, which appears to improve safety without compromising efficacy. In fact, the 24F PCNL is being favored by more and more urologists around the World, because it can greatly reduce the complications caused by the large tract. Encouragin-

gly, mini-PCNL (<24F) is evolving rapidly to achieve improved efficacy while retaining the safety benefits of mini-PCNL (28, 29). Smaller tract sizes, better efficacy, and lower complication rates will surely be achieved over time.

There were some limitations in this meta-analysis. First, the tract sizes of standard-PCNL used in included studies were only 30F and 24F, lacking data of 26F and 28F, which may increase the risk of selective bias. Second, high heterogeneity was detected among some studies, which can partly influence the accuracy of our study. Although a sensitivity analysis was performed, some of the heterogeneity was difficult to explain. Third, some other complications, such as postoperative pain, were not evaluated in this meta-analysis due to the lack of reports in the included studies. Fourth, relatively few studies were included in our meta-analysis because retrospective studies and case-control studies were excluded.

CONCLUSIONS

For the treatment of >2cm renal stones, mini-PCNL should be considered an effective and reliable alternative to 30F standard-PCNL. It achieves a comparable SFR to the latter, but with less blood loss, lower transfusion rate and shorter hospitalization. However, the mini-PCNL does not show a significant advantage over the 24F standard-PCNL. On the contrary, this procedure takes a longer operation time. Of note, the relatively long operation time and potential risk of fever associated with mini-PCNL should be taken seriously. Further research involving more high-quality evidence is necessary to support and supplement this conclusion.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Türk C, Neisius A, Petrik A, Seitz C, Skolarikos A, Thomas K, et al. EAU Guidelines on Urolithiasis. European Association of Urology 2020. [Internet]. Available at. <https://uroweb.org/guideline/urolithiasis/>
2. Kukreja R, Desai M, Patel S, Bapat S, Desai M. Factors affecting blood loss during percutaneous nephrolithotomy: prospective study. J Endourol. 2004; 18:715-22.
3. Jackman SV, Docimo SG, Cadeddu JA, Bishoff JT, Kavoussi LR, Jarrett TW. The "mini-perc" technique: a less invasive alternative to percutaneous nephrolithotomy. World J Urol. 1998; 16:371-4.
4. Helal M, Black T, Lockhart J, Figueroa TE. The Hickman peel-away sheath: alternative for pediatric percutaneous nephrolithotomy. J Endourol. 1997; 11:171-2.
5. Kandemir E, Savun M, Sezer A, Erbin A, Akbulut MF, Sarılar Ö. Comparison of Miniaturized Percutaneous Nephrolithotomy and Standard Percutaneous Nephrolithotomy in Secondary Patients: A Randomized Prospective Study. J Endourol. 2020; 34:26-32.
6. Sakr A, Salem E, Kamel M, Desoky E, Ragab A, Omran M, et al. Minimally invasive percutaneous nephrolithotomy vs standard PCNL for management of renal stones in the flank-free modified supine position: single-center experience. Urolithiasis. 2017; 45:585-9.
7. Giusti G, Piccinelli A, Taverna G, Benetti A, Pasini L, Corinti M, et al. Miniperc? No, thank you! Eur Urol. 2007; 51:810-4.
8. Knoll T. Is mini-percutaneous nephrolithotomy the way to go for renal stones? No! Curr Opin Urol. 2019; 29:312-3.
9. Ruhayel Y, Tepeler A, Dabestani S, MacLennan S, Petřík A, Sarica K, et al. Tract Sizes in Miniaturized Percutaneous Nephrolithotomy: A Systematic Review from the European Association of Urology Urolithiasis Guidelines Panel. Eur Urol. 2017; 72:220-35.
10. Zhu W, Liu Y, Liu L, Lei M, Yuan J, Wan SP, et al. Minimally invasive versus standard percutaneous nephrolithotomy: a meta-analysis. Urolithiasis. 2015; 43:563-70.
11. Deng J, Li J, Wang L, Hong Y, Zheng L, Hu J, et al. Standard versus Mini-Percutaneous Nephrolithotomy for Renal Stones: A Meta-Analysis. Scand J Surg. 2020:1457496920920474.

12. Zeng G, Cai C, Duan X, Xu X, Mao H, Li X, et al. Mini Percutaneous Nephrolithotomy Is a Noninferior Modality to Standard Percutaneous Nephrolithotomy for the Management of 20-40mm Renal Calculi: A Multicenter Randomized Controlled Trial. Eur Urol. 2021; 79:114-21.
13. Granados-Duque V, García-Perdomo HA. Systematic review and meta-analysis: Which pitfalls to avoid during this process. Int Braz J Urol. 2021; 47:1037-41.
14. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009; 339:b2700.
15. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018; 27:1785-805.
16. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014; 14:135.
17. [No authors]. Oxford Centre for Evidence-Based Medicine: Levels of Evidence (March 2009). Centre for Evidence-Based Medicine. [Internet]. Available at. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009 (accessed 10 March 2021).
18. Güler A, Erbin A, Ucpinar B, Savun M, Sarilar O, Akbulut MF. Comparison of miniaturized percutaneous nephrolithotomy and standard percutaneous nephrolithotomy for the treatment of large kidney stones: a randomized prospective study. Urolithiasis. 2019; 47:289-95.
19. Wu C, Hua LX, Zhang JZ, Zhou XR, Zhong W, Ni HD. Comparison of renal pelvic pressure and postoperative fever incidence between standard- and mini-tract percutaneous nephrolithotomy. Kaohsiung J Med Sci. 2017; 33:36-43.
20. Cheng F, Yu W, Zhang X, Yang S, Xia Y, Ruan Y. Minimally invasive tract in percutaneous nephrolithotomy for renal stones. J Endourol. 2010; 24:1579-82.
21. Song L, Chen Z, Liu T, Zhong J, Qin W, Guo S, et al. The application of a patented system to minimally invasive percutaneous nephrolithotomy. J Endourol. 2011; 25:1281-6.
22. Schilling D, Hüsch T, Bader M, Herrmann TR, Nagele U; Training and Research in Urological Surgery and Technology (T.R.U.S.T.)-Group. Nomenclature in PCNL or The Tower Of Babel: a proposal for a uniform terminology. World J Urol. 2015; 33:1905-7.
23. Melo PAS, Vicentini FC, Perrella R, Murta CB, Claro JFA. Comparative study of percutaneous nephrolithotomy performed in the traditional prone position and in three different supine positions. Int Braz J Urol. 2019; 45:108-17.
24. Ozdemir H, Erbin A, Sahan M, Savun M, Cubuk A, Yazici O, et al. Comparison of supine and prone miniaturized percutaneous nephrolithotomy in the treatment of lower pole, middle pole and renal pelvic stones: A matched pair analysis. Int Braz J Urol. 2019; 45:956-64.
25. Xu S, Shi H, Zhu J, Wang Y, Cao Y, Li K, et al. A prospective comparative study of haemodynamic, electrolyte, and metabolic changes during percutaneous nephrolithotomy and minimally invasive percutaneous nephrolithotomy. World J Urol. 2014; 32:1275-80.
26. Kallidonis P, Liourdi D, Liatsikos E, Tsaturyan A. Will Mini Percutaneous Nephrolithotomy Change the Game? Eur Urol. 2021; 79:122-3.
27. Zhong W, Zeng G, Wu K, Li X, Chen W, Yang H. Does a smaller tract in percutaneous nephrolithotomy contribute to high renal pelvic pressure and postoperative fever? J Endourol. 2008; 22:2147-51.
28. Alam R, Matlaga BR, Alam A, Winoker JS. Contemporary considerations in the management and treatment of lower pole stones. Int Braz J Urol. 2021; 47:957-68.
29. Çakici MÇ, Keser F, Atis RG, Yildirim A. Mini-percutaneous nephrolithotomy in a child with multiple urogenital anomalies and a solitary duplex kidney. Int Braz J Urol. 2021; 47:464-7.

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ORIGINAL ARTICLE

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Incontinence outcomes in women undergoing retropubic mid-urethral sling: a retrospective cohort study comparing Safyre™ and handmade sling

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ABSTRACT

Purpose: This study examined and compared efficacy, safety, satisfaction, and complications of the retropubic Safyre™ sling and a retropubic hand-made synthetic sling (HMS) in a short-, mid- and long-term follow-up.

Methods: We retrospectively reviewed a prospectively maintained database of women who underwent Safyre™ or HMS between March 7ths 2005 and December 27ths, 2017. Patients had first assessment (7-10 days), second (40-45 days), and third (sixth month) postoperatively. Between September and December 2018, patients who completed at least one year of surgery, received a telephone call. Follow-up compared quartiles of follow-up time to determine complications (Clavien-Dindo), success rates (International Consultation on Incontinence Modular Questionnaire for Urinary Incontinence Short Form – ICIQ-UI SF), and patient satisfaction.

Results: Three hundred fifty-one patients underwent surgery and 221 (63%) were evaluated after a median of 78.47 (± 38.69) months, 125 (55%) in the HMS, and 96 (45%) in the Safyre™ group. Higher intraoperative bladder injury was observed with Safyre™ (0% vs. 4.2%, p=0.034), and a tendency for urinary retention, requiring indwelling urinary catheter over 24 hours (2.4% vs. 8.3%, p=0.061). Both HMS (p<0.001) and Safyre™ (p<0.001) presented improvements on ICIQ-UI SF. There were no differences in satisfaction, subjective cure rates, ICIQ-UI SF, or complications between groups.

Conclusions: Both HMS and Safyre™ have similar satisfaction and subjective cure rates, with marked ICIQ-UI SF score improvement. Higher rates of intraoperative bladder injury were seen in patients who received Safyre™ retropubic sling.

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INTRODUCTION

Midurethral synthetic slings (MUS) became the most commonly performed minimally-invasive procedure for treating female stress urinary incontinence (SUI) worldwide (1, 2) and are regarded as the gold standard surgical treatment (3, 4). There are different types and brands of commercial synthetic slings, each with their own characteristics, which can be related to dis-

tinct complications (5-7).

However, commercial kits can be expensive, especially in developing countries, restricting their access, particularly in the public health system (8-12). Therefore, low-cost hand-made synthetic slings (HMS) have been proposed as an alternative to expand their access (8-12).

Safyre™ is a hybrid tape developed as a re-adjustable sling (11). It is based on the fibrotic encapsulation induced by the silicone columns and allows the anchoring tails moving up or downwards (13, 14).

Our hypothesis is that the HMS has a similar performance in comparison to the Safyre™ sling. This study aimed to present efficacy, safety, satisfaction, and complications of the retropubic Safyre™ sling vs HMS for female SUI in a long-term follow-up.

MATERIALS AND METHODS

This study protocol was submitted and approved by local ethics committee (number 223/2009 from May 5th, 2010). We retrospectively reviewed a prospectively maintained database with SUI patients over 18 years of age who underwent retropubic Safyre™ or retropubic HMS between March 7ths 2005, and December 27ths 2017, performed by a single surgeon, with a minimum follow-up of 1 year postoperatively. Patients with urgency-predominant mixed urinary incontinence, neurogenic lower urinary tract dysfunction, and pelvic organ prolapse (grade $\geq$ 2) were excluded. Baseline assessment included a detailed clinical history, urogynecological examination, urodynamic evaluation, and International Consultation on Incontinence Modular Questionnaire for Urinary Incontinence Short Form (ICIQ-UI SF) (15).

Women were allocated in two groups: retropubic hand-made sling (HMS) or retropubic Safyre™ (commercial kit – *Promedon, Cordoba, Argentina*). The choice for each of the groups was based on the mesh availability at the institution during the study period. A routine medical counseling provided patients with information about different treatment options, pros, and potential cons of these treatments. All patients received a comprehensive guidance concerning distinct surgical techniques, including synthetic and autologous slings, and Burch colposuspension procedure. Risks and benefits of different approaches were included in informed consent form. The medical team explored ideas, expectations, fears, and motivations of patients, aligning their expectations regarding the surgical treatment.

Safyre™ consists of a 100g/m2 monofilament and macroporous polypropylene mesh as suburethral support, measuring 42mm long and 13mm wide, connected to two solid polydimethylsiloxane (silicone) elastomer fixation arms, which allow adjustment of the tension of the mid-urethral sling intra and postoperatively (14, 16).

The HMS was performed with a standardized technique by cutting a 80mm long and 15mm wide rectangle from monofilament and macroporous polypropylene mesh (Parietene™ Standard – *Medtronic, Minneapolis, USA*) 75g/m2, attached with polyglycolic acid sutures at its edges (10), and using a resterilized Safyre™ needle. The 15mm-wide cut had the objective of leaving the mesh edge with complete braiding, and without denting, to maintain its integrity and reduce tissue damage during its traction. Sutures were passed through into the needles for retropubic positioning and no additional sutures were used for fixation.

Surgical steps and materials, including needles, were the same for both groups. Spinal anesthetic block was performed and 2g of prophylactic cefazolin was administered. A vertical 3 cm incision was made in the anterior vaginal wall and the periurethral space was then dissected. Needles were passed retropubic (upside-down) through a 1cm suprapubic incision and the sling allocated under the middle urethra without tension (17). Urethrocystoscopy was performed at the end of the procedure. Indwelling urinary catheter was maintained for 12 to 24 hours. After spontaneous voiding, patients were discharged. Any post-operative readjustment was performed in the operating room (loosening and tightening) before hospital discharge, similarly, to proposed by Toledo et al. (18).

First in-person, postoperative medical assessment was performed 7-10 days after surgery, second after 40-45 days, and the third in the sixth postoperative month. Patients with any complications were revaluated in-person even after this period. Postoperative assessments aimed to recognize complications, such as urinary retention, voiding and storage lower urinary tract symptoms (LUTS),

persistent incontinence, *de novo* urgency, hematoma, persistent pain, bleeding, vaginal discharge (any bleeding intensity referred by women), urinary tract infection, vaginitis, dyspareunia or hispareunia, mesh extrusion, and macroscopic hematuria. Postoperative urinary retention was evaluated in-person at office until the sixth postoperative month and considered when ultrasound demonstrated > 100mL of post void residual volume. Complications were reported according to Clavien-Dindo classification.

Medical records were reviewed between September and December 2018, and patients who had completed at least one year of surgery, received a telephone call from a trained researcher (who was blinded to the sling subtype). During the telephone evaluation, subjective cure (defined as the absence of SUI reported by the patient) and overall satisfaction with surgery (classified dichotomously as satisfied or unsatisfied) were assessed. ICIQ-UI SF was also reapplied, and patients were asked about voiding symptoms, SUI, urgency and urgency urinary incontinence, chronic pain, and dyspareunia. Medical records were additionally reviewed in search for additional surgical procedures, medical treatments, and other unrelated complications.

P-value <0.05 was considered statistically significant, with a 95% confidence interval (CI). Initially, the Kolmogorov-Smirnov test was applied to evaluate the normal distribution of continuous variables. Continuous variables with normal distribution are reported as means and standard deviations and those without normal distribution as medians and interquartile variation. Categorical variables are presented in frequencies and percentages. Differences between HMS and Safyre™ groups were evaluated by the T-test for independent samples for continuous variables with normal distribution; the Mann-Whitney U test for continuous variables without normal distribution; and for categorical variables, the chi-square test or Fisher's exact test, when samples were small (20<n<40 and expected frequency <5). Paired samples were analyzed by the Wilcoxon test. Chi-square test for trend was used to compare ordinal variables. Satisfaction rate, subjective cure, and ICIQ-UI SF were compared between the groups after patients had been divided into quartiles according to the period of follow-up.

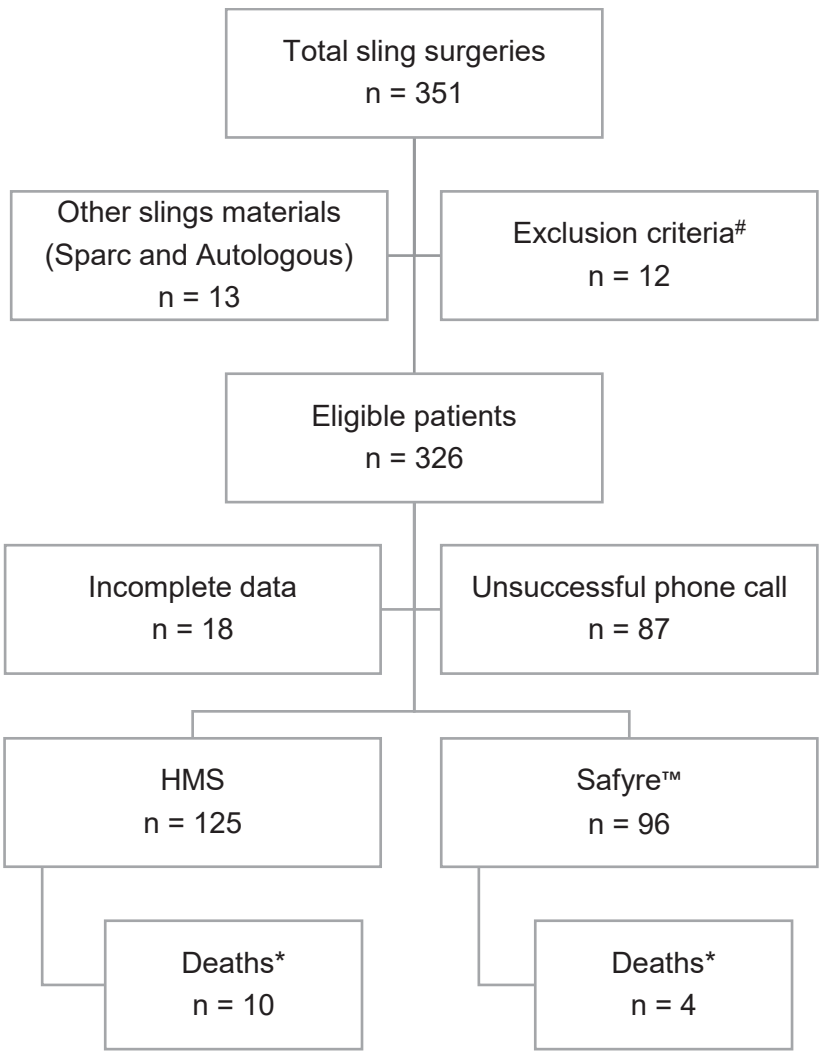
RESULTS

A total of 351 patients underwent surgical treatment between 2005 and 2017, and 221 (63%) were able to complete the study protocol, with follow-up ranged from 13 to 165 months (Figure-1). Mean age was 59.55 (±11.89) years, ranging from 31 to 84 years. Mean follow-up was 78.47 (±38.69) months, ranging from 13 to 165 months. Number of deaths in this period was 14 (10 in the HMS group and 4 in the Safyre™ group [p=0.246]), not related with the procedure (2 of metastatic breast cancer, 1 of lung cancer, 1 of leukemia, 1 due car accident, 8 of cardiovascular disease, 1 due diverticular disease).

There were no statistical differences between groups in relation to age, body mass index (BMI), previous surgical procedures (synthetic and autologous slings or Burch colposuspension procedure), hormonal status, number of pregnancies, birth routes, comorbidities (hypertension, obesity, depression, diabetes mellitus, chronic obstructive lung diseases, smoking, and congestive heart failure), and urodynamic data. Safyre™ patients had higher percent use of daily pads before surgery (60.4% vs. 40%, p=0.004), but the preoperative ICIQ-UI SF was similar in both groups (p=0.164) (Table-1).

Intraoperative bladder injury was higher in the Safyre™ group (0% vs. 4.2%, p=0.034). There was a tendency for urinary retention, requiring indwelling urinary catheter over 24 hours in the Safyre™ group (2.4% vs. 8.3%, p=0.061) (Table-2). In the HMS group, 7 patients (5.6%) required mesh adjustment (loosening: 3, tightening: 1, and urethrolysis: 3), while in the Safyre™ group, a total of 8 patients (8.3%) needed readjustments (loosening: 2, tightening: 2, and urethrolysis: 4) (p=0.434). Medical records at the sixth postoperative month revealed no differences between groups regarding SUI, urgency incontinence, mixed leakage, or pain (Table-2). All observed vaginal extrusions were on the suture line, smaller than 1 cm, and without infection. Extrusions occurred in 12.8% vs. 6.2%, (p=0.107), respectively in the HMS and the Safyre™ groups, initially treated with topical estrogen therapy and, if unsuccessful, with partial extruded mesh removal under local anesthesia. One patient in the Safyre™ group presented bladder erosion requiring

Figure 1. Flowchart of study selection process



HMS: Handmade Sling

*Deaths occurred at follow-up due to other causes (neoplasm, trauma, diverticular disease); data were used only for preoperative evaluations

#Neurogenic bladder, previous bladder augmentation, pelvic organs prolapse (grade ≥ 2)

surgical removal (Table-2). Median onset of vaginal extrusion was 6.0 (2.0 - 12.0) months in the HMS group and 3.0 months (2.0 – 4.0) in the Safyre™ group (p=0.120). There were no differences between groups for Grade II (3.2% vs. 2.1%), IIIa (4.0% vs. 3.1%), and IIIb (12.0% vs. 8.3%) Clavien-Dindo complications, respectively (p=0.282) (Table-2).

Mean follow-up was longer in the HMS group (85.05 vs. 69.90 months, p=0.004), but there were no differences between groups regarding complications, patient satisfaction, and median pre and postoperative ICIQ-UI SF. ICIQ-UI SF scores showed improvements from pre to postoperative measurements in both HMS (10 vs. 3, p<0.001)

Table 1 - Baseline data and urodynamic profile of patients according to the type of sling performed.

		HMS n=125 (56%)	Safyre™ n=96 (44%)	p-value
Age (years), mean (SD)		58.94 (±11.62)	60.33 (±12.26)	0.391[b]
Concomitant surgery		33 (26.4%)	26 (27.1%)	0.909[a]
BMI (kg/m²), mean (SD)		28.38 (±5.19)	27.69 (±4.64)	0.307[b]
Hormonal Status	Menopause without HR	81 (64.8%)	48 (50.0%)	0.149[d]
	Menopause with HR	18 (14.4%)	27 (28.1%)	
	Premenopausal	26 (20.8%)	21 (21.9%)	
Pads usage	Daily	50 (40.0%)	58 (60.4%)	**0.004[a]**
	If necessary	25 (20.0%)	18 (18.8%)	
	None	50 (40.0%)	20 (20.8%)	
Preoperative ICIQ-UI SF, median (IR)		10 (9.0 – 11.0)	10 (9.0 – 12.0)	0.164[c]
Parity, median (IR)	Pregnancies	3.0 (2.0 – 3.25)	2.0 (2.0 – 3.0)	0.156[c]
	Normal birth	2.0 (0 – 3.0)	2.0 (0 – 3.0)	0.264[c]
	Cesarean section	0 (0 – 1.25)	1.0 (0 – 2.0)	0.330[c]
Previous surgeries	Incontinence	19 (15.2%)	17 (17.7%)	0.617[a]
	Pelvic Organ Prolapse	39 (31.2%)	23 (24.0%)	0.235[a]
	Hysterectomy	34 (27.2%)	26 (27.1%)	0.985[a]
	Abdominal (others)	23(18.4%)	19 (19.8%)	0.794[a]
VLPP (cmH_20), mean (SD)		103.48 (±38.01)	103.04 (±40.83)	0.934[b]
Leakage type	Stress	111 (88.8%)	82 (85.4%)	0.453[a]
	Mixed	14 (11.2%)	14 (14.6%)	
Post-voiding residual urine	<30mL	93 (74.4%)	82 (85.4%)	0.665[d]
	30-100mL	21 (16.8%)	4 (4.2%)	
	>100mL	11 (8.8%)	10 (10.4%)	

HMS = Handmade Sling; **BMI** = Body Mass Index; **HR** = Hormonal Replacement; **ICIQ-UI SF** = International Consultation on Incontinence Modular Questionnaire for Urinary Incontinence Short Form; **VLPP** = Valsalva leak-point pressure; **SD** = standard deviation; **IR** = interquartile range

[a] Chi-squared test; [b] T-Test; [c] Mann-Whtney U test; [d] Chi-squared test for trend; [e] Fisher's exact test

and Safyre™ (10 vs. 3.5, p<0.001) groups. Loss of follow-up was similar in both groups (p=0.163) (Table-3). Tables 4 an 5 (supplementary files) present additional information about the ICIQ-IU SF scores (pre and postoperatively), according to follow-up quartiles, between sling groups.

DISCUSSION

To our knowledge, this is the first study describing HMS vs retropubic SafyreTM sling outcomes at long-term follow-up. Analysis demonstrated similar satisfaction, subjective cure rates, and improvement in the ICIQ-UI SF in up to 13

Table 2 - Complications according to the type of sling performed.

		HMS n=125 (56%)	Safyre™ n=96 (44%)	p-value
Intraoperative bladder injury		0 (0.0%)	4 (4.2%)	**0.034**[e]
Urinary infection		14 (11.2%)	10 (10.4%)	0.853[a]
Vaginal bleeding		28 (22.4%)	18 (18.8%)	0.508[a]
LIC>24h		3 (2.4%)	8 (8.3%)	0.061[e]
Sling readjustment	None	118 (94.4%)	88 (91.7%)	0.434[e]
	Tightening [g]	1 (0.8%)	2 (2.4%)	
	Loosening [g]	3 (2.4%)	2 (2.1%)	
	Urethrolysis [h]	3 (2.4%)	4 (4.2%)	
6th month office reassessment				
Stress Incontinence		12 (9.6%)	11 (11.5%)	0.654[a]
Urgency Incontinence		23 (18.4%)	24 (25.0%)	0.235[a]
Mixed Incontinence		5 (4.0%)	10 (10.4%)	0.060[a]
Pain		24 (19.2%)	14 (14.6%)	0.367[a]
Vaginal extrusion		16 (12.8%)	6 (6.2%)	0.107[a]
Time (months), median (IR)		6.0 (2.0 – 12.0)	3.0 (2.0 – 4.0)	0.120[c]
Treatment	None	109 (87.2%)	90 (93.7%)	0.118[e]
	Topical	12 (9.6%)	4 (4.2%)	
	Surgical	4 (3.2%)	2 (2.1%)	
Clavien-Dindo	None	101 (80.8%)	83 (86.5%)	0.282[e]
	II	4 (3.2%)	2 (2.1%)	
	IIIa	5 (4.0%)	3 (3.1%)	
	IIIb	15 (12.0%)	8(8.3%)	

HMS = Handmade Sling; **LIC>24h** = Long-term indwelling catheter for more than 24 hours.
IR = Interquartile Range
[a] Chi-squared test; [c] Mann-Whitney U test; [e] Fisher's exact test; [g] Performed before discharged; [h] Performed before sixth postoperative month

years follow-up comparing SafyreTM with a retropubic handmade sling. Patients undergoing SUI surgery using HMS or Safyre™ retropubic slings presented similar satisfaction and subjective cure rates. Perioperative bladder injuries were more frequent in the Safyre™ group, besides a higher tendency for indwelling bladder catheterization. Loss of follow-up in the study (37%) may have been seen as an inherent limitation, but similar rates have been previously reported by Kuprasertkul and Zimmern, who demonstrated rates of loss ranging from 10 to 49% over 10 years follow-up (19).

Table 3 - Telephone evaluation according type of sling performed.

	HMS n=115 (56%)	Safyre™ n=92 (44%)	p-value
Deaths*	10 (8.0%)	4 (4.2%)	0.246[a]
Loss of follow-up	58 (31.7%)	31 (24.4%)	0.163[a]
Follow-up (months), mean (SD)	85.05 (±40.93)	69.90 (±33.90)	0.004[b]
Postoperative ICIQ-UI SF, median (IR)	3 (0.0 –12.75)	3.5 (0.0 – 9.5)	0.476[c]
ICIQ-UI SF dif (pre – post), median (IR)	6 (2 – 8)	6 (4 – 8)	0.142[c]
De novo urgency	46 (40.0%)	39 (42.4%)	0.728[a]
Urinary Tract Infection	20 (17.4%)	17 (18.5%)	0.839[a]
Vaginal bleeding	3 (2.6%)	0 (0.0%)	0.256[e]
Voiding symptoms	13 (11.3%)	4 (4.3%)	0.070[a]
Pelvic pain	8 (7.0%)	5 (5.4%)	0.654[a]
Dyspareunia	0 (0.0%)	3 (3.3%)	0.086[e]
Satisfaction	91 (79.1%)	76 (82.6%)	0.529[a]
Subjective Cure	79 (68.7%)	73 (79.3%)	0.085[a]

HMS = Handmade Sling; **ICIQ-UI SF** = International Consultation on Incontinence Modular Questionnaire for Urinary Incontinence Short Form; **dif** = difference.
SD = Standard Deviation; **IR** = Interquartile Range;
a Chi-squared test; b T-test; c Mann-Whitney U test; e Fisher's exact test
* Not related to the procedure

Table 4. Median (IR) of preoperative and postoperative ICIQ-UI SF according to the follow-up quartiles and type of sling performed.

	HMS		
Follow-up (months)	Preoperative ICIQ-UI SF	Postoperative ICIQ-UI SF	p-value
13 – 42 (n=27)	9 (8.5 – 12)	0 (0 – 12)	**0.002**[f]
43 – 79 (n=21)	10 (9 – 12)	9 (0 – 16)	0.163f
80 – 103 (n=28)	10 (9 – 10.5)	3 (0 – 13.5)	**0.005**[f]
104 – 165 (n=39)	9 (8 – 12)	5 (0 – 13)	**0.008**[f]
Total (n=115)	10 (9 – 11)	3 (0 – 13)	**<0.001**[f]
	Safyre™		
13 – 42 (n=24)	9.5 (8.25 – 11)	1.5 (0 – 8)	**0.006**[f]
43 – 79 (n=31)	10 (8.5 – 13)	5 (0 – 13)	**0.002**[f]
80 – 103 (n=24)	11 (8.5 – 13.5)	5 (0 – 8)	**<0.001**[f]
104 – 165 (n=13)	9.5 (9 – 12.5)	3 (0 – 11)	**0.007**[f]
Total (n=92)	10 (9 – 12)	3.5 (0 – 9.75)	**<0.001**[f]

HMS = Handmade Sling; **ICIQ-UI SF** = International Consultation on Incontinence Modular Questionnaire for Urinary Incontinence Short Form.
IR = Interquartile Range
[f] Wilcoxon test

Table 5 - Comparison of difference in ICIQ-UI SF (pre – post), satisfaction, and subjective cure, according to follow-up quartiles, between sling groups.

Follow-up (months)	HMS	Safyre™	p-value
ICIQ-UI SF difference (pre – post), median (IR)			
13 – 42 (n=51)	8 (-2.25 – 9) (n=27)	7 (1.5 – 10) (n=24)	0.813[c]
43 – 79 (n=52)	3 (-4.25 – 10) (n=21)	5 (-0.5 – 9) (n=31)	0.386[c]
80 – 103 (n=52)	7 (-2.5 – 9) (n=28)	6.5 (2 – 10.5) (n=24)	0.138[c]
104 – 165 (n=52)	6 (-3 – 9) (n=39)	6 (2.5 – 9) (n=13)	0.336[c]
Satisfaction, n (%)			
13 – 42 (n=51)	24 (89%)	22 (91.7%)	0.890[a]
43 – 79 (n=52)	12 (57.2%)	27 (87.1%)	**0.034[a]**
80 – 103 (n=52)	21 (75%)	18 (75%)	0.748[a]
104 – 165 (n=52)	34 (87.2%)	9 (69.2%)	0.290[a]
Subjective Cure, n (%)			
13 – 42 (n=51)	21 (77.8%)	20 (83.3%)	0.884[a]
43 – 79 (n=52)	14 (66.7%)	25 (80.6%)	0.414[a]
80 – 103 (n=52)	19 (67.9%)	20 (83.3%)	0.335[a]
104 – 165 (n=52)	25 (64.1%)	8 (61.6%)	0.868[a]

HMS = Handmade Sling; **ICIQ-UI SF**, International Consultation on Incontinence Modular Questionnaire for Urinary Incontinence Short Form. **IR** = Interquartile Range
[a] Chi-squared test; [c] Mann-Whitney U test

A limited number of publications have studied Safyre™ and all of them used a transobturator approach, with bladder perforation rates varying between 0 – 4.2% (1, 9, 10). Risk factors for bladder injury in this context may include previous pelvic surgeries (cesarean section, colposuspension, rectocele), inexperienced surgeons, local anesthesia, younger patient age and lower body mass index (BMI) (4, 20). In the current study, previous surgeries and BMI were similar in both groups. Additionally, the surgeon had extensive experience with both slings, and the needles were the same for both groups. Although our study design does not allow us to understand the exact mechanism behind higher rates of intraoperative bladder perforation in the Safyre™ group, since cystoscopy was performed at the end of the procedure, further research should focus on the design of this sling, particularly on its solid elastomer (silicone) fixation arms. Kuschel S and Schuessler B, in a prospective trail, founded vaginal sling extrusion in 8.8% of the patients and a pre-erosive state in another 13.9% (concerning the central polypropylene part). The lateral silicone column could be palpated medial to the pubic bone in 47% of the patients indicating dislocation (13).

The retropubic Safyre™ group also demonstrated a higher tendency for indwelling bladder catheterization, similar to the urinary retention data observed in literature with Safyre TOT (12, 16, 21). Palma et al. reported urinary retention in 3% of patients after a transobturator Safyre™ sling, which may be treated by loosen the sling tension (16). We used the retropubic approach, which is known to present higher risk for retention since the sling band can become more compressive around the urethra. In our study, 3 (2.4%) patients in the HMS group and 4 (4.2%) patients in the Safyre™ group required urethrolysis due persistent emptying LUTS.

The importance of reporting the presence of vaginal extrusions has increased in recent years. Several authors who have published studies with homemade slings do not report local complications with the mesh, prioritizing only the reporting of voiding complications (8-12). Vaginal extrusion rates showed a higher tendency in the HMS group. Ciftci et al. reported a higher rate in HMS group (14.6% vs. 1.6%) after 12 months of follow-up (8), using a transobturator approach, and ElSheemy MS 10% (17). Other studies with Safyre™ reported extrusion rates between 5 – 8.8% up to 96 months of follow-up (13, 14, 21). Our overall vaginal extrusion rate was 9.9% and the median time to onset of extrusion was 4.5 months. It is difficult to compare these results, since extrusion definition varies in literature, besides vaginal extrusion correlates with several variables such as characteristics of the mesh, follow-up extension, intrinsic patient factors and the surgical route of the sling (5, 6). Furthermore, long-term extrusions may not be properly assessed by teleconsultations, especially those asymptomatic patients. Certainly, an in-face clinical visit with a vaginal exam would be better. It is not also possible to draw definitive conclusions regarding this specific complication, as the sample size was not calculated based on the expected complication rate.

Telephone evaluation performed during the study revealed persistence of SUI in 20.7% – 31.3% and urgency incontinence in 40% – 42.4% in the mid and long-term follow--up. Other studies using Safyre™ have found recurrent incontinence ranging from 17.6 – 21% in up to 96 months of follow-up (13, 21). Subjective success rate in the long-term follow-up was 68,7% in HMS and 79,3% in the Safyre™ group, which was lower than the reported by Kenton et al. (79% – 85%) or Sahin et al. (88%) after 5 years (3, 22). In fact, a decline in the mid- and long-term MUS treatment success has been repeatedly reported (23-25).

In a retrospective study comparing transobturator HMS and commercial slings, Ciftci et al. reported similar subjective cure rates in both groups after a 12-month follow-up (8) and Lourenço et al. found a comparable rate of subjective cure rates (9). Other authors found subjective cure rates between 59% and 90% (13, 15, 21). Palma et al., using transobturator Safyre™, observed a subjective cure rate of 90% in the first and sixth postoperative months, reporting that they were able to maintain such results due to the possibility of sling adjustments (16). Similarly, but using a handmade sling, Toledo et al. demonstrated that it is possible to adjust it, which can prevent immediate failures (18).

Limitations of this study include the retrospective design, lack of randomization, and use of postoperative telephone calls at different follow-up times. Nevertheless, telephone standardized validated questionnaires helped to reach many patients and has been described as an appropriate follow-up method (26). Especially after Covid 19 pandemic, telephone assessment has been increasingly accepted, as the telephone evaluation allows a safe and efficacious follow-up for MUS patients (27).

CONCLUSION

Patients undergoing SUI surgery using HMS or Safyre™ presented similar satisfaction and subjective cure rates, with no significant differences in quality-of-life on urinary incontinence scores. Higher rates of intraoperative bladder injury were seen in patients who received Safyre™ retropubic sling.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015;(7):CD006375.
2. Glavind K, Shim S. Incidence and treatment of postoperative voiding dysfunction after the tension-free vaginal tape procedure. Int Urogynecol J. 2015;26:1657-60.

3. Kenton K, Stoddard AM, Zyczynski H, Albo M, Rickey L, Norton P, et al. 5-year longitudinal followup after retropubic and transobturator mid urethral slings. J Urol. 2015;193:203-10.
4. Gomes CM, Carvalho FL, Bellucci CHS, Hemerly TS, Baracat F, de Bessa J Jr, et al. Update on complications of synthetic suburethral slings. Int Braz J Urol. 2017;43:822-34.
5. Petri E, Ashok K. Complications of synthetic slings used in female stress urinary incontinence and applicability of the new IUGA-ICS classification. Eur J Obstet Gynecol Reprod Biol. 2012;165:347-51.
6. Ackerman AL, Raz S. Difference of opinion - Are syntetic slings safe? Opinion: No. Int Braz J Urol. 2016;42:640-4.
7. Chapple CR, Cruz F, Deffieux X, Milani AL, Arlandis S, Artibani W, et al. Consensus Statement of the European Urology Association and the European Urogynaecological Association on the Use of Implanted Materials for Treating Pelvic Organ Prolapse and Stress Urinary Incontinence. Eur Urol. 2017;72:424-31.
8. Ciftci S, Ozkurkcugil C, Ustuner M, Yilmaz H, Yavuz U, Gulecen T. Comparison of transobturator tape surgery using commercial and hand made slings in women with stress urinary incontinence. Urol J. 2015;12:2090-4.
9. Lourenço DB, Korkes F, Vetorazzo JE Filho, Carramão SDS, Auge APF, de Toledo LGM. Functional outcomes and quality of life after transobturatory slings: hand - made vs. commercial slings. Int Braz J Urol. 2018;44:543-9.
10. Ignjatovic I, Potic M, Basic D, Dinic L, Medojevic N, Laketic D, et al. Self-created transobturator tape treatment of stress urinary incontinence without prior urodynamic investigation. Eur J Obstet Gynecol Reprod Biol. 2014;182:76-80.
11. Rodrigues FR, Maroccolo Filho R, Maroccolo RR, Paiva LC, Diaz FA, Ribeiro EC. Pubovaginal sling with a low-cost polypropylene mesh. Int Braz J Urol. 2007;33:690-4.
12. Brito LM, Sousa Ade P, de Figueiredo Neto JA, Duarte TB, Pinheiro Gdo L, Chein MB. Comparison of the outcomes of the sling technique using a commercial and hand-made polypropylene sling. Int Braz J Urol. 2011;37:519-27.
13. Kuschel S, Schuessler B. Results on function and safety of the Safyre-t, a hybrid transobturator vaginal sling for the treatment of stress urinary incontinence. Neurourol Urodyn. 2008;27:403-6.
14. Palma P, Riccetto C, Herrmann V, Dambros M, Thiel M, Bandiera S, et al. Transobturator SAFYRE sling is as effective as the transvaginal procedure. Int Urogynecol J Pelvic Floor Dysfunct. 2005;16:487-91.
15. Tamanini JTN, Dambros M, D 'ancona CAL, Palma PCR, Netto Jr NR. Validation of the "International Consultation on Incontinence Questionnaire - Short Form" (ICIQ-SF) for Portuguese. Rev Saúde Pública. [Internet]. 2004; 38:1–6. [cited 2017 May 14]. Available from: <www.fsp.usp.br/rsp>
16. Palma PC, Dambros M, Riccetto CZ, Thiel M, Netto NR Jr. The Ibero-American experience with a re-adjustable minimally invasive sling. BJU Int. 2005;95:341-5.
17. ElSheemy MS, Fathy H, Hussein HA, Elsergany R, Hussein EA. Surgeon-tailored polypropylene mesh as a tension-free vaginal tape-obturator versus original TVT-O for the treatment of female stress urinary incontinence: a long-term comparative study. Int Urogynecol J. 2015;26:1533-40.
18. de Toledo LGM, Zanotti RR, Matos AC. Female sling: handmade adjustable threads. Int Braz J Urol. 2021;47:211-3.
19. Kuprasertkul A, Zimmern P. Challenges of Very Long-term Reporting in Stress Urinary Incontinence Surgeries in Women. Urology. 2020;139:50-9.
20. Kuhlmann PK, Dallas K, Masterson J, Patel DN, Chen A, Castaneda P, et al. Risk Factors for Intraoperative Bladder Perforation at the Time of Midurethral Sling Placement. Urology. 2021;148:100-5.
21. Töz E, Balsak D, Basogul N, Özdemir AA, Okay G, Apaydın N, et al. Outcomes of Transobturator Tape Surgery with Safyre T® Slings for Female Stress Urinary Incontinence after 96 Months of Follow-Up. Gynecol Obstet Invest. 2015;20. Epub ahead of print.
22. Sahin MO, Sen V, Irer B, Yildiz G. The effects of menopause on the quality of life and long-term outcomes of transobturator tape treatment in women with stres urinary incontinence. Int Braz J Urol. 2020;46:716-24.
23. Malek JM, Kissane LM, Martin KD, Meyer I, Powell TC, Richter HE. Short-, mid-, and long-term incontinence outcomes in women undergoing mid-urethral sling procedures: a retrospective cohort study. Int Urogynecol J. 2021;32:609-14.
24. Braga A, Caccia G, Sorice P, Cantaluppi S, Coluccia AC, Di Dedda MC, et al. Tension-free vaginal tape for treatment of pure urodynamic stress urinary incontinence: efficacy and adverse effects at 17-year follow-up. BJU Int. 2018;122:113-7.
25. Ford AA, Ogah JA. Retropubic or transobturator mid-urethral slings for intrinsic sphincter deficiency-related stress urinary incontinence in women: a systematic review and meta-analysis. Int Urogynecol J. 2016;27:19-28.

26. Kuprasertkul A, Christie AL, Zimmern P. A standardized telephone interview with validated questionnaires for very long-term evaluation of women lost to follow-up after a stress urinary incontinence procedure. Low Urin Tract Symptoms. 2021;13:366-71.

27. Giusto LL, Derisavifard S, Zahner PM, Rueb JJ, Deyi L, Jiayi L, et al. Telemedicine follow-up is safe and efficacious for synthetic midurethral slings: a randomized, multi-institutional control trial. Int Urogynecol J. 2021;20:1–9. Epub ahead of print.

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EDITORIAL COMMENT

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The evolution of stress urinary incontinence treatment techniques of the last three decades

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COMMENT

The authors retrospectively studied a database of 221 patients who underwent correction of stress urinary incontinence (SUI) through the implantation of a SAFYRE VS retropubic sling (96 women) or a homemade polypropylene retropubic sling - HMS (125 patients) between March 2005 and December 2007, comprising a median follow-up of 78.47 (± 38.69) months (1). The evaluation included a telephone call made by a blinded trained researcher for those patients who had completed at least one year of surgery. The HMS was made of a 75g/m^2, 15mm-wide polypropylene mesh attached with polyglycolic acid sutures at its edges. Both HMS and SAFYRE VS groups presented significant improvements on International consensus on Incontinence – Urinary Incontinence Short Form questionnaire (ICIQ-UI SF) and there were no differences in satisfaction, subjective cure rates, ICIQ-UI SF, or complications between groups, but a significantly higher frequency of patients of SAFYERE VS group required indwelling urinary catheter over 24 hours (2.4% vs. 8.3%, p=0.061) as well as a higher frequency of bladder injury was observed in the SAFYRE VS group (0% vs. 4.2%, p=0.034).

In the present study (1), the use of the SAFYRE VS was not advised for patients with severe or recurrent SUI or those with expected need of postoperative readjustment that are the primary population for which readjstuble sinthetic slings have been currently proposed (2, 3). In fact, authors disclosured that the allocation of patients for HMS or SAFYRE VS implant was exclusively conditioned to their availability at the time of surgery. Furthermore, no significant sociodemographic or clinical differences were detected between patients in both groups, which allowed for reasonable data comparison despite the retrospective and non randomized study design.

In fact, there are few publications focused on both types of suburethral slings which were studied in the current series. The SAFYRE VS sling kit developed in Latin America, and together with REEMEX readjustable System (Neomedic Int, Spain) correspond to the only two slings that propose to allow an easy postoperative readjustment feature (4). However, publications on long-term follow-up are rare for both devices so the present series is a good reference on the performance of SAFYRE VS in longer follow--up periods than previously published (refer to article's references).

Publications about homemade polypropylene slings are even rarer and much more difficult to evaluate, due to the biomechanical differences and the wide range of of the meshe's size resulted from the surgeon's tailoring. In addition, detailed descriptions of the procedures used for the primary adjustment and sling fixation are often missed in the publications (5), leaving no answer as to how it should be performed, i.e., if similar to the adjustment of a classic aponeurotic sling or as the same manner as used for polypropylene midurethral slings sets.

Contrary to the results presented in this article, it could be assumed that the rate of prolonged urethral catheterization would possibly be higher in the HMS group, either because of the difficulties inherent in fitting a non-industrialized sling, or because of the authors' option of using a slightly wider sling (15mm) than the available minimally invasive midurethral slings sets. The authors attributed their findings to the design of the SAFYRE VS silicone columns. In this sense, we could hypothesize that, according to the authors, the lower friction of the silicone columns against the host tissues, or even an eventual elastic effect of the silicone columns could add a risk of excessive traction by the surgeon and so some obstruction effect. In this sense, it should be reasonable to advise those that intent to implant a SAFYRE VS sling that additional care should be taken when adjusting this kind of sling. Additionally, one should consider that it seems that tightening the SAFYRE VS should be simpler than loosening it.

In conclusion, the publication of such article rescues interesting aspects the evolution of SUI treatment techniquesof the last three decades. We congratulate the authors for their willingness to share their results and thoughs.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Terziotti F, Gregório EP, Averbeck MA, Almeida SHM. Incontinence outcomes in women undergoing retropubic midurethral sling: a retrospective cohort study comparing Safyre™ and handmade sling. Int Braz J Urol. 2022;48: 649-59.
2. Caldwell L, White AB. Stress Urinary Incontinence: Slings, Single-Incision Slings, and Nonmesh Approaches. Obstet Gynecol Clin North Am. 2021;48:449-66.
3. Sukhikh S, Kasyan G, Grigoryan B, Pushkar D. Suburethral Synthetic Adjustment-controlled Tape Compared with Conventional Treatment for Female Stress Urinary Incontinence: A Randomized Controlled Trial. Eur Urol Focus. 2022:S2405-4569(21)00328-X.
4. Ros C, Escura S, Anglès-Acedo S, Larroya M, Bataller E, Amat L, et al. Mid-term results of the Remeex® readjustable sling for female complex stress urinary incontinence and sonographic hypomobile urethra. Int Urogynecol J. 2022;33:903-10.
5. Brito LM, Sousa Ade P, de Figueiredo Neto JA, Duarte TB, Pinheiro Gdo L, et al. Comparison of the outcomes of the sling technique using a commercial and hand-made polypropylene sling. Int Braz J Urol. 2011;37:519-27.

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Efficacy of intravaginal electrical stimulation with different treatment frequency in women with refractory idiopathic overactive bladder

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ABSTRACT

Objective: The aim of this study is to evaluate the effect of intravaginal electrical stimulation (IVES) therapies with different treatment frequencies (two or five days in a week) added to bladder training (BT) on incontinence-related quality of life (QoL) and clinical parameters in women with refractory idiopathic overactive bladder (OAB).
Material and Methods: Fifty-two women with refractory idiopathic OAB were randomized into two groups as follows: Group 1 (n:26) received BT and IVES, two times in a week, for 10 weeks and Group 2 (n:26) received BT and IVES five times in a week, for 4 weeks. IVES was performed 20 minutes in a day, a total of 20 sessions for both groups. Women were evaluated for incontinence severity (24h pad test), pelvic floor muscles strength (perineometer), 3-day voiding diary (frequency of voiding, nocturia, incontinence episodes, and the number of pads), symptom severity (OAB-V8), quality of life (IIQ-7), treatment success (positive response rate), cure/improvement rate and treatment satisfaction (Likert scale).
Results: There was no statistically significant differences in all parameters between the two groups at the end of the treatment. It was found that the treatment satisfaction scores, cure/improvement and positive response rates were not significantly different between two groups (p>0.05).
Conclusion: We concluded that the application of IVES twice a week or 5 times a week added to BT were both effective on incontinence-related QoL and clinical parameters in women with refractory idiopathic OAB. These two IVES frequencies had similar clinical efficacy and patient satisfaction with a slight difference between them; 5 times per week IVES has a shorter treatment duration.

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INTRODUCTION

Overactive bladder (OAB) is a symptom complex defined as urgency, with or without urgency urinary incontinence (UUI), usually with frequency and nocturia in the absence of urinary tract infection (1). Currently, a wide range of therapeutic options exists for the treatment of OAB.

Electrical stimulation (ES) is one of the techniques used in urogynecological physiotherapy, which uses implanted or non-implanted electrodes (2). Intravaginal ES (IVES) is a con-

servative treatment option used in patients with OAB and UUI for detrusor inhibition. It has been suggested that IVES probably targets the detrusor muscle or pelvic floor muscle (PFM) or afferent innervation in UUI. According to the European Association Urology Guidelines, ES may improve urinary incontinence compared to sham treatment in adults with urinary incontinence (3). The duration of IVES programs varied from 4 weeks to 6 months in women with idiopathic OAB in the literature, although IVES was applied for 4-12 weeks commonly in practice (4-11). In most studies, IVES was applied 2-3 times a week (4-11), whereas it was applied more frequently in fewer studies (12-14). Despite that, no randomized study compared the different IVES treatment frequencies in women with idiopathic OAB, and thus, there is no evidence for which frequency of treatment is the most effective one. It should be kept in mind that the different stimulation frequencies may lead to different results. Some studies evaluating the efficacy of IVES included subjects were not used antimuscarinics within the last 4 week or antimuscarinic-naive patients with OAB (4, 15), while some included patients with OAB who were unresponsive or intolerant to antimuscarinics (5, 16). As a result, IVES appears to be a non-invasive and effective therapy used both as first-line treatment, as well as in managing of refractory patients with idiopathic OAB.

Our study is the first prospective randomized trial that compares the efficacy of IVES with different treatment frequencies in women with refractory idiopathic OAB. In this study, we aimed to assess the effect of IVES applied for 2 times vs 5 times in a week added to bladder training (BT) on quality of life (QoL) and the clinical parameters associated with idiopathic OAB. The results of our study will be of great benefit in determining the effectiveness of different treatment frequencies of IVES in women with idiopathic OAB. Thus, more effective treatment frequency of IVES (2 or 5 times in a week) can be determined or if they are of similar effectiveness, the frequency and duration of treatment may be left to the choice of the patients and the physicians taking into account non-treatment conditions.

MATERIAL AND METHODS

This study was planned as a prospective, randomized clinical trial. The trial was carried out in the Urogynecological Rehabilitation Unit of Physical Medicine and Rehabilitation Department, between February 2021 and August 2021. The local ethics committee approved the study (E-60116787-020-4274). This study was registered with ClinicalTrials.gov number, NCT04734301. All women were informed about the purpose and contents of the study and all women signed written consent to participate in the study.

Considering a 50% or greater improvement in incontinence episodes in the previously study, the optimum sample size should be 26 cases in each arm (a total of 52 women) with a level of significance of 95% (α=5%), a power of 95% (ß=0.05) (4). Sample size calculation was performed by the physician who was blinded to groups using G*Power 3.1 Statistical Power Analysis for Microsoft Windows and Mac. Statistics.

We recruited 74 women with complaints of OAB who were referred to the Urogynecological Rehabilitation Unit and other related outpatient clinics. Women over the age of 18 with the clinical diagnosis of idiopathic OAB, and who were intolerant or unresponsive to antimuscarinics and discontinued at least 4 weeks ago, and who were able to give written informed consent and understand the procedures were included in this study. The criteria for exclusion were as follows: women who had stress urinary incontinence; a history of conservative therapy (BT, ES) for OAB within 6 months; urogynecological surgery within 3 months; current vulvovaginitis or urinary tract infections or malignancy; pregnancy; cardiac pacemaker or implanted defibrillator; anatomic structural disorders of the genital region that did not allow to apply the vaginal probe; the strength of PFM less than 3/5 (graded as modified Oxford scale, min:0-max:5); the pelvic organ prolapse quantification (POP-Q) (stage 2 or more); neurogenic bladder; the peripheral or central neurologic pathology; ultrasonographic evidence of post-void residual urine volume more than 100 mL (using Telemed Micrus portable ultrasonography (the Lithuania) device (17), and allergy to

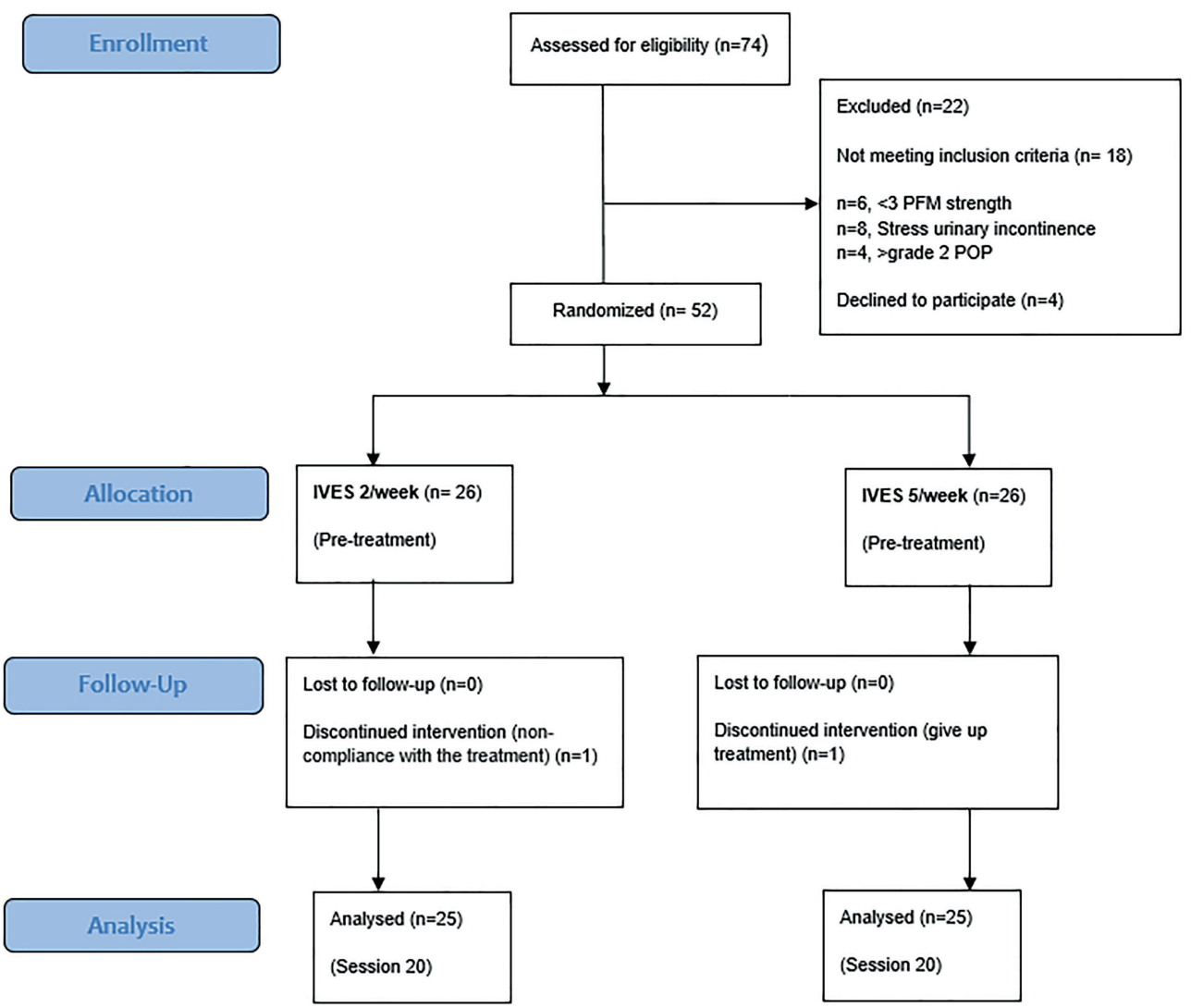
condom or lubricant gel that is used with perineometer/vaginal probe were excluded.

Seventy-four women with idiopathic OAB were recruited for eligibility and fifty-two of them who fulfilled the inclusion/exclusion criteria were included for this study. The flow chart is shown in Figure-1. By using a random number generator, 52 women were randomized into two groups as follows: Group 1 received BT+IVES (2 times in a week) (n:26), Group 2 received BT+IVES (5 times in a week) (n:26) (Figure-1). A random allocation sequence was generated at a 1:1 ratio.

Bladder Training (BT)

All women were informed about BT that consisted of four stages and lasted for 30 minutes. Then, it was given as a written brochure to be implemented as a home program. At the first stage, the women were familiarized with the location of the PFM and the pelvic anatomy and pathophysiology. After that information session,

Figure 1 - CONSORT participant flow diagram for randomized, controlled trials of non pharmacologic treatment.



IVES = Intravaginal electrical stimulation; **PFM** = pelvic floor muscle; **POP** = pelvic organ prolapse

squeezing the PFM was shown in practice at least once to use in the urgency suppression strategies via digital palpation technique. The second stage including urgency suppression strategies was aimed to delay urination, inhibit detrusor contraction, and prevent urgency by squeezing the PFM several times on a row, breathing deeply, giving their attention to another job for a while, and self-motivating. In the third stage, a timed voiding program was started. It was carried out in 2 steps: a timed voiding and increasing the time between urination considering the voiding diary. At the last stage, the women were encouraged to continue BT (4, 5, 18, 19).

Group 1: Two times IVES in a week (2/week IVES)

IVES was applied in addition to BT in this group. IVES was performed in lithotomy position via a stimulation device (Enraf Nonius Myomed 632) with a vaginal probe. IVES was performed two days a week, a total of 20 sessions for 10 weeks. Every session lasted 20 minutes. The stimulation parameters were a 10 Hz of frequency, a 5-10 s of work-rest cycle duration and, a 100 ms of pulse width. The symmetric biphasic pulse wave could be delivered over a range of 1-100 mA (with respect to the patient's discomfort level feedback) (4,5,11,20).

Group 2: Five times IVES in a week (5/week IVES)

This group was also treated with the IVES in addition to all components of the BT in Group 1. IVES was performed in the same way as Group 1, except for the frequency and the total duration of treatment. IVES was performed five days a week, a total of 20 sessions for 4 weeks. Every session lasted 20 minutes. Stimulation parameters were the same as Group 1 (4, 5, 11, 20).

IVES sessions were performed by an experienced urogynecological rehabilitation nurse in all groups. During the treatment, all women were advised to continue the medical treatment which was not related to incontinence. Participants were asked to fill in a one-day bladder diary once every 5 sessions to continue the timed voiding program, which is part of BT in both groups. Compliance with the BT was achieved with the daily checklist during 20 sessions and the bladder diaries of women were checked every 5 sessions to rearrange the timed voiding program. Women who did not fill in more than 20% of the daily checklist and women who missed any therapy sessions for two groups were excluded from the study (5, 8).

Evaluation Parameters

The primary outcome measure was accepted as the improvement in incontinence episodes (positive response rate), according to literatüre (14, 21). To determine positive response rate, reduction in incontinence episodes was collected from the 3-day bladder diary. Women with ≥ a 50% reduction in incontinence episodes were considered positive responders (4, 22). Furthermore, the severity of incontinence, PFM strength, symptom severity, frequency of voiding, nocturia, number of pads as well as QoL were secondary outcome measures. The 24-hour pad test was carried out to evaluate the severity of incontinence (23). PFM strength was evaluated with Peritron 9300 device (24). Overactive Bladder Questionnaire (OAB-V8) was used to evaluate the symptom severity in patients with OAB in this study. The OAB-V8 consists of 8 questions in which the patients can be classified with respect to the symptom severity: none (0), very little (1), a little (2), quite a few (3), very (4), and too many (5). The total score ranges from 0-40 (25, 26). The frequencies of voiding, nocturia, and the number of pads used were collected from the 3-day bladder diary. The Quality of Life-Incontinence Impact Questionnaire (IIQ7) was used to assess specific QoL related to incontinence (27). In addition, cure-improvement rate and treatment satisfaction were evaluated. In a 24-hour pad test, amount of urine that was under 1.3 gr was considered as a cure. The improvement rate was assessed in terms of 50% and more reduction in wet weight compared to baseline measurements in the 24-hour pad test (23). Women evaluated the change in their urinary incontinence on a 5-point Likert scale (5, very satisfied; 1, very unsatisfied) (4,5). All the evaluation tests were performed by another physician who was blinded

to the groups in the initial visit and at the end of the treatment (20th session), except for the positive response rate, cure/improvement rate, and the treatment satisfaction parameters which were evaluated only at the 20th sessions.

Statistics

SPSS17.0 software (SPSS, Chicago, IL) was used for the statistical analysis. In each group, measurable parameters were tested with the Kolmogorov-Smirnov test for the evaluation of normal distribution. Because the distributions were not normal, non-parametric tests were used in the statistical evaluation. Mann-Whitney U-test and $\chi 2$ test were used for inter-group comparisons. Wilcoxon tests were used for intra-group comparison of parameters at different point of times. $P<0.05$ was accepted as statistically significant.

RESULTS

One woman was withdrawn because of doing BT irregularly in Group 1 and one woman gave up treatment in Group 2. The data of drop outs were excluded from the study (Figure-1).

The demographic data at the beginning was shown in Table-1. There were no statistically significant differences in the demographic data. Table-2 shows the comparison of the assessment parameters at the baseline and the end of the treatment (20th session) for each group. Both groups were not significantly different for the severity of incontinence, PFM strength, frequency of voiding, incontinence episodes, nocturia, number of pads, symptom severity, and QoL parameters at baseline ($p>0.05$) (Table-2).

Statistically significant improvements were found in the severity of incontinence, PFM strength, frequency of voiding, incontinence episodes, nocturia, number of pads, symptom severity, and QoL parameters for the two groups at the end of the treatment (20th session) compared to the baseline values ($p<0.05$). There was no statistically significant differences in all parameters between the two groups at the end of the treatment. Moreover, it was observed that the treatment satisfaction scores were similar in both groups ($p>0.05$) (Table-2). Similar values were found between Groups 1 and 2 in both positive response and cure/improvement rates ($p=0.193$ and $p=0.637$, respectively). Positive response rates in Group 1 and Group 2 were 88% and 92%, respectively. The cure and improvement rates were 44% and 88% in Group 1, while they were 52% and 92% respectively in Group 2.

No serious adverse events were reported in both groups except temporary discomfort due to vaginal irritation in two women in each group.

DISCUSSION

In this prospective, randomized clinical trial, we have investigated the effectiveness of both "twice a week" and "5 times a week" IVES treatment added to BT for a total of 20 sessions on QoL and clinical parameters associated with incontinence in women with refractory idiopathic OAB. As a result, we have observed significant improvements in terms of incontinence severity, PFM strength, frequency of voiding, incontinence episodes, nocturia, number of pads, symptom severity, and QoL at the 20th session evaluations in both groups when compared with baseline. There was no significant difference between "twice a week IVES" and "5 times a week IVES" groups in all parameters. It was observed that the treatment satisfaction scores, cure/improvement, and positive response rates were similar in both groups.

There was no randomized study that compared different electrical current parameters or different treatment frequencies and thus, there was no evidence of which parameters or treatment frequencies were the most effective ones. In this context, our study is the first study to compare the efficacy of different IVES treatment frequencies in women with idiopathic OAB. Our findings indicated that these two IVES frequencies (twice a week and 5 times a week) had similar clinical efficacy and patient satisfaction. The most commonly reported electrical current frequency by the authors was 10 Hz for OAB. Working and resting times of the current ranged from 2 sn to 10 sn in the literature, and the most commonly used ones were 5 sn and 10 sn, respectively. All

Table 1 - Demographic data of women with idiopathic overactive bladder.

	Group 1 n:25	Group 2 n:25	P[1]	P[2]
Age (year) (mean±SD)	56.64±10.02	58.72±14.20	0.560	
Height (cm) (mean±SD)	158.76±6.12	158.68±5.72	0.899	
Weight (kg) (mean±SD)	75.00±12.76	76.52±10.68	0.907	
BMI (kg/m^2) (mean±SD)	29.82±5.16	30.39±4.27	0.816	
Duration of incontinence (month) (mean±SD)	81.60±67.79	79.68±82.16	0.640	
Education, n(%)				
Primary	18(72)	19(76)		
High school	4(16)	3(12)		
>High school	3(12)	3(12)		0.952
Smoking, n(%)				
No	20 (80)	18(72)		
Yes	5(20)	7(28)		0.293
Cup of tea/day, n(%)				
1-2 cup	9(36)	7(28)		
≥3 cup	16(64)	18(72)		0.424
Cup of coffee/day, n(%)				
No	12(48)	12(48)		
1-2 cup	12(48)	12(48)		
≥3 cup	1(4)	1(4)		1.000
Alcohol intake, n(%)				
No	25(100)	25(100)		
Yes	0(0)	0(0)		1.000
Delivery, n(%)				
No	1(4)	2(8)		
1-3	17(68)	16(64)		
≥4	7(28)	7(28)		0.794
Delivery type, n(%)				
No	1(4)	2(8)		
NSVD	23(92)	20(80)		
Sectio	1(4)	3(12)		0.363
Episiotomy, n(%)				
No	16(64)	13(52)		
Yes	9(36)	12(48)		0.416
Menopausal status, n(%)				
Premenopause	7(28)	8(32)		
Postmenopause	18(72)	17(68)		0.758
HRT use, n(%)				
No	24(96)	20(80)		
Yes	1(4)	5(20)		0.082

Group 1 - Two times in a week intravaginal electrical stimulation (2/week IVES); **Group 2** - Five times in a week intravaginal electrical stimulation (5/week IVES); **HRT**, Hormone replacement therapy; **BMI** = Body mass index; **NSVD** = normal spontaneous vaginal delivery; **P1** = Mann-Whitney U-test; **P2** = Pearson $\chi 2$ test.

authors who described the intensity of electrical current used the maximum intensity depending on the patient's tolerance (max 100 mA). In most cases, the application time used was 20 minutes (2, 4, 5). In our study, the most frequently used electrical current parameters and application time were used in accordance with the literature (2, 4, 5). However, better methodological quality studies are needed to know the optimal current modality and parameters for OAB.

Up to our knowledge, there are only three studies including BT+IVES treatment arm in women with idiopathic OAB in the literature (4, 5, 19). In the first of these studies, BT+IVES was not

Table 2 - Comparison of groups with respect to evaluation parameters.

	Group 1 n:25 (mean±SD)	Group 2 n:25 (mean±SD)	Mann-Whitney-U test p
Severity of incontinence - 24h Pad test (gr)			
Pretreatment	40.22±22.76	43.24±39.23	0.614
Session 20	7.60±9.88 *	9.84±15.19 *	0.899
PFM strength - Perineometer (cmH_2O)			
Pretreatment	22.72±10.74	20.76±11.79	0.559
Session 20	27.44±13.25 *	24.92±11.78 *	0.697
Bladder diary			
a. Frequency			
Pretreatment	11.64±3.63	10.92±4.22	0.232
Session 20	6.24±1.69 *	6.40±1.93 *	0.819
b. Nocturia			
Pretreatment	2.68±2.21	2.80±1.77	0.599
Session 20	1.00±0.91 *	0.84±0.98 *	0.433
c. Incontinence episodes			
Pretreatment	4.12±2.86	5.20±4.78	0.492
Session 20	0.68±1.14 *	1.00±1.29 *	0.268
d. Number of pads			
Pretreatment	3.40±2.19	3.00±1.97	0.538
Session 20	1.56±1.44 *	0.88±0.88 *	0.087
Symptom severity - OAB-V8			
Pretreatment	26.12±5.20	27.84±7.39	0.484
Session 20	8.28±4.56 *	8.88±7.38 *	0.861
Quality of life - IIQ7			
Pretreatment	14.12±5.73	14.60±5.84	0.719
Session 20	6.20±6.05 *	6.00±7.27 *	0.604
Treatment satisfaction (1-5)			
Session 20	4.48±0.71	4.40±0.81	0.825

Group 1 - Two times in a week intravaginal electrical stimulation (2/week IVES); **Group 2** - Five times in a week intravaginal electrical stimulation (5/week IVES); **OAB-V8** = Overactive Bladder Questionnaire; **IIQ-7** = Incontinence Impact Questionnaire; **PFM** = Pelvic floor muscle; * = $P<0.05$: Wilcoxon test compare with baseline values

found to be effective compared to BT alone. Women received relatively few treatment sessions (once a week, 9 sessions), besides the improvement and positive response rates were not mentioned in this study (19). Two recent randomized controlled studies reported that BT+IVES was more effective than BT alone, when IVES was applied to women 3 times a week for a total of 24 sessions (4, 5). These studies used the improvement rate which was determined according to the 24-hour pad test results, and positive response rate which was calculated from the ≥50% reduction in incontinence episodes in accordance with our study. The improvement rates (82.4% and 89.7%, respectively), and positive response rates (88.2% and 86.2%, respectively) of these studies were similar to our study (4, 5). However, it should be taken into account that the frequency of IVES applied in each group was different from these studies in our study. It should be kept in mind that different treatment frequencies other than these may lead to different results. We think that this issue is still open for research.

It has been reported that a minority of women developed adverse effects such as pain, discomfort, hypersensitivity, irritation, tingling in the thigh, hemorrhage, diarrhea, bladder spasm, and vaginal or urinary infection related to IVES (2). In general, IVES was well tolerated by women except for temporary discomfort due to vaginal irritation in two women in each group in our study.

The scientific and clinical importance of our study results are as follows: (i) This is the first randomized clinical trial to evaluate the efficacy of IVES at different treatment frequencies in women with idiopathic OAB; (ii) Clinical efficacy is similar for "twice a week IVES" and "5 times a week IVES" treatments added to BT; (iii) The results of our study will be of great benefit in preferring the treatment frequency (two or five times in a week) and thus the treatment duration (10 or 4 weeks) of IVES for the women with idiopathic OAB and their physicians.

There are some limitations in our study. One of the limitations of this study was that there was no data about the long-term follow-up of the patients. Another limitation was that there was no data about urodynamics. The lack of an isolated BT group makes it impossible to rule out the possibility of an isolated BT effect on the result with potentially null action for IVES in women with idiopathic OAB. In addition, when interpreting our study results, it should be taken into account that the BT program takes longer in women who received IVES twice a week compared to women who received IVES 5 times a week (10 weeks and 4 weeks respectively).

CONCLUSIONS

We concluded that both the twice-a-week IVES and the 5 times a week IVES added to BT were effective on both incontinence-related QoL and clinical parameters in women with refractory idiopathic OAB. These two IVES frequencies had similar clinical efficacy and patient satisfaction with a slight difference between them; 5 times per week IVES has a shorter duration of treatment. It will be of great benefit in preferring the treatment frequency or treatment duration for the women with idiopathic OAB and their physicians.

ABBREVIATIONS

BT = Bladder Training
ES = Electrical Stimulation
IVES = Intravaginal Electrical Stimulation
OAB = Overactive Bladder
PFM = Pelvic Floor Muscle (PFM)
QoL = Quality of Life
UUI = Urgency Urinary Incontinence

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Bo K, Frawley HC, Haylen BT, Abramov Y, Almeida FG, Berghmans B, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for the conservative and nonpharmacological management of female pelvic floor dysfunction. Int Urogynecol J. 2017;28:191-213.

2. Jerez-Roig J, Souza DL, Espelt A, Costa-Marín M, Belda-Molina AM. Pelvic floor electrostimulation in women with urinary incontinence and/or overactive bladder syndrome: a systematic review. Actas Urol Esp. 2013;37:429-44. English, Spanish.
3. Burkhard FC, Bosch JLHR, Cruz F, Lemack GE, Nambiar AK, Thiruchelvam N, et al. The European Association of Urology (EAU) Guidelines. EAU Guidelines on urinary incontinence in adults. In: EAU Guidelines, 2019. [Internet]. Available at: <http://uroweb.org/guideline/urinary-incontinence/>
4. Firinci S, Yildiz N, Alkan H, Aybek Z. Which combination is most effective in women with idiopathic overactive bladder, including bladder training, biofeedback, and electrical stimulation? A prospective randomized controlled trial. Neurourol Urodyn. 2020;39:2498-508.
5. Yildiz N, Alkan H, Sarsan A. Efficacy of intravaginal electrical stimulation added to bladder training in women with idiopathic overactive bladder: A prospective randomized controlled trial. Int Braz J Urol. 2021;47:1150-9.
6. Ozdedeli S, Karapolat H, Akkoc Y. Comparison of intravaginal electrical stimulation and trospium hydrochloride in women with overactive bladder syndrome: a randomized controlled study. Clin Rehabil. 2010;24:342-51.
7. Wang AC, Chih SY, Chen MC. Comparison of electric stimulation and oxybutynin chloride in management of overactive bladder with special reference to urinary urgency: a randomized placebo-controlled trial. Urology. 2006;68:999-1004.
8. Barroso JC, Ramos JG, Martins-Costa S, Sanches PR, Muller AF. Transvaginal electrical stimulation in the treatment of urinary incontinence. BJU Int. 2004;93:319-23.
9. Spruijt J, Vierhout M, Verstraeten R, Janssens J, Burger C. Vaginal electrical stimulation of the pelvic floor: a randomized feasibility study in urinary incontinent elderly women. Acta Obstet Gynecol Scand. 2003;82:1043-8.
10. Arruda RM, Castro RA, Sousa GC, Sartori MG, Baracat EC, Girão MJ. Prospective randomized comparison of oxybutynin, functional electrostimulation, and pelvic floor training for treatment of detrusor overactivity in women. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19:1055-61.
11. Wang AC, Wang YY, Chen MC. Single-blind, randomized trial of pelvic floor muscle training, biofeedback-assisted pelvic floor muscle training, and electrical stimulation in the management of overactive bladder. Urology. 2004;63:61-6.
12. Brubaker L, Benson JT, Bent A, Clark A, Shott S. Transvaginal electrical stimulation for female urinary incontinence. Am J Obstet Gynecol. 1997;177:536-40.
13. Siegel SW, Richardson DA, Miller KL, Karram MM, Blackwood NB, Sand PK, et al. Pelvic floor electrical stimulation for the treatment of urge and mixed urinary incontinence in women. Urology. 1997;50:934-40.
14. Yamanishi T, Yasuda K, Sakakibara R, Hattori T, Suda S. Randomized, double-blind study of electrical stimulation for urinary incontinence due to detrusor overactivity. Urology. 2000;55:353-7.
15. Wang S, Lv J, Feng X, Lv T. Efficacy of Electrical Pudendal Nerve Stimulation versus Transvaginal Electrical Stimulation in Treating Female Idiopathic Urgency Urinary Incontinence. J Urol. 2017;197:1496-501.
16. Scaldazza CV, Morosetti C, Giampieretti R, Lorenzetti R, Baroni M. Percutaneous tibial nerve stimulation versus electrical stimulation with pelvic floor muscle training for overactive bladder syndrome in women: results of a randomized controlled study. Int Braz J Urol. 2017;43:121-6.
17. Goode PS, Locher JL, Bryant RL, Roth DL, Burgio KL. Measurement of postvoid residual urine with portable transabdominal bladder ultrasound scanner and urethral catheterization. Int Urogynecol J Pelvic Floor Dysfunct. 2000;11:296-300.
18. Lee HE, Cho SY, Lee S, Kim M, Oh SJ. Short-term Effects of a Systematized Bladder Training Program for Idiopathic Overactive Bladder: A Prospective Study. Int Neurourol J. 2013;17:11-7.
19. Berghmans B, van Waalwijk van Doorn E, Nieman F, de Bie R, van den Brandt P, et al. Efficacy of physical therapeutic modalities in women with proven bladder overactivity. Eur Urol. 2002;41:581-7.
20. Berghmans LC, Hendriks HJ, De Bie RA, van Waalwijk van Doorn ES, Bø K, et al. Conservative treatment of urge urinary incontinence in women: a systematic review of randomized clinical trials. BJU Int. 2000;85:254-63.
21. Abdelbary AM, El-Dessoukey AA, Massoud AM, Moussa AS, Zayed AS, Elsheikh MG, et al. Combined Vaginal Pelvic Floor Electrical Stimulation (PFS) and Local Vaginal Estrogen for Treatment of Overactive Bladder (OAB) in Perimenopausal Females. Randomized Controlled Trial (RCT). Urology. 2015;86:482-6.
22. Nygaard IE, Kreder KJ, Lepic MM, Fountain KA, Rhomberg AT. Efficacy of pelvic floor muscle exercises in women with stress, urge, and mixed urinary incontinence. Am J Obstet Gynecol. 1996;174(1 Pt 1):120-5.
23. O'Sullivan R, Karantanis E, Stevermuer TL, Allen W, Moore KH. Definition of mild, moderate and severe incontinence on the 24-hour pad test. BJOG. 2004;111:859-62.

24. Rahmani N, Mohseni-Bandpei MA. Application of perineometer in the assessment of pelvic floor muscle strength and endurance: a reliability study. J Bodyw Mov Ther. 2011;15:209-14.
25. Tarcan T, Mangır N, Özgür MÖ, Akbal C. OAB-V8 Overactive Bladder Questionnaire Validation Study. (Turkish) Üroloji Bülteni 2012;21:113-6. [Internet] Available at. <https://kontinansdernegi.org/wp-content/uploads/2021/08/oab-v8-asiri-aktif-mesane-sorgulama-formu.pdf>
26. Acquadro C, Kopp Z, Coyne KS, Corcos J, Tubaro A, Choo MS, et al. Translating overactive bladder questionnaires in 14 languages. Urology. 2006;67:536-40. Erratum in: Urology. 2007;69:202. Oh, Seung June [added].
27. Cam C, Sakalli M, Ay P, Cam M, Karateke A. Validation of the short forms of the incontinence impact questionnaire (IIQ-7) and the urogenital distress inventory (UDI-6) in a Turkish population. Neurourol Urodyn. 2007;26:129-33.

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ORIGINAL ARTICLE

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In utero myelomeningocele repair and high-risk bladder pattern. a prospective study

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ABSTRACT

Objectives: High-risk bladder pattern can be defined by Urodynamic Evaluation (UE) as overactive bladder with detrusor leak point pressure higher than 40 cmH2O and/or higher filling pressures also above 40 cmH2O. We wanted to evaluate response to treatment in myelomeningocele patients operated *in utero* in this subgroup.
Patients and Methods: From our prospective cohort of *in utero* MMC we have identified patients in the high-risk group. Treatment consisted of anticholinergics (Oxybutynin 0.2 mg/Kg) 2 or 3 times daily in association with CIC. At every UE, patients were reclassified in high-risk or low-risk patterns. Patients not responding were proposed bladder reconstruction or diversion according to age.
Results: Between 2011 to 2020, we have been following 121 patients and 60 (49.6%) of them were initially categorized as high-risk. The initial UE was performed at a mean age of 7.9 months and detrusor overactivity was found in 83.3% (mean maximum pressure of 76.5cmH20). When evaluating patients with 2 or more UE, we identified 44 patients (follow-up: 36.8months). It was observed in the group of patients who underwent 2 to 5 UE, that response to treatment was validated by the finding of 40% of low-risk bladder patterns in the second UE and between 62% to 64% in the third to the fifth UE. The incidence of surgery was 13.3%.
Conclusions: Early urological treatment of high-risk bladder pattern was effective in approximately 60%. We reinforce the need to correctly treat every patient with myelomeningocele, in accordance with UE, whether undergoing *in utero* or postnatal treatment.

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INTRODUCTION

In utero myelomeningocele (MMC) repair has shown benefits with reduced need for ventriculoperitoneal shunt and improved motor status according to data published in 2011 in MOMS (Management of Mylomeningocele Study) (1). The potential improvement in the bladder function is a controversial subject, as the different studies published in the post-MOMS era are conflicting. When analyzing

prospective studies, the American groups involved in MOMS (2, 3) and the Zurich group (4, 5) suggest benefits of *in utero* MMC to the bladder function, while our studies in São Paulo go in the opposite direction and shows no improvements to bladder function, regardless if MMC closure had been *in utero* or postnatal (6-12).

The knowledge about myelomeningocele and urological presentation and outcome in ongoing advocates early clean intermittent catheterization (CIC) and antimuscarinic drugs should be indicated upon results of urodynamic studies. (13) There are still no serum indicators that allow recording renal damage before the lesion established on DMSA scintigraphy (14). Reconstructive surgery (such as enterocystoplasty) was indicated for patients who were refractory to clinical treatment. For those who were at an early age, vesicostomy should be regarded as an alternative in order to postpone definitive surgery (15).

Our cohort is characterized by a prospective follow-up of patients who underwent *in utero* surgery as of 2011. We propose urological treatment based on initial categorization of four main patterns of bladder behavior at first presentation and subsequently after each appointment. (7)

Most studies assessing response to treatment of high-risk bladder patterns in myelomeningocele are retrospective and belong to the postnatal MMC repair aera. To our knowledge, this is the first paper to study specifically the outcome of patients operated *in utero* treated with anticholinergics and CIC only in a prospective course and this is the rationale of our manuscript.

The aim of this study after selecting the subgroup of patients categorized as high-risk pattern (overactive bladder with detrusor leak point pressure higher than 40 cmH2O and higher filling pressures also above 40 cmH2O) was to define the rate of response to treatment and clinical evolution after initiation of anticholinergics and CIC.

PATIENTS AND METHODS

In 2011 we started a prospective urological follow-up protocol of patients with MMC operated in utero. This protocol received approval from our Ethic Committee and IRB 34234. This study was based on a prospective protocol to categorize and treat patients with the same procedures and retrospective analysis of patients' files searching outcomes according to the aim of the study. After clinical evaluation and radiological exams: urinary tract ultrasound (US), voiding cystourethrography (VCUG) and urodynamic evaluation (UE), patients were categorized[7] and treated as follows: 1) High-Risk Pattern (overactive pattern with detrusor leak point pressure higher than 40 cm H2O and/or higher filling pressures above 40 cm H2O in the absence of a detrusor contraction) anticholinergics (oxybutynin 0.2 mg/Kg) 2 or 3 times daily in association with CIC every 4 hours, 5 times a day, 2) Incontinent Pattern (overactive bladder with detrusor leak point pressure lower than 40 cm H2O or stable bladder but leaking below 40 cm H2O) and Normal Pattern (stable bladder cystometry without leakage) - only clinical surveillance, and 3) Underactivity Pattern (underactive bladder with post-void residual urine) - Only CIC. Our protocol suggests assessments at 6-month intervals until stability of the urodynamic pattern and then yearly controls with further US and UE. All urodynamic evaluations were performed using the same device and by the same investigators. We estimate bladder capacity according to the Holmdahl formula, bladder capacity in mL = 38 + 2.5 x age in months (16).

The high-risk group is known to be that one with higher risk to the upper urinary tract and the cutoff of 40 cm H2O of detrusor pressure is well recognized in the literature. Thus, we retrospectively reviewed our prospectively fed database. All clinical information, imaging exam results, response to initial treatment and serial urodynamic evolution were collected. At every urodynamic evaluation in the clinical follow-up, patients were reclassified at high-risk or low-risk risk pattern, if the findings of overactive bladder with detrusor leak point pressure higher than 40 cmH2O and higher filling pressures also above 40 cm H2O were normalized. Thus, it was possible to serially define the percentage of response to the proposed treatment. Another interesting aspect was to be able to define the incidence of lower urinary tract surgery in this high-risk group.

RESULTS

Within the interval from 2011 to December 2020, our cohort was formed by 121 patients, and of these, 60 were categorized at high-risk (49.6%) and included in this study. The mean time of follow-up was 27.9 months, and the median was 22 months (ranging from 1 to 91 months). The mean gestational age at diagnosis was 21.1 weeks and mean age at *in utero* surgery was 25.7 weeks. The mean age at birth was 31.1 weeks. The incidence of ventriculoperitoneal shunts was 12.1% (n=7). The mean age of the first urological evaluation was 6.9 months (median 5 months). The initial ultrasound was performed with a mean of 7.31 months (median 5 months) in 58 patients. Hydronephrosis was observed in 27.6% (n=16) and thick-walled bladder in 34.5%.

The VCUG was performed in 58 patients at a mean age of 9 months (median 6 months), showing irregularly shaped bladder in 39.7%, dilatation of the urethra in 36.8%, suggesting vesico-sphincter dyssynergia in 36.8%. The diagnosis of vesicoureteral reflux was made in 27.6% of the cases (n=16), being bilateral in 10.3% (n=6). The grade distribution per renal units (RU) was: GIII: 3, GIV: 11, and GV: 7 RU.

The initial UE was performed at a mean age of 7.9 months (median 5 months) and showed hyperactivity in 83.3%, with mean maximum pressure of 76.5 cm H20 (median 72.5 cm H20). Bladder compliance was normal in 13.6%, decreased in 61%, and could not be determined in 25.4% due to leakage. Similarly, bladder capacity was normal in 37.3%, decreased in 57.6% and could not be determined in 5.1% due to leakage.

When evaluating patients with 2 or more UE, we identified 44 patients, who were followed for a mean follow-up period of 36.8 months (median 28.5 months). Demographic data of this group is presented in Table-1. This subgroup allowed us to evaluate the response to treatment according to objective parameters and mainly based on the UE. We observed episodes of urinary tract infection (UTI) in 28 patients (63.6%), with a mean of 1.9 episodes per patient. The need for hospitalization to treat UTI was 25%. We define UTI as a febrile event with abnormal urinalysis and positive cultures yielding more than 100,000 colonies per mL.

The second UE was performed at a mean age of 18.8 months (median 17.5 months) and showed overactive detrusor contractions in 32.6% (n=14), mean maximum pressure of 49.1 cmH2O (median 50 cmH2O), normal bladder compliance in 54.4%, decreased compliance in 40.9% and could not be determined due to leakage in 4.5%. The recategorization of the bladder pattern by the classification of Leal da Cruz et al. (7) was high-risk in 61.4% (n=27) and low-risk in 38.6% (n=17) in the second exam.

Table 1 - Demographic data.

Demographic Data		
n	44	
Sex	Female	Male
	21 (47.7%)	23 (52.3%)
Age at first presentation	Average	Median
	6.8 months	5.0 months
Age at last appointment	Average	Median
	45.3 months	40 months
Response to clinical treatment (at last urodynamic evaluation)	High-risk	Low-risk
	24 (54.5%)	20 (45.5%)

Figure-1 shows the evolution of the maximum pressure obtained in the subsequent urodynamic evaluations registered during the follow-up period. Maximum detrusor pressure was the main parameter to recategorize patients at each follow-up.

The records of serial urodynamic evaluations allow us to categorize the bladder pattern at every exam, and Figure-2 shows the percentage of high--risk and low-risk patterns according to the number of UE performed. It is observed that patients who underwent 3, 4 and 5 urodynamic evaluations had a response close to 60% of change in the bladder pattern to low-risk.

The precise values of the mean maximum pressure in the high and low-risk subgroups according to data from the second to the fifth urodynamic evaluations can be seen in Table-2.

In this series, the following procedures were performed: vesicostomy (n: 3), surgery for treatment of vesicoureteral reflux (n: 2. Note: 1 patient with 2 surgeries), and bladder augmentation (3, one patient with associated Macedo-Malone), which signified a surgery incidence of 13.3%. The decision between bladder reconstruction (augmentation) or diversion (vesicostomy) has been taken according to age with 3 years and half as a cutoff.

DISCUSSION

The proactive management of children with spina bifida is based on early bladder pattern categorization. We have followed the same urological protocol for neuropathic bladders since 1999 and this has enabled us to compare the clinical presentation of patients with myelomeningoceles operated *in utero* and postnatally (10). We were not able to follow high-risk bladder patterns simultaneously for postnatal MMC repair because in our Institution all cases are referred for *in utero* repair since 2011. We are aware that the progression of kidney failure towards end-stage renal disease can be reduced if adequately treated.

Although there is preliminary literature available comparing initial bladder patterns after *in utero*

Figure 1. Evolution of the maximum detrusor pressure throughout the urodynamic evaluations registered during the follow-up period.

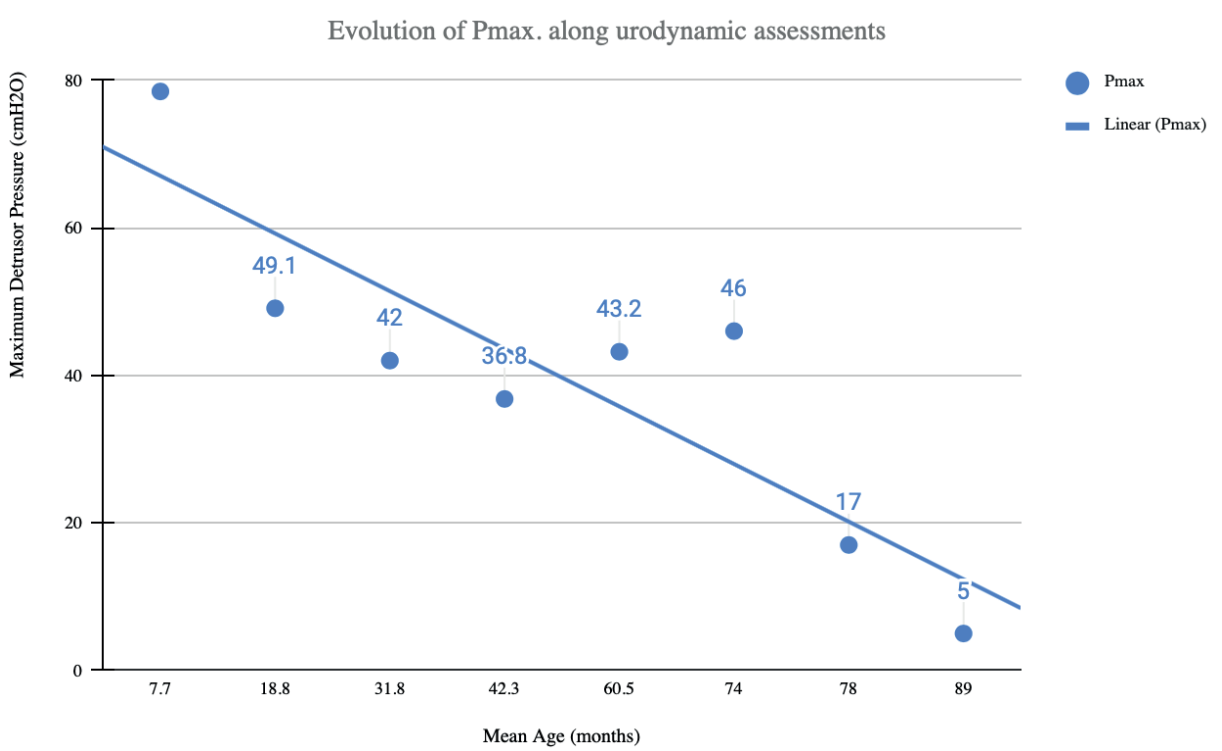

Figure 2. Number of patients by sequence of urodynamic evaluations (EU) performed UE1 (n:60) UE2 (n:44), UE3 (n:32), UE4 (n:18), UE5 (n:11), UE6 (n:4), UE7 (n:1), UE8 (n:1) and percentage of high risk and low risk bladder patterns.

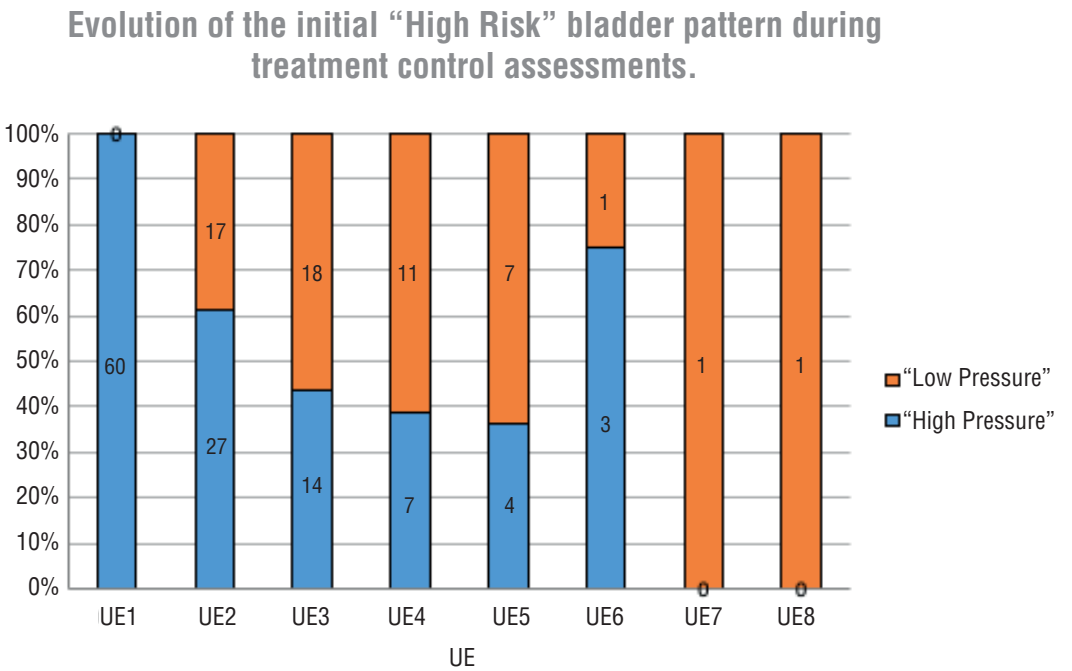

Table 2 - Mean maximum pressure in the high and low-risk subgroups according to the second to the fifth urodynamic evaluations.

Bladder Pattern	Pmax. UED2 (cmH2O)	Pmax. UED3 (cmH2O)	Pmax. UED4 (cmH2O)	Pmax. UED5 (cmH2O)
Low-risk	16.76	18.78	16.91	17.14
High-risk	69.52	71.93	68	88.75

MMC repair, there is little information about the clinical outcome after treatment for this new subgroup of patients.

The MOMS urological follow-up study showed that 24% in the prenatal group vs 4% in the postnatal group (RR 5.8, 95% CI 1.8-18.7) were reported to be voiding volitionally (3). Augmentation cystoplasty, vesicostomy and urethral dilation did not differ between the two groups. Authors reported that in spite that most patients were in diapers or in a CIC regimen, there was a trend for higher volitionally voiding in the *in utero* operated patients. Interestingly, the conclusion of the authors was that *in utero* closure should not be performed solely based on urological outcome (3). One aspect that is not clear in the manuscript was that this beneficial conclusion came out from a non-reported number of cases by parental information through phone interviews only and not confirmed by medical analysis. The meaning of volitional voiding by neuropathic patients is accepted only if no residual volumes are found and the authors did not respond on that. Another limiting factor of this paper was the presence of multiple clinical providers during follow-up, not necessarily having the same protocol in their counseling.

The Zurich group recently presented their data for *in utero* MMC repair and urological outcome. They performed UDS at 2 weeks, 6, 12, 18 and 24 months, followed by yearly control and included 82 patients. The last UDS was normal in 25 patients

(32%), in contrast to 66% (54/82) in the newborn period. Only 35 patients had a 3 year follow-up showing normal bladder parameters in 6 cases (17%) (5). Their most recent findings are in correspondence with our results that suggest no protective effect of fetal myelomeningocele surgery towards the lower urinary tract. One strong aspect of this paper is that, similarly to our data, these authors present a very homogeneous follow-up protocol with validated UE.

We have recently reported on our experience in patients operated *in utero* and presenting with sphincter insufficiency patterns. We were able to follow 30 patients in a database of 117 patients operated *in utero* categorized in the incontinent pattern (leaking at lower pressure: < 40cm H20). From those, 23 had repeated UDS available to record clinical outcome with a follow-up of 24.5 months (median: 15 months). We observed that no change in the pattern was found in 43.47% and for those leaking at a lower pressure (<30cm H20), we could predict maintenance of the incontinent pattern in 70% (12).

Other authors have performed similar studies after post-natal MMC repair. Sager et al. did a retrospective analysis after studying 60 cases of MMC presenting at an age below 1 year. They observed the incidence of high-risk bladder patterns in 50% of their population and 30% had a diagnosis of detrusor-sphincter dyssynergia (17). This data is very similar to our findings. In a study performed with the first 100 patients of prospective follow-up, of which 95 underwent urodynamic evaluation, we found that the high-risk group represented 52.6% (10).

We wanted to estimate in this prospective analysis, the response to treatment and the incidence of surgery, which indirectly represents failure of conservative treatment. Importantly, in this group we reviewed 172 urodynamic evaluations only for the high-risk group, which gave us a mean of 3.9 evaluations per patient. Noteworthy, all evaluations were performed in the same device and by the same investigator (AMJ), which provides homogeneity to the UE data never seen in neurological patients. At our service, a urodynamic exam is performed at the office and together with the medical visit, with the assistance of an urotherapist nurse. The immediate analysis of the results by the attending physician allows for decision-making during the medical appointment.

An interesting characteristic of our service is also the adherence of patients from several localities in the country, who return on a yearly basis for control with the neurosurgeon (SC), pediatric orthopedics and pediatric urologist (AMJ). As additional data, the geographic origin of the 60 patients initially enrolled in this study is observed: North: 5%; Northeast: 8,3%; Midwest: 10%; South: 6.7%; Southeast: 68.3%; and another country: 1.7%.

The UE findings that allow classifying the bladder pattern as high-risk and low-risk are shown in Graph 2. It was observed, mainly in the group of patients who underwent 2 to 5 UE, that the presumable response to treatment could be validated by the finding of 40% of low-risk bladder patterns in the second UE and between 62% to 64% in the third to the fifth UE.

The incidence of surgery is ultimately considered a failure of conservative treatment (anticholinergics and CIC). In this series, the following procedures were performed: vesicostomy (n: 3), surgery for treatment of vesicoureteral reflux (n: 2. Note: 1 patient with 2 surgeries), and bladder enlargement (3, one patient with associated Macedo-Malone), which signified a surgery incidence of 13.3%.

A limitation of our study was that a small number of patients have abandoned the treatment in our Institution. On the other hand, it did not affect our conclusions, as far as only the interval between first and last appointment with us have been counted for our mean follow-up in the study.

CONCLUSIONS

Thus, we can conclude that early urological treatment using anticholinergics and CIC of patients with myelomeningocele and who initially presented with a high-risk bladder pattern was effective in approximately 60% of the cases. The incidence of surgery was 13.3% in this group, with a mean follow-up of 36.8 months (median 28.5 months). Therefore, we reinforce the need to correctly treat every patient with myelomeningocele, in accordance with objective parameters and based on urodynamic evaluation, whether undergoing *in utero* or postnatal treatment.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Adzick NS, Thom EA, Spong CY, Brock JW 3rd, Burrows PK, Johnson MP, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med. 2011;364:993-1004.
2. Brock JW 3rd, Carr MC, Adzick NS, Burrows PK, Thomas JC, Thom EA, et al. Bladder Function After Fetal Surgery for Myelomeningocele. Pediatrics. 2015;136:e906-13.
3. Brock JW 3rd, Thomas JC, Baskin LS, Zderic SA, Thom EA, Burrows PK, et al. Effect of Prenatal Repair of Myelomeningocele on Urological Outcomes at School Age. J Urol. 2019;202:812-8.
4. Horst M, Mazzone L, Schraner T, Bodmer C, Möhrlen U, Meuli M, et al. Prenatal myelomeningocele repair: Do bladders better? Neurourol Urodyn. 2017;36:1651-8.
5. Mazzone L, Hölscher AC, Moehrlen U, Gobet R, Meuli M, Horst M. Urological Outcome after Fetal Spina Bifida Repair: Data from the Zurich Cohort. Fetal Diagn Ther. 2020;47:882-8.
6. Macedo A Jr, Leal M, Rondon A, Ortiz V, Moron AF, Cavalheiro S. Urological evaluation of patients that had undergone in utero myelomeningocele closure: A prospective assessment at first presentation and early follow-up. Do their bladder benefit from it? Neurourol Urodyn. 2015;34:461-4.
7. Leal da Cruz M, Liguori R, Garrone G, Leslie B, Ottoni SL, Carvalheiro S, et al. Categorization of bladder dynamics and treatment after fetal myelomeningocele repair: first 50 cases prospectively assessed. J Urol. 2015;193(5 Suppl):1808-11.
8. Leal da Cruz M, Liguori R, Garrone G, Ottoni SL, Cavalheiro S, Moron AF, et al. A 4-Year Prospective Urological Assessment of In Utero Myelomeningocele Repair-Does Gestational Age at Birth Have a Role in Later Neurogenic Bladder Pattern? J Urol. 2017;197:1550-4.
9. Macedo A Jr, Ottoni SL, Garrone G, Liguori R, Cavalheiro S, Moron A, et al. In utero myelomeningocoele repair and urological outcomes: the first 100 cases of a prospective analysis. Is there an improvement in bladder function? BJU Int. 2019;123:676-81.
10. Parizi JLG, Leal da Cruz M, Andrade MC, Garrone G, Ottoni SL, Cavalheiro S, et al. A Comparative Analysis of Bladder Pattern of Patients who Underwent In Utero Versus Postnatal Myelomeningocele Repair. J Urol. 2020;203:194-9.
11. Macedo A Jr, Cavalheiro S, Moron A, Lobountchenko T, Dini FS, Ottoni SL, Garrone G, Ligori R, Leal da Cruz M. Urinary and Fecal Continence in 5-Year-Old Patients Who Underwent in utero Myelomeningocele Repair: A Prospective Study. Fetal Diagn Ther. 2019;46:319-22.
12. Macedo A Jr, Di Migueli RDD, Cavalheiro S, Moron A, da Cruz ML. In utero myelomeningocele repair: The natural history of patients with incontinent pattern (sphincteric deficiency: leakage below 40 CMH20). Neurourol Urodyn. 2020;39:2373-8.
13. Sager C, Barroso U Jr, Bastos JM Netto, Retamal G, Ormaechea E. Management of neurogenic bladder dysfunction in children update and recommendations on medical treatment. Int Braz J Urol. 2022;48:31-51.
14. do Amaral CMCA, Casarini DE, Andrade MC, da Cruz ML, Macedo A Jr. Study of serum and urinary markers of the renin-angiotensin-aldosterone system in myelomeningocele patients with renal injury detected by DMSA. Int Braz J Urol. 2020;46:805-13.
15. Macedo A Jr, Ottoni SL, Garrone G, Mattos RM, da Cruz ML. Conversion of vesicostomy into continent catheterizable reservoirs in myelomeningocele. Int Braz J Urol. 2021;47:470-1.
16. Holmdahl G, Hanson E, Hanson M, Hellström AL, Hjälmås K, Sillén U. Four-hour voiding observation in healthy infants. J Urol. 1996;156:1809-12.
17. Sager C, Burek C, Corbetta JP, Weller S, Ruiz J, Perea R, et al. Initial urological evaluation and management of children with neurogenic bladder due to myelomeningocele. J Pediatr Urol. 2017;13:271.e1-271.e5.

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Presenting signs and symptoms of artificial urinary sphincter cuff erosion

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ABSTRACT

Purpose: To characterize the most common presentation and clinical risk factors for artificial urinary sphincter (AUS) cuff erosion to distinguish the relative frequency of symptoms that should trigger further evaluation in these patients.

Materials and Methods: We retrospectively reviewed our tertiary center database to identify men who presented with AUS cuff erosion between 2007 – 2020. A similar cohort of men who underwent AUS placement without erosion were randomly selected from the same database for symptom comparison. Risk factors for cuff erosion – pelvic radiation, androgen deprivation therapy (ADT), high-grade prostate cancer (Gleason score ≥ 8) – were recorded for each patient. Presenting signs and symptoms of cuff erosion were grouped into three categories: obstructive symptoms, worsening incontinence, and localized scrotal inflammation (SI).

Results: Of 893 men who underwent AUS placement during the study interval, 61 (6.8%) sustained cuff erosion. Most erosion patients (40/61, 66%) presented with scrotal inflammatory changes including tenderness, erythema, and swelling. Fewer men reported obstructive symptoms (26/61, 43%) and worsening incontinence (21/61, 34%). Men with SI or obstructive symptoms presented significantly earlier than those with worsening incontinence (SI 14 ± 18 vs. obstructive symptoms 15 ± 16 vs. incontinence 37 ± 48 months after AUS insertion, p<0.01). Relative to the non-erosion control group (n=61), men who suffered erosion had a higher prevalence of pelvic radiation (71 vs. 49%, p=0.02).

Conclusion: AUS cuff erosion most commonly presents as SI symptoms. Obstructive voiding symptoms and worsening incontinence are also common. Any of these symptoms should prompt further investigation of cuff erosion.

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INTRODUCTION

Despite its wide acceptance and high treatment success, the artificial urinary sphincter (AUS) remains prone to complications requiring replacement or removal of the device in an estimated one third of patients (1-5). Urethral cuff erosion remains one of the more common and most devastating long-term complications. Although cuff design updates have decreased erosion rates since the device's inception, recent long-term observational series continue to suggest that approximately 8% of patients undergoing AUS placement will eventually develop a cuff erosion (1-5).

To date, most literature on AUS cuff erosion focuses on its risk factors. History of prior

pelvic radiation has been associated with both a shorter time to and higher likelihood of cuff erosion (5-12). Other implicated risk factors include hypertension (12), diabetes (13), cardiovascular disease (12, 13), low testosterone (14), urethral catheter (15), penile prosthesis placement (16), prior urethral surgery (9, 17, 18), and prior cuff erosion (7, 9, 10, 19, 20).

Despite abundant literature on medical conditions linked with AUS cuff erosion, less information exists addressing the specific presenting signs and symptoms of this troublesome condition. Signs and symptoms which have been attributed to cuff erosion include hematuria, dysuria, and recurrent SUI (21-23). We predicted that physical exam findings of scrotal inflammation predict AUS cuff erosion. Herein, we review the presenting signs and symptoms of AUS cuff erosion cases from our tertiary center in an effort to promote timely identification by clinicians, thereby facilitating intervention prior to the development of additional local or systemic complications.

MATERIALS AND METHODS

We retrospectively reviewed our large tertiary center database, identifying men who presented with AUS cuff erosion between 2007 and 2020 (IRB: STU-2020-1187). The primary endpoint was to identify presenting signs and symptoms of cuff erosion. A secondary objective was to gauge clinical risk factors for cuff erosion – for this analysis, a comparison control group of the same size was randomly selected from our AUS database of men without AUS cuff erosion using a number generator tool.

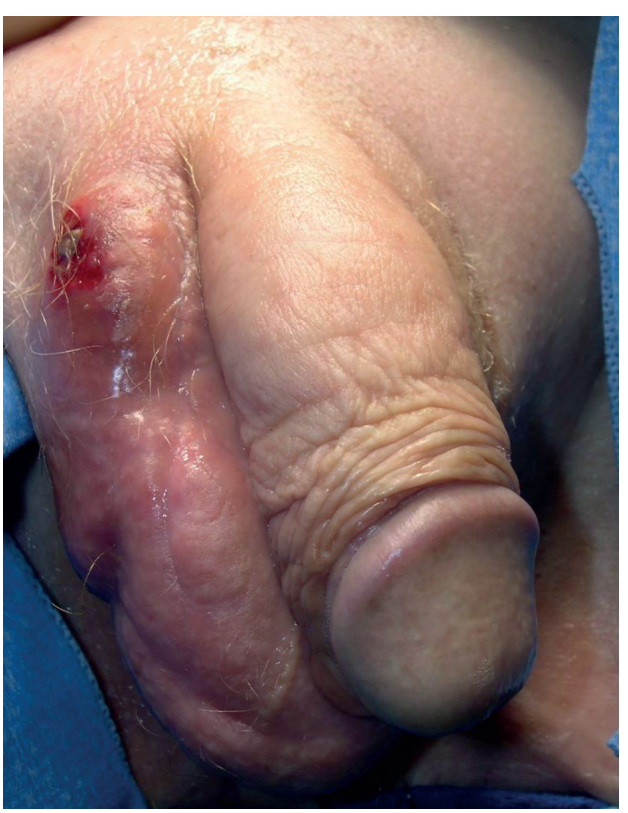
Established risk factors for cuff erosion – pelvic radiation, androgen deprivation therapy (ADT), and high-grade prostate cancer (Gleason score ≥ 8) – were recorded for each patient. Presenting signs and symptoms of cuff erosion were identified by chart review of patient notes in the electronic medical record system. History and exam findings were grouped into three categories: obstructive symptoms, worsening incontinence, and localized scrotal inflammation (SI) around the AUS pump i.e. "pump-itis". We also evaluated signs and symptoms at follow up of our non-eroded control cohort.

Demographic data were collected and compared between symptom groups. Multivariable logistic regression was employed to assess for any association between presenting symptoms and time to cuff erosion. All statistical analyses were performed in SPSS (Armonk, NY: IBM Corp.) with $p<0.05$ considered statistically significant.

RESULTS

Among 893 men who underwent AUS placement during the period examined, 61 (6.8%) sustained cuff erosion. The average age at time of AUS removal was 74.8±7.2 years old. No patients in either group had tandem cuffs. Most erosion patients (40/61, 66%) presented with SI changes including tenderness, erythema, and swelling (Figure-1). Fewer men reported obstructive symptoms (26/61, 43%) and worsening incontinence (21/61, 34%). Three AUS cuff erosions presented with all three groups of symptoms - SI, obstructive symptoms, and worsening incontinence (3/61, 5%). Roughly one-third presented with two out

Figure 1 - Photo representation of a patient with Scrotal Inflammation, i.e, "Pump-itis"



of three symptom groups – SI and obstructive symptoms (12/61, 20%), compared to the less common combinations of SI and worsening incontinence (5/61, 8%) and obstructive symptoms and worsening incontinence (3/61, 5%, Figure-2). The average length of time from AUS placement to cuff erosion was 22.2 months ± 33.7. Men with SI or obstructive symptoms presented significantly earlier than those with worsening incontinence (SI 14 ± 18 vs. obstructive symptoms 15 ± 16 vs. incontinence 37 ± 48 months after AUS insertion, p<0.01).

In the non-eroded control group, office notes from the most recent follow up visit (written by either the primary investigator or reconstruction fellows) indicated that the majority (55/61, 90.2%) presented without complaints, were pleased with their device, and satisfied with dryness, with either complete continence or with very mild incontinence requiring one safety pad per day. Of the 6 with any complaint, 4/6 had worsening incontinence of more than two pads per day, one had urge urinary incontinence, and one had chronic penile pain unrelated to his AUS. All (61/61, 100%) presented with a normal exam, characterized by documentation of "no inflammation, swelling, redness, or tenderness" on examination, with normal pump positioning and no evidence of pressure-regulating balloon herniation.

Prevalence of comorbidities was evaluated in the erosion cohort - hypertension (53, 86.9%), diabetes mellitus (20, 32.8%), coronary artery disease (33, 54.1%), smokers (43, 70.5%), (Table-1). Of note, 43 men (70.5%) had a history of radiation for the treatment of prostate cancer. Other prior treatments included prostatectomy (47, 77%), prior AUS placement (31, 50.8%), urethroplasty (15, 24.6%), transurethral resection of prostate (5, 8.2%), prolonged catheterization with AUS in place (6, 9.8%). Of these 61 cases, nine had a prior AUS cuff erosion (15%). Cuffs were replaced transcorporally in 8/9 (89%) patients.

Figure 2 - Presenting Signs and Symptoms of Artificial Urinary Sphincter Cuff Erosion

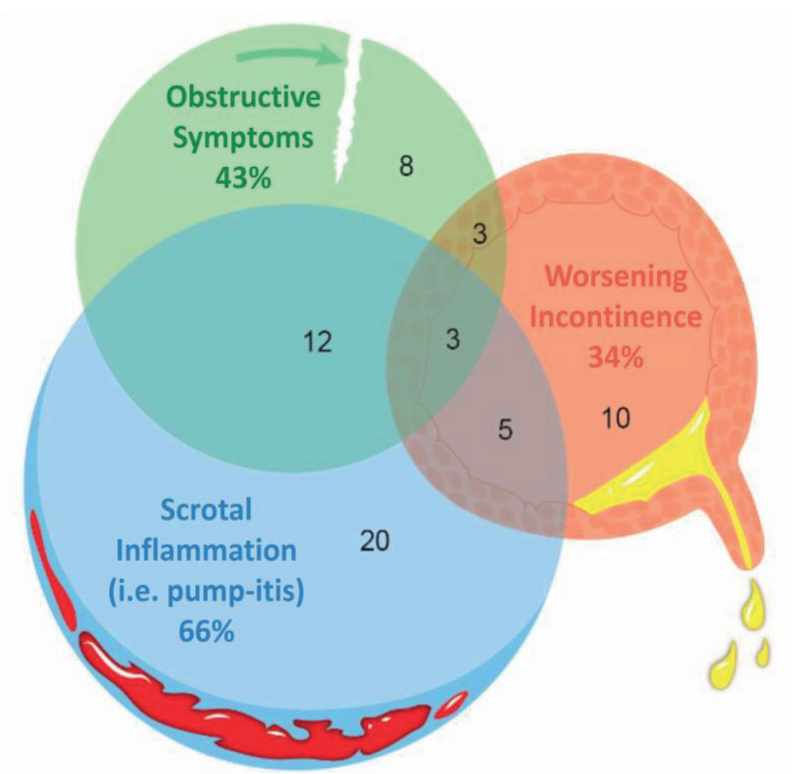


Table 1 - Patient demographics and treatment history.

	Overall n=61	Scrotal Inflammation n=40	Obstructive Symptoms n=26	Worsening Incontinence n=21	P-value
Patient Demographics					
Age at AUS Removal mean, (st dev)	74.86 (7.21)	74.28 (7.35)	75.69 (6.41)	75.30 (6.96)	0.702
BMI at AUS Removal mean, (st dev)	28.58 (5.12)	28.85 (4.90)	29.09 (5.31)	27.29 (4.04)	0.395
Months to Erosion mean, (st dev)	22.19 (33.75)	14.19 (18.8)	15.38 (16.61)	37.38 (48.94)	0.009
HTN	53 (86.9%)	36 (90.0%)	22 (84.65%)	16 (76.2%)	0.355
Diabetes	20 (32.8%)	15 (37.5%)	9 (34.6%)	7 (33.3%)	0.558
CAD	30 (49.2%)	24 (60.0%)	14 (53.8%)	7 (33.3%)	0.061
Smoking	43 (70.5%)	28 (70.0%)	16 (61.5%)	16 (90.4%)	0.548
Treatment History					
Radiation	43 (70.5%)	30 (75.0%)	19 (73.1%)	10 (47.6%)	0.088
Prostatectomy	49 (80.3%)	33 (82.5%)	19 (73.1%)	16 (76.2%)	0.504
TURP	4 (6.5%)	2 (5.0%)	1 (3.8%)	2 (9.5%)	0.681
Prior Urethroplasty	12 (19.6%)	8 (20.0%)	4 (15.4%)	4 (19.1%)	0.891
Prior AUS Placement	28 (45.9%)	18 (45.0%)	10 (38.5%)	12 (57.1%)	0.436

AUS = artificial urinary sphincter; **St dev** = standard deviation; **BMI** = body mass index; **HTN** = hypertension; **CAD** = coronary artery disease; **TURP** = transurethral resection of prostate

Relative to the non-erosion control group (n=61), men who eroded had higher rates of pelvic radiation (71 vs. 49%, p=0.02, see Table-2). They also had higher rates of hypertension (87 vs. 64%, p=0.003), coronary artery disease (54 vs. 12 %, p<0.00001), and smoking history (71 vs. 51%, p=0.03). Rates of treatment with ADT (41 vs. 38 %, p=0.77), high-grade prostate cancer (39 vs. 39 %, p=0.98), and comorbid diabetes (33 vs. 20%, p=0.09) were similar. There were no statistically significant relationships found between patient demographics, comorbidities, or treatment history and presenting symptoms of AUS cuff erosion (Table-1).

DISCUSSION

This series highlights the typical clinical presentation of AUS cuff erosion – a devastating scenario for both incontinence patients and their urologists. Men with severe AUS cuff erosion are prone to develop secondary complications including urethral stricture, diverticulum, and fistula (26). These complications often necessitate additional surgeries which can further disrupt any chance for acceptable continence. We believe that earlier recognition facilitates expedient treatment, thereby reducing risk of attendant complications and hastening recovery.

Table 2 - Demographic and Treatment History – Erosion vs Non-Erosion Cohort.

	Erosion (n=61)	Non-Erosion (n=61)	P-Value
Pelvic Radiation	43 (71%)	30 (49%)	**0.02**
Hypertension	53 (87%)	39 (64%)	**0.00**
Coronary artery disease	33 (54%)	7 (12%)	**0.00**
Smoking	43 (71%)	31 (51%)	**0.03**
Androgen deprivation therapy	17 (41%) n=42	23 (38%)	0.70
High grade prostate cancer	9 (39%) n=23	24 (39%)	0.98
Diabetes	20 (33%)	12 (20%)	0.09

Presenting signs and symptoms of erosion

Anecdotal reports suggest that late obstructive symptoms and worsening incontinence are potential signs of cuff erosion that should prompt cystoscopy (21, 23). The present large case series underscores these concepts but advances the importance of SI symptoms ("pump--itis" - scrotal tenderness, erythema, and swelling around the pump) as the most common early manifestations of AUS cuff erosion. We hypothesize the SI develops due to ongoing urinary seepage from the urethra, passing along the AUS tubing to the pump, where it becomes secondarily inflamed and in many cases, overtly infected.

Notably, more than half of men with erosion who expressed a complaint of obstructive symptoms also complained of SI and vice-versa (Figure-2). Although each of these individual symptoms should prompt suspicion for cuff erosion, their combination especially suggests a high reliability for this serious complication.

Time to erosion

Men with recurrent SUI were diagnosed with AUS cuff erosion significantly later than men without this symptom. Prior studies report a wide range of time to erosion from 1.9 months to 3 years (2, 4, 8). From our data, it is not possible to determine the underlying reason for later erosion identification in these men. We hypothesize that progressive cuff erosion leads to worsening SUI that only becomes apparent to the patient and/or provider when a certain threshold of bother is reached. In these cases, it is alternatively possible that cuff erosion was present asymptomatically for an extended time while another time-dependent process, such as urethral atrophy or mechanical failure, independently led to incontinence and delayed evaluation (1, 2, 7, 24).

Erosion post-radiation and additional risk factors

Our finding of increased risk of cuff erosion in patients with history of pelvic radiation is consistent with prior studies (5-12). Supporting the concept that microvascular and histologic tissue changes after radiation negatively impact tissue integrity (25). We did not identify differences in cuff erosion rates for those with prior transurethral resection of prostate, urethroplasty, or other medical comorbidities (Table-1). Power remains an issue in confirming any of the above relationships, as only a small fraction of AUS patients had undergone any of the above interventions. For men in the erosion cohort, average testosterone level at time of erosion was 222.0 ng/dL$\pm$177 ng/dL (IQR 237.5). As previously described, low testosterone is a known risk factor for AUS cuff erosion (14). We did not have testosterone levels for the non-erosion cohort as these are not routinely drawn.

Limitations

We recognize several limitations of our study. Although the retrospective design limits the inference of causal relationships, as a descriptive study, this design was suitable for our primary aims. We suspect that some patients were lost to follow up or followed up with their local urologists as we operate at a large tertiary referral center, thus introducing an attrition bias. We believe that patients with complications are more likely to follow up, leading to selection bias. As a single center study, results may have been impacted by surgeon technique and patient population factors, though these are unlikely to have affected our primary endpoint. There is an intrinsic difficulty in identifying patients with cuff erosion given a lack of established guidance in the literature about presenting symptoms of erosion, but the work-up is almost always symptom-driven.

We did not perform routine cystourethroscopy on the control cohort to rule out subclinical erosion, so it is unclear whether any small cuff erosions remain asymptomatic in our patient population or if any may have been asymptomatic with significant lead time prior to identification. Urinalyses as well as urine and device cultures were not consistently performed on this patient group, so these findings were not included in our study. Only 5 of the erosion patients complained of gross hematuria at presentation, so this symptom was not included as a presentation group. There are several areas for future study direction on this topic. It would be interesting to determine whether the severity of clinical presenting signs and symptoms of erosion correlate with larger degree of urethral cuff erosion and also whether the size of erosion affects final outcomes for patients as it relates to long term urethral patency, complications, repeat infections, and ability to have another AUS inserted at a later date.

CONCLUSION

AUS cuff erosion most commonly presents with scrotal inflammatory symptoms. Obstructive voiding symptoms and worsening incontinence are also common. Patients with prior pelvic radiation are at a higher risk of AUS cuff erosion. Heightened awareness of these common clinical presentations may aid in prompt identification and subsequent timely treatment of cuff erosions.

DISCLOSURES

Dr. Allen Morey receives honoraria for being a guest lecturer/meeting participant for Boston Scientific and Coloplast Corp. Dr. Steven Hudak receives honoraria for being a guest lecturer/consultant for Boston Scientific Corp. No other authors have disclosures to present.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Van der Aa F, Drake MJ, Kasyan GR, Petrolekas A, Cornu JN; Young Academic Urologists Functional Urology Group. The artificial urinary sphincter after a quarter of a century: a critical systematic review of its use in male non-neurogenic incontinence. Eur Urol. 2013;63:681-9.
2. Linder BJ, Rivera ME, Ziegelmann MJ, Elliott DS. Long-term Outcomes Following Artificial Urinary Sphincter Placement: An Analysis of 1082 Cases at Mayo Clinic. Urology. 2015;86:602-7.
3. Kim SP, Sarmast Z, Daignault S, Faerber GJ, McGuire EJ, Latini JM. Long-term durability and functional outcomes among patients with artificial urinary sphincters: a 10-year retrospective review from the University of Michigan. J Urol. 2008;179:1912-6.
4. Singla N, Singla AK. Review of single-surgeon 10-year experience with artificial urinary sphincter with report of sterile cuff erosion managed nonsurgically. Urology. 2015;85:252-6.
5. Radomski SB, Ruzhynsky V, Wallis CJD, Herschorn S. Complications and Interventions in Patients with an Artificial Urinary Sphincter: Long-Term Results. J Urol. 2018;200:1093-8.
6. Rivera ME, Linder BJ, Ziegelmann MJ, Viers BR, Rangel LJ, Elliott DS. The Impact of Prior Radiation Therapy on Artificial Urinary Sphincter Device Survival. J Urol. 2016;195(4 Pt 1):1033-7.
7. Fuller TW, Ballon-Landa E, Gallo K, Smith TG 3rd, Ajay D, Westney OL, et al. Outcomes and Risk Factors of Revision and Replacement Artificial Urinary Sphincter Implantation in Radiated and Nonradiated Cases. J Urol. 2020;204:110-4.

8. Kaufman MR, Milam DF, Johnsen NV, Cleves MA, Broghammer JA, Brant WO, et al. Prior Radiation Therapy Decreases Time to Idiopathic Erosion of Artificial Urinary Sphincter: A Multi-Institutional Analysis. J Urol. 2018;199:1037-41.
9. McGeady JB, McAninch JW, Truesdale MD, Blaschko SD, Kenfield S, Breyer BN. Artificial urinary sphincter placement in compromised urethras and survival: a comparison of virgin, radiated and reoperative cases. J Urol. 2014;192:1756-61.
10. Brant WO, Erickson BA, Elliott SP, Powell C, Alsikafi N, McClung C, et al. Risk factors for erosion of artificial urinary sphincters: a multicenter prospective study. Urology. 2014;84:934-8.
11. Kretschmer A, Hüsch T, Anding R, Pottek T, Rose A, Struss W, et al. The impact of perioperative complications on favorable outcomes after artificial urinary sphincter implantation for post-prostatectomy incontinence. Int Braz J Urol. 2020;46:632-9.
12. Raj GV, Peterson AC, Webster GD. Outcomes following erosions of the artificial urinary sphincter. J Urol. 2006;175:2186-90; discussion 2190.
13. Godwin CA, Linder BJ, Rivera ME, Ziegelmann MJ, Elliott DS. Effects of Smoking Status on Device Survival Among Individuals Undergoing Artificial Urinary Sphincter Placement. Am J Mens Health. 2018;12:1398-402.
14. Wolfe AR, Ortiz NM, Baumgarten AS, VanDyke ME, West ML, Dropkin BM, et al. Most men with artificial urinary sphincter cuff erosion have low serum testosterone levels. Neurourol Urodyn. 2021;40:1035-41.
15. Seideman CA, Zhao LC, Hudak SJ, Mierzwiak J, Adibi M, Morey AF. Is prolonged catheterization a risk factor for artificial urinary sphincter cuff erosion? Urology. 2013;82:943-6.
16. Sundaram V, Cordon BH, Hofer MD, Morey AF. Is Risk of Artificial Urethral Sphincter Cuff Erosion Higher in Patients with Penile Prosthesis? J Sex Med. 2016;13:1432-7.
17. Keihani S, Chandrapal JC, Peterson AC, Broghammer JA, Chertack N, Elliott SP, et al. Outcomes of Urethroplasty to Treat Urethral Strictures Arising From Artificial Urinary Sphincter Erosions and Rates of Subsequent Device Replacement. Urology. 2017;107:239-45.
18. Cohen AJ, Boysen W, Kuchta K, Faris S, Milose J. Artificial urinary sphincter longevity following transurethral resection of the prostate in the setting of prostate cancer. World J Urol. 2019;37:2755-61.
19. Raj GV, Peterson AC, Toh KL, Webster GD. Outcomes following revisions and secondary implantation of the artificial urinary sphincter. J Urol. 2005;173:1242-5.
20. Ortiz NM, Wolfe AR, Baumgarten AS, Ward EE, VanDyke ME, Hudak SJ, et al. Artificial Urinary Sphincter Cuff Erosion Heat Map Shows Similar Anatomical Characteristics for Transcorporal and Standard Approach. J Urol. 2020;204:1027-32.
21. Dobberfuhl AD, Comiter CV. A Systematic Approach to the Evaluation and Management of the Failed Artificial Urinary Sphincter. Curr Urol Rep. 2017;18:18.
22. Khouri RK Jr, Ortiz NM, Dropkin BM, Joice GA, Baumgarten AS, Morey AF, et al. Artificial Urinary Sphincter Complications: Risk Factors, Workup, and Clinical Approach. Curr Urol Rep. 2021;22:30.
23. Wessels H, Vanni AJ. Surgical Procedures for Sphincteric Incontinence in the Male. In: Partin AW, Dmochowski RR, Kavoussi LR, Peters CA, Wein AJ, eds. Campbell Walsh Wein Urology. 12th ed. Elsevier; 2020; pp. 2993-3009.
24. Chung E, Cartmill R. Diagnostic challenges in the evaluation of persistent or recurrent urinary incontinence after artificial urinary sphincter (AUS) implantation in patients after prostatectomy. BJU Int. 2013;112(Suppl 2):32-5.
25. Hughes M, Caza T, Li G, Daugherty M, Blakley S, Nikolavsky D. Histologic characterization of the post-radiation urethral stenosis in men treated for prostate cancer. World J Urol. 2020;38:2269-77.

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EDITORIAL COMMENT

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Impact of artificial urinary sphincter erosion in the reimplantation of the device

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COMMENT

In this article, the authors assess the clinical presentation of patients with urethral cuff erosion after the implant of an Artificial Urinary Sphincter (AUS) and also attempt to establish risk factors in this patient population (1). As well pointed out by the authors, this complication has an extreme impact on the treatment of these patients, both in the acute phase, associated with the inflammatory and infectious condition, and late related to the reimplantation of the device. Replantation of AUS after erosion is certainly one of the most challenging conditions in the management of male urinary incontinence. Despite the literature describing statistical data and risk factors for erosion, these hardly describe details about the evolution characteristics of this process. As observed by the authors, most patients present with inflammatory signs in the scrotum, but a significant part of patients (about 1/3) do not present these symptoms, and will exclusively have urinary symptoms (obstruction or incontinence relapse) (2). This is an important finding because even in the absence of inflammatory signs, erosion should be suspected when there are urinary symptoms, whether obstructive or incontinence relapse. In the case of obstructive symptoms, it is important to analyze whether there is a reference to urethral stenosis or urethro-vesical anastomosis in the patient's clinical history for the differential diagnosis. In the case of incontinence relapse, it is usually more acute when compared to other causes such as urethral atrophy. As well demonstrated in the study, these symptoms can present in combination. In the study, inflammatory symptoms are more associated with obstruction, perhaps due to greater urine leakage, a fact that also justifies lower rates of the combination of incontinence relapse and inflammation. The presence of radiotherapy was more common in patients with erosion when compared to those without erosion, as well as hypertension, coronary heart disease and smoking. The identification of risk factors is essential for patient consent, as well as for technical interventions to be taken to prevent the problem at the time of implantation of the prosthesis. The authors did not demonstrate previous procedures such as urethroplasty as risk factors in this study, but in our opinion, all patients who have an established impact on urethral vascularization a risk factor for cuff erosion. In the specific case of urethroplasty, we should try to preserve the urethra vascularization in all patients who are at risk of developing postoperative incontinence. Early recognition of cuff erosion is critical for an early approach that is likely to be associated with less urethral damage.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Diao L, Nealon SW, Carpinito GP, Badkhshan S, Wolfe AR, Dropkin BM, et al. Presenting signs and symptoms of artificial urinary sphincter cuff erosion. Int Braz J Urol. 2022;48: 679-85.
2. Kretschmer A, Hüsch T, Anding R, Pottek T, Rose A, Struss W, et al. The impact of perioperative complications on favorable outcomes after artificial urinary sphincter implantation for post-prostatectomy incontinence. Int Braz J Urol. 2020;46:632-9.

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Rates of False-Negative Screening in Prostate Specific Antigen Secondary to 5-Alpha Reductase Inhibitor Usage: A Quality-Improvement Initiative

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ABSTRACT

Purpose: Patients often take 5-alpha reductase inhibitors (5-ARIs) for the management of benign prostatic hyperplasia. However, 5-ARIs can decrease prostate specific antigen (PSA) by approximately half and therefore may lead to false negative PSA tests. We investigated false-screening rates in men on 5-ARIs undergoing PSA testing and whether ordering physicians noticed false negative findings.

Materials and Methods: A single institution, retrospective study was conducted on patients with a PSA value documented between 2014 and 2017. Patient demographics, PSA results, 5-ARI usage, and providing clinician characteristics were collected. Published normal PSA values were used to determine PSA test positivity; values for those on 5-ARIs were doubled.

Results: A total of 29,131 men were included. 1,654 (5.7%) were prescribed 5-ARIs at least 12 months prior to PSA evaluation. 118 men (7.1%) had a value that would be positive if corrected for 5-ARI usage, 33 (27.9%) of which had no indication that the provider had noted this. There was no effect on rates of false negative values if the PSA was ordered by a different provider than the one who prescribed the 5-ARI (p = 0.837). However, if the provider who ordered the PSA test was an urologist, the likelihood that a false negative value would be identified was lower (p=0.001).

Conclusions: More than a quarter of men with false negative tests were missed. This occurred more often when the ordering provider was not an urologist. An educational opportunity exists to improve the quality of PSA testing by preventing false negative tests.

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INTRODUCTION

Prostate cancer (PCa) is the most commonly diagnosed and second most lethal cancer of men in the United States (1, 2). Despite the recent controversy and discovery of additional novel biomarkers for PCa, prostate specific antigen (PSA) remains the most widely used tool for PCa screening and plays a key role in decreasing mortality from the disease (1, 3). Patients with PCa often also present with the comorbidity of benign prostatic hyperplasia (BPH), an exceedingly common condition affecting the aging male population (4). BPH is frequently managed with 5-alpha reductase inhibitors (5-ARI): finasteride and dutasteride. 5-ARIs inhibit the production of dihydrotestosterone and reduce prostate gland size

and vascularity, thereby improving lower urinary tract symptoms (LUTS) (5-7).

Although 5-ARIs are effective in treating BPH, there are rising concerns regarding its usage in patients being screened for PCa. 5-ARIs not only decrease DHT but also systemic levels of PSA by about half (8) which may delay detection and intervention in cases of undiagnosed PCa. Doubling PSA values has been a technique used to account for decreased levels due to 5-ARI treatment and has been shown to increase the sensitivity of PSA for PCa diagnosis (9). However, certain clinicians may not routinely implement this technique in clinical practice, as they may be unaware of 5-ARIs' suppressive effects on PSA (8, 10). This study sought to determine the false--screening rate in men on 5-ARIs undergoing PSA testing and determine whether ordering physicians had noticed these false negative findings. We hypothesized a high false-screening rate in men on 5-ARIs undergoing PSA testing and that these rates would be higher if the PSA was ordered by a non-urologist when compared to a urologist.

MATERIALS AND METHODS

Study Design and Patient Population

After obtaining IRB approval (IRB#2013-2712), we conducted a cross-sectional study of all patients who had PSA values at our academic hospital institution (which provides comprehensive primary care and urologic care) from January 2014 to July 2017. Using Clinical Looking Glass (Streamline Health, Atlanta, GA), a system of querying our institutional database of electronic medical records, we built a cohort of adult patients who had a PSA test (11) and excluded those with any history of PCa. Then, we examined the cohort for prescriptions for 5-ARIs within 12 months prior to the PSA test, and also collected patient demographics (e.g. age at PSA test, self-reported race/ethnicity, preferred language), clinical characteristics (e.g. PSA value, 5-ARI type (finasteride vs. dutasteride)), and whether the physician who ordered the PSA test was an urologist or non-urologist.

Among the subset of patients with a 5-ARI prescription, we determined if the physician who ordered the PSA test was the same physician who prescribed the 5-ARI. When determining PSA test positivity, we utilized published normal values per age, in which the cutoff values for a positive PSA for men aged <50, 50-59, 60-69, and 70-79 was 2.5, 3.5, 4.5, and 6.5 ng/mL, respectively (12). Parameters including PSA density and percentage of free PSA were not used to determine PSA positivity. For men with a 5-ARI prescription, PSA results were doubled (13). A PSA test was considered to be a false negative if no subsequent workup (ex. repeat PSA, prostate biopsy) was ordered when the adjusted PSA result was positive. Manual chart review was conducted to determine if the physician who ordered the PSA test was aware of the effect of the 5-ARI.

Statistical Analysis

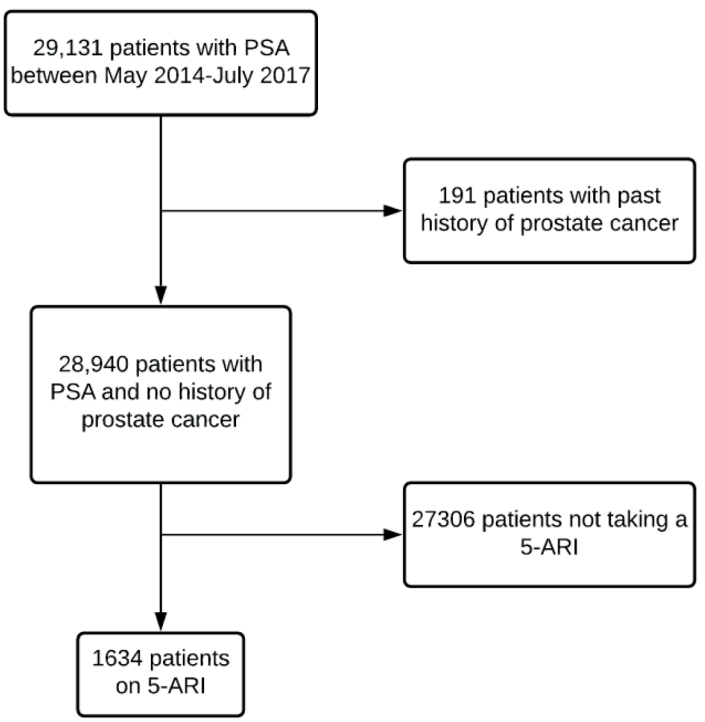
Categorical variables were compared using the $\chi 2$-test and continuous, normally distributed and non-normally distributed variables were compared using the independent samples t-test and the Mann--Whitney *U* test, respectively. We then constructed 2x2 tables comparing false negative rates among patients taking a 5-ARI, based on whether an urologist had ordered the 5-ARI, and whether the physician who prescribed the 5-ARI had ordered the PSA test. All statistical tests were two-sided with a significance threshold of $p \leq 0.05$. All analysis was conducted in Stata v16.1 (StataCorp, College Station, TX).

RESULTS

A total of 29,131 men met inclusion criteria, 191 of which were excluded due to a history of PCa. Therefore, the total cohort consisted of 28,940 men (Figure-1). Of the 28,940 men, 1,654 (5.7%) were reported as being prescribed a 5-ARI in the 12 months prior to the incident PSA screening test (Table-1). Men who took 5-ARIs were typically older (mean age 69.5±10.5 yrs) compared to men who did not take 5-ARIs (58.9±10.8 yrs, $p<0.00001$). Additionally, the proportion of non-Hispanic White (NHW) men were higher among those on 5-ARIs (22.2%) when compared to NHW men not on 5-ARIs (13.9%, $p<0.0001$).

Among the 1,654 men on 5-ARIs, 118 (7.1%) had a PSA value that would be positive if corrected for 5-ARI use (Table-1). Furthermore, among the 1,654 men, those with a false negative PSA were more likely to be prescribed dutasteride as their

Figure 1 - Flow chart of participants in cohort study.



5-ARI (21, 18.1%) when compared to those without a false negative PSA (272, 17.9%, p=0.0025). There was no significant difference in age at PSA test, race/ethnicity, and preferred language of men with a false negative PSA when compared to those without a false negative PSA.

Of the 118 men with a false negative PSA value, 33 (27.9%) had no indication that the provider had noted the false negative result (Table-2). However, there was an increase in the likelihood that a false negative value would be identified if the provider who ordered the PSA test was an urologist than if the provider was a non-urologist (p=0.001). There was no significant difference in the identification of false negative rates if the PSA test was ordered by a different provider than the one who prescribed the 5-ARI (p=0.837).

DISCUSSION

To our knowledge, this study is the first to analyze the rates of false negative PSA tests during 5-ARI therapy in patients under two scenarios: PSA tests ordered either by an urologist vs non-urologist, and concordance in providers prescribing 5-ARI and ordering PSA screenings. Our study found that there are significantly more missed false negative tests when the ordering provider is a non-urologist but no difference when looking at concordance of care.

5-ARIs represent a first line medical therapy for patients with benign prostatic enlargement. Multiple studies have supported their safety and efficacy in treating BPH related symptoms and increasing PSA test sensitivity for PCa if interpreted correctly (14-16). The doubling of PSA values for PCa screening has been an effective technique used to correct for decreased levels in patients taking 5-ARIs, although alternative strategies have been suggested, such as a PSA increase from nadir >0.3 ng/mL (17). However, non-urologists may not be aware of this practical rule, especially since the American Society of Clinical Oncology, American Urological Association, and National Comprehensive Cancer Network Prostate Cancer Early Detection do not clearly state a PSA cutoff in men taking 5-ARIs to indicate prostate biopsy (18, 19).

Table 1 - Patient and clinical characteristics of all patients, stratified by 5-alpha reductase inhibitor (5-ARI) use.

	All patients	5-ARI		
Characteristics		No	Yes	
	N=28,940	N=27285 (94.4%)	N=1634 (5.7%)	p
Age at PSA Test, mean, SD (yrs)	59.5, 11.1	58.9, 10.8	69.5, 10.5	<0.00001
Age category, N (%)				<0.0001
18-39.9	561 (2.0)	548 (2.0)	12 (0.7)	
40-49.9	4574 (15.8)	4526 (16.6)	46 (2.8)	
50-59.9	9912 (34.3)	9710 (35.6)	197 (12.1)	
60-69.9	8646 (29.9)	8098 (29.7)	541 (33.1)	
≥70	5247 (18.1)	4403 (16.1)	838 (51.3)	
Self-reported Race/Ethnicity, N (%)				<0.0001
Non-Hispanic White	4161 (14.4)	3798 (13.9)	363 (22.2)	
Non-Hispanic Black	8870 (30.7)	8417 (30.9)	453 (27.7)	
Hispanic	9062 (31.3)	8573 (31.4)	489 (29.9)	
Others/Declined*	6826 (23.6)	6497 (23.8)	329 (20.1)	
Preferred Language, N (%)				<0.0001
English	23143 (80.0)	21894 (80.2)	1249 (76.4)	
Spanish	4718 (16.3)	4394 (16.1)	324 (19.8)	
Others/Declined	1079 (3.7)	997 (3.7)	61 (3.7)	
PSA, median (IQR) (ng/mL)	0.94 (0.50-2.0)	0.9 (0.5-1.9)	2.2 (0.9-5.4)	
Urologist ordered PSA, N (%)				<0.0001
No	26285 (90.8)	25035 (91.8)	1230 (75.3)	
Yes	2655 (9.2)	2250 (8.3)	404 (24.7)	

P value refers to independent samples T-test (age) or χ^2-test (categorical variables).
*Includes Asians and American Indians/Alaskan Natives, which made up <3% of the total population.
**Includes Dutasteride in combination with Tamsulosin.

Consequently, increasing providers' awareness of doubling PSA may increase its effectiveness as a viable tool for men undergoing PCa screening.

There have been concerns regarding 5-ARI use and PCa outcomes. Multiple studies have found that the use of 5-ARIs is associated with delayed diagnosis and increase in PCa mortality (10, 20). Recently, Busato et al. (8) expressed their concerns that in Brazil, 5-ARIs are often prescribed by non-urologists and that about 90% of PSA screening tests are ordered by primary care physicians while only 7% are ordered by urologists. In our study, of the total patients who were taking 5-ARIs, 75% were prescribed by non-urologists and 75% of PSA screening tests were ordered by primary care physicians. Therefore, our study also supports that physician prescribing the 5-ARIs and ordering PSA tests are often non-urologist who may not be aware about 5-ARI induced PSA suppression. It should be noted that a positive PSA should be confirmed after a few weeks

Table 2 - A) Patient and clinical characteristics of patients on 5-ARI, stratified by whether they had a false negative value, or not, and B) observed false negative rate among patients treated with 5-ARI, if the PSA was ordered by an urologist vs non-urologist or (C) if the PSA was ordered by the same clinician who ordered the 5-ARI.

	All patients	False Negative		
A. Characteristics		No	Yes	
	N=1634	N=1518 (92.9%)	N=118 (7.1%)	p
Age at PSA Test, mean, SD (yrs)	69.5, 10.5	69.6, 10.7	68.6, 7.1	0.31
Age category, N (%)				0.13
18-39.9	12 (0.7)	12 (0.7)	0 (0)	
40-49.9	46 (2.8)	43 (2.8)	3 (2.6)	
50-59.9	197 (12.1)	189 (12.5)	8 (6.9)	
60-69.9	541 (33.1)	492 (32.4)	49 (42.2)	
≥70	838 (51.3)	782 (51.5)	56 (48.3)	
Self-reported Race/Ethnicity, N (%)				0.96
Non-Hispanic White	363 (22.2)	339 (22.3)	24 (20.7)	
Non-Hispanic Black	453 (27.7)	420 (27.7)	33 (28.5)	
Hispanic	489 (29.9)	455 (30.0)	34 (29.3)	
Others/Declined*	329 (20.1)	304 (20.0)	25 (21.6)	
Preferred Language, N (%)				0.21
English	1249 (76.4)	1166 (76.8)	83 (71.6)	
Spanish	324 (19.8)	294 (19.4)	30 (25.9)	
Others/Declined	61 (3.7)	58 (3.8)	3 (2.6)	
PSA, median (IQR) (ng/mL)	0.94 (0.5-2.0)	0.94 (0.5-1.9)	3.5 (2.9-4.5)	<0.00001
5-ARI Type				0.0025
Dutasteride**	293 (17.9)	272 (17.9)	21 (18.1)	
Finasteride	1341 (82.1)	1246 (82.1)	95 (81.9)	
	N=118	N=33 (27.9)	N=85 (72.1)	
B. Urologist				0.001
No	81 (68.6)	30 (90.9)	51 (60.0)	
Yes	37 (31.4)	3 (9.1)	34 (40.0)	
C. Concordant				0.837
No	67 (56.8)	18 (54.5)	49 (57.6)	
Yes	51 (43.2)	15 (45.5)	36 (42.4)	

P value refers to independent samples T-test (age) or χ^2-test (categorical variables).
*Includes Asians and American Indians/Alaskan Natives, which made up <3% of the total population.
**Includes Dutasteride in combination with Tamsulosin

under standardized conditions, such as ejaculation, manipulations, or urinary tract infections, in the same laboratory before considering further interventions (21). Although multiple interventions to improve the issue at hand can be considered, our study justifies a concerted effort in educating non-urologists who prescribe 5-ARIs and order PSA tests.

A systematic review of adverse effects and safety of 5-ARIs conducted by Hirshburg et al. (22) in 2016 summarized that although there is no increase in incidence of PCa, there is an increased risk of high-grade PCa when detected. They did not find negative impact on the survival rates of patients with PCa who had a history of 5-ARI use. While it is possible that 5-ARI use could make patients more susceptible to develop high-grade disease, it is also plausible that 5-ARI use delays PCa detection, with patients subsequently presenting with higher stage disease due to seemingly normal screening; however, further studies should investigate these specifics and the possibility of both contributing factors should be considered.

The results from our study create an opportunity for intervention through education and integration of computerized clinical decision support tools. Professional organizations, including the American Society of Clinical Oncology, American Urological Association, and National Comprehensive Cancer Network Prostate Cancer Early Detection, can join efforts in creating specific guidelines in interpreting PSA values in men taking 5-ARIs. Additionally, clinical decision support technology tools integrated into electronic health record softwares have demonstrated to reduce medical errors and improve patient outcomes across a variety of health care settings (23, 24). Therefore, a potential intervention is the integration of corrected PSA values in men using 5-ARIs into electronic health record softwares in order to improve accuracy of PCa risk assessment and biopsy referral.

This study is not without limitations. The retrospective nature and involvement of a single center can introduce selection bias and decrease generalizability. Additionally, there were small sample sizes in some of the cohorts and thus there could be shifts in statistical significance with larger sample sizes. Furthermore, while 5-ARIs are well documented to decrease PSA levels, there are also other medications that we did not control for, including non-steroid anti-inflammatory drugs, statins, and thiazide diuretics that have also been shown to decrease PSA levels up to 36% (25). Additionally, there are other factors that can affect PSA, such as prostate volume, BPH, and prostatitis, that were not controlled for in the study. Nonetheless, despite these limitations, we believe our data offers insight into the importance of considering whether patients are on 5-ARIs during PSA screening. This group is working on a subsequent study aiming to delineate real-time physician practice in the community, focusing on the patterns and trends in PSA screening and 5-ARI prescribing.

CONCLUSION

Despite their important role in the treatment of BPH, 5-ARIs may contribute to false-negative PSA screening tests. Non-urologists had missed more false negative tests compared to urologists, however, there was no difference in noticed rates of false negative tests when we examined concordance of care. Given the considerable morbidity and mortality associated with PCa, we recommend community-wide efforts to further educate clinicians on the effects of 5-ARIs on PSA levels.

PRESENTATIONS

An earlier version of this article was presented at American Urological Association in 2018. See Fram EB, Maria P. MP77-16 Incidence of false negative prostate cancer screening in patient taking 5-alpha reductase inhibitors. J Urol 2018, 199(4S): e1033-4.

ETHICS

The institutional review board of the Albert Einstein College of Medicine approved of this study under protocol # 2013-2712.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Tabayoyong W, Abouassaly R. Prostate Cancer Screening and the Associated Controversy. Surg Clin North Am. 2015; 95:1023-39.
2. Guo Z, Gu C, Li S, Gan S, Li Y, Xiang S, et al. Periodontal disease and the risk of prostate cancer: a meta-analysis of cohort studies. Int Braz J Urol. 2021; 47:1120-30.
3. Eastham JA, Evans CP, Zietman A. What is the optimal management of high risk, clinically localized prostate cancer? Urol Oncol. 2010; 28:557-67.
4. Pettaway CA, Lamerato LE, Eaddy MT, Edwards JK, Hogue SL, Crane MM. Benign prostatic hyperplasia: racial differences in treatment patterns and prostate cancer prevalence. BJU Int. 2011; 108:1302-8.
5. Boyle P, Roehrborn C, Harkaway R, Logie J, de la Rosette J, Emberton M. 5-Alpha reductase inhibition provides superior benefits to alpha blockade by preventing AUR and BPH-related surgery. Eur Urol. 2004; 45:620-6.
6. Cindolo L, Pirozzi L, Fanizza C, Romero M, Tubaro A, Autorino R, et al. Drug adherence and clinical outcomes for patients under pharmacological therapy for lower urinary tract symptoms related to benign prostatic hyperplasia: population-based cohort study. Eur Urol. 2015; 68:418-25.
7. Kim EH, Brockman JA, Andriole GL. The use of 5-alpha reductase inhibitors in the treatment of benign prostatic hyperplasia. Asian J Urol. 2018; 5:28-32.
8. Busato WFS Júnior. Use of 5αreductase inhibitor and delay in prostate cancer diagnosis and treatment. Int Braz J Urol. 2020; 46:456-8.
9. Thompson IM Jr, Tangen CM, Kramer B. 5αReductase Inhibitor Use in Patients with Prostate Cancer. JAMA Intern Med. 2019; 179:1440.
10. Sarkar RR, Parsons JK, Bryant AK, Ryan ST, Kader AK, McKay RR, et al. Association of Treatment With 5αReductase Inhibitors With Time to Diagnosis and Mortality in Prostate Cancer. JAMA Intern Med. 2019; 179:812-819.
11. Bellin E, Fletcher DD, Geberer N, Islam S, Srivastava N. Democratizing information creation from health care data for quality improvement, research, and education-the Montefiore Medical Center Experience. Acad Med. 2010; 85:1362-8.
12. Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. JAMA. 1993; 270:860-4.
13. Modi P, Helfand BT, McVary KT. Medications and surgical interventions for benign prostatic hyperplasia are potential confounders of prostate-specific antigen. Curr Urol Rep. 2010; 11:224-7.
14. Feneley MR, Span PN, Schalken JA, Harper M, Griffiths K, Holmes K, et al. A prospective randomized trial evaluating tissue effects of finasteride therapy in benign prostatic hyperplasia. Prostate Cancer Prostatic Dis. 1999; 2:277-81.
15. Kaplan SA, Chung DE, Lee RK, Scofield S, Te AE. A 5-year retrospective analysis of 5αreductase inhibitors in men with benign prostatic hyperplasia: finasteride has comparable urinary symptom efficacy and prostate volume reduction, but less sexual side effects and breast complications than dutasteride. Int J Clin Pract. 2012; 66:1052-5.
16. Kaplan SA, Lee JY, Meehan AG, Kusek JW; MTOPS Research Group. Long-term treatment with finasteride improves clinical progression of benign prostatic hyperplasia in men with an enlarged versus a smaller prostate: data from the MTOPS trial. J Urol. 2011; 185:1369-73.
17. Marks LS, Andriole GL, Fitzpatrick JM, Schulman CC, Roehrborn CG. The interpretation of serum prostate specific antigen in men receiving 5alpha-reductase inhibitors: a review and clinical recommendations. J Urol. 2006; 176:868-74.
18. Carroll PH, Mohler JL. NCCN Guidelines Updates: Prostate Cancer and Prostate Cancer Early Detection. J Natl Compr Canc Netw. 2018; 16:620-3.
19. Kramer BS, Hagerty KL, Justman S, Somerfield MR, Albertsen PC, Blot WJ, et al. Use of 5-alpha-reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. J Clin Oncol. 2009; 27:1502-16. Erratum in: J Clin Oncol. 2009; 27:2742.
20. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, et al. Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman CA Jr. The influence of finasteride on the development of prostate cancer. N Engl J Med. 2003; 349:215-24.
21. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2021; 79:243-62.

22. Hirshburg JM, Kelsey PA, Therrien CA, Gavino AC, Reichenberg JS. Adverse Effects and Safety of 5-alpha Reductase Inhibitors (Finasteride, Dutasteride): A Systematic Review. J Clin Aesthet Dermatol. 2016; 9:56-62.
23. Garg AX, Adhikari NK, McDonald H, Rosas-Arellano MP, Devereaux PJ, Beyene J, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. JAMA. 2005; 293:1223-38.
24. Hunt DL, Haynes RB, Hanna SE, Smith K. Effects of computer-based clinical decision support systems on physician performance and patient outcomes: a systematic review. JAMA. 1998; 280:1339-46.
25. Chang SL, Harshman LC, Presti JC Jr. Impact of common medications on serum total prostate-specific antigen levels: analysis of the National Health and Nutrition Examination Survey. J Clin Oncol. 2010; 28:3951-7.

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ORIGINAL ARTICLE

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Contemporary techniques of da Vinci SP radical prostatectomy: multicentric collaboration and expert opinion

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ABSTRACT

Background: The da Vinci SP robot consists of an innovative single port trocar that houses a flexible camera and three biarticulated arms, which minimizes the number of incisions to assess the surgical site, allowing a less invasive procedure. However, due to its recent release in the market, the current literature reporting SP-RARP is still restricted to a few centers. In this scenario, after performing a literature search with all available techniques of SP-RARP, our objective is to report a multicentric opinion of referral centers on different techniques to approach SP-RARP.

Results: The SP literature is provided by only a few centers due to the limited number of this new console in the market. Five different approaches are available: transperitoneal, extraperitoneal, Retzius-Sparing, transperineal and transvesical. None of the current studies describe long-term functional or oncological outcomes. However, all approaches had satisfactory operative performance with minimum complication rates.

Conclusions: Several techniques of SP-RARP have been reported in the literature. We performed a multicentric collaboration describing and illustrating the most challenging steps of this surgery. We believe that the details provided in this article are useful teaching material for new centers willing to adopt the SP technology.

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INTRODUCTION

The da Vinci Robot was first introduced into urologic surgery in the United States in 1999 after FDA approval (1). Since then, robotic-assisted radical prostatectomy (RARP) using the multi-port system has developed into the gold standard for surgical management of prostate cancer in the USA. In this scenario, during several da Vinci generations, urologists and robotic surgeons continue to develop minimally invasive techniques to reduce morbidity and maximize outcomes. As a result, surgical times, intraoperative performances, complication rates, and postoperative outcomes have improved drastically.

After numerous multiport consoles, the first da Vinci single port (SP) clinical investigation system in urology was reported in December 2014 by Kaouk et al. (2), although the Food and Drug Administration (FDA) approved selling the SP system only a few years later, in November 2018 (3). The new SP robot incorporates a single port that houses a flexible camera and three biarticulated arms, which minimizes the number of incisions required to assess the surgical site, allowing a less invasive procedure (4). However, due to its recent release in the market, the current literature reporting SP RARP is still restricted to a few centers. Therefore, the aim of this study is to report the experience and opinion of SP referral centers regarding crucial aspects of this platform on radical prostatectomies.

PATIENTS AND METHODS

On July 25th, 2021, during the Society of Robotic Surgery (SRS) annual meeting, referral centers on SP surgery discussed crucial aspects of the SP approach to radical prostatectomy. Each center shared their experience and challenges from the da Vinci SP implementation until the operative routine after achieving the learning curve. We have described in detail the critical aspects of this consensus on each surgical approach of this article.

RESULTS

SP system implementation

Training for SP surgery (animal and cadaver), simulator and certification

The training for SP surgery relates to the initial background of the surgeons. A faster learning curve is expected for surgeons with previous robotic experience, but such a learning curve continues to exist. For non-robotic surgeons, the learning curve is usually steeper. SP system training is a must for all surgeons before implementing SP applications. It starts with a didactic dry lab course on how to use the robot in terms of joysticks, pedals, and the functionality of controls.

The next step is an optional wet lab training, if possible, followed by taking advantage of several courses with SP experts to learn the landscape and expected outcomes. Tips and tricks from surgeons already using the SP platform are also useful. The next stage is case observation of SP procedures, suggesting around 5 cases, followed by performing at least 2-3 select cases in a proctored fashion. The final stage of SP training and implementation is performing SP surgeries with an experienced SP robotic surgeon being available if needed. Certificates of proficiency should be issued upon training by program directors of the corresponding institutes.

Selection criteria for SP-RARP

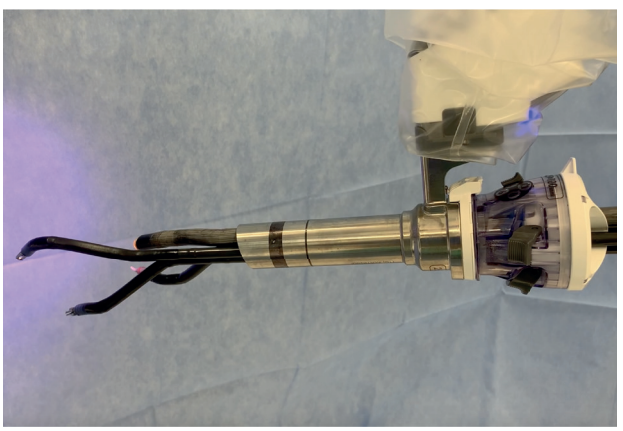
The patients should be always informed about the learning curve experience. Cases should be selected in a fashion that is less complex before progressing into the more complex pathologies. Body habitus should be selected to be favorable, and a start with an easier procedure such as pelvic surgeries (simple or radical prostatectomy) is recommended. Favorable pathologies such as low or intermediate-risk prostate cancer should be first selected before proceeding to higher-risk patients. Finally, establishing a local database to track outcomes helps in optimizing future patient selection criteria and technical adjustments.

Floating trocar technique and considerations

The single port platform has been originally designed to be used mostly in the peritoneal cavity. The single metallic trocar was supposed to be inserted through the fascia all the way into the peritoneum (Figure-1). This approach though poses multiple issues. Having the trocar completely inserted doesn't allow to perform "pure" single port surgery given the need of an extra trocar for suction. Additionally, the single port instruments require at least 10 cm of distance from the tip of the trocar to articulate. Therefore, the trocar inside the cavity makes it virtually impossible to efficiently work in shallow spaces such as the retro or extra peritoneal. A specific way of docking called "floating dock" allow to overcome this issue.

Essentially the trocar is docked outside of the cavity and it "floats" exterior to the abdomen giving the chance to perform "pure" single port surgery while working in small, shallow spaces. To efficiently perform the "floating dock", two different devices can be used: the Mini GelPOINT

Figure 1 - SP trocar and instruments attached to the robotic arm.



(Applied Medical) or the SP access port (Intuitive) as illustrated by Figure-2A and 2B.

In both cases the trocar is docked at least 10 cm away from the skin level, therefore allowing the instruments to enter the cavity and articulate almost immediately. To make the floating dock technique more efficient and avoid instruments, both the camera and flexible suction pass through the same incision as a "sidecar" trocar as depicted in Figures 1 and 2. This trocar can be a 5 or a 12 mm and is essentially placed through the same skin incision, different fascial incision and eventually through the retractor of the Mini Gel Point or the SP Access Port under direct digital control.

Single Port Transperitoneal considerations

Transperitoneal access is one of the options to approach SP-RARP. With this technique, we usually place the robotic trocar on the midline 15 to 20cm from the pubic bone using Hasson's technique (Figure-3) (5, 6). However, several techniques of transperitoneal SP-RARP have been described using infraumbilical incision and "floating trocar" (7, 8).

The transperitoneal approach allows a full access to the abdominal cavity without space restrictions or limitations to perform an extended lymphadenectomy. It allows accessing multiple quadrants while minimizing technique modifications from the multiport RARP technique, being the easiest and recommended transition from the multiport to the SP robot. However, transperitoneal surgery can face challenges in patients with several previous procedures and complex bowel adhesions.

Figure 2 – A) SP Access Kit (Intuitive). B) Mini Gel Point (Applied Medical) with an assistant trocar placed laterally.

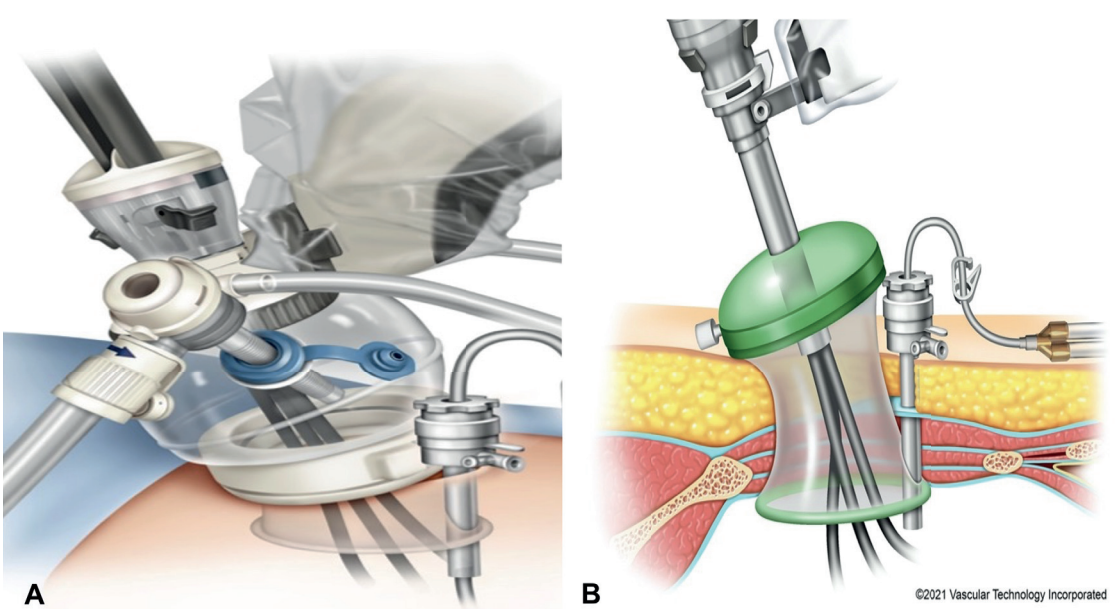
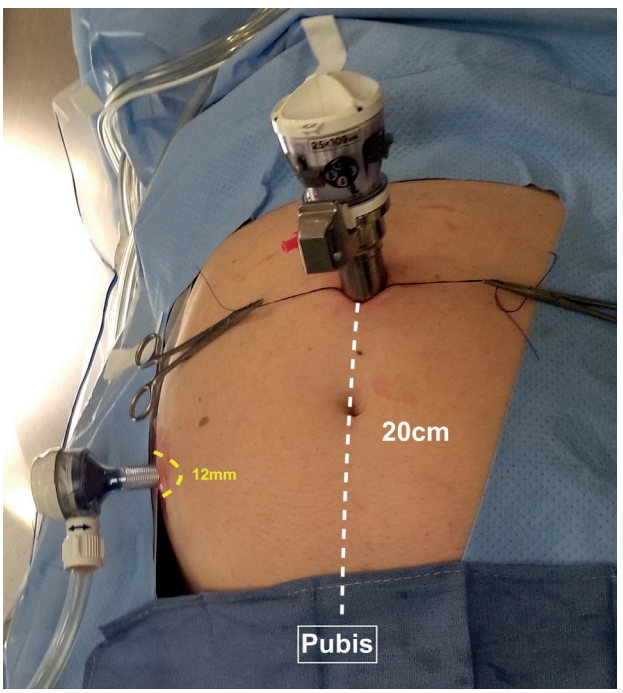


Figure 3 - SP+ one transperitoneal trocar placement.



SP Transperitoneal Port placement

In general, two types of port placement have been described in transperitoneal SP-RARP. One type is the "pure SP" which is usually placed with the GelPOINT (Applied Medical) or the Intuitive access kit. The second type is the "SP plus one" which typically does not require auxiliary devices and allows easier transition from multiport to the pure SP due to minimal modifications in surgical technique and minimal increase in operative time. It is also associated with reduced intraoperative disposable costs (9).

Transperitoneal SP-RARP Technique

The SP robot imposes some technical modifications and a new learning curve to approach new camera settings and instrument modifications. However, the surgery follows the same concept and steps described in previous series of multiport RARP (10-15).

1. Patient positioning and trocar placement (Single port plus one);
2. Bladder dropping and Retzius space access;
3. Anterior bladder neck dissection;
4. Posterior bladder neck dissection and seminal vesicles approach;
5. Nerve sparing (posterior access and lateral dissection);
6. Prostatic pedicles control with Hem-o-lock clips;
7. Minimal apical dissection;
8. DVC control with running suture and urethra division;
9. Posterior reconstruction and anastomosis;
10. Lymphadenectomy.

Single Port Extraperitoneal considerations

Extraperitoneal robot assisted radical prostatectomy aims to duplicate the previously known "gold standard" open radical retropubic prostatectomy. In the latter, a midline incision provides direct access to the target organ upon entry into the space of Retzius. While Multiport robotic surgery continues to replace open radical prostatectomy at most centers, Single Port robotic prostatectomy promises to truly replicate the open approach when performed extraperitoneally using a small (<3cm midline) incision, with the added accuracy of the robotic technology, and further limitation of the surgical invasiveness.

We have developed a reproducible technique to develop the extraperitoneal space for multiport, which we have adapted to the single port robot. Briefly, we use a 3 cm midline incision, about 5 cm from the umbilicus and exposing the linea alba which is entered. Once the perivesical fat is identified, a balloon dilator is inserted to the level of the pubic symphysis. With a camera placed in the balloon dilator, the space is created under direct vision. Important landmarks include the pubic symphysis caudally, the epigastric vessels anteriorly. No additional dilation is necessary once the epigastric vessels are visualized. When using a "Plus One" technique, the additional trocar can be placed directly into the balloon dilator. Alternatively, the surgeon can place a finger through the midline incision, over which the additional trocar is guided. In addition, the "dreaded peritoneotomy" which can result from the balloon dilation is not encountered. A peritoneotomy is common in cases of prior mesh inguinal hernia repair,

appendectomy, or other interventions causing scarring of the peritoneum which can lead to tearing when stretched by the balloon.

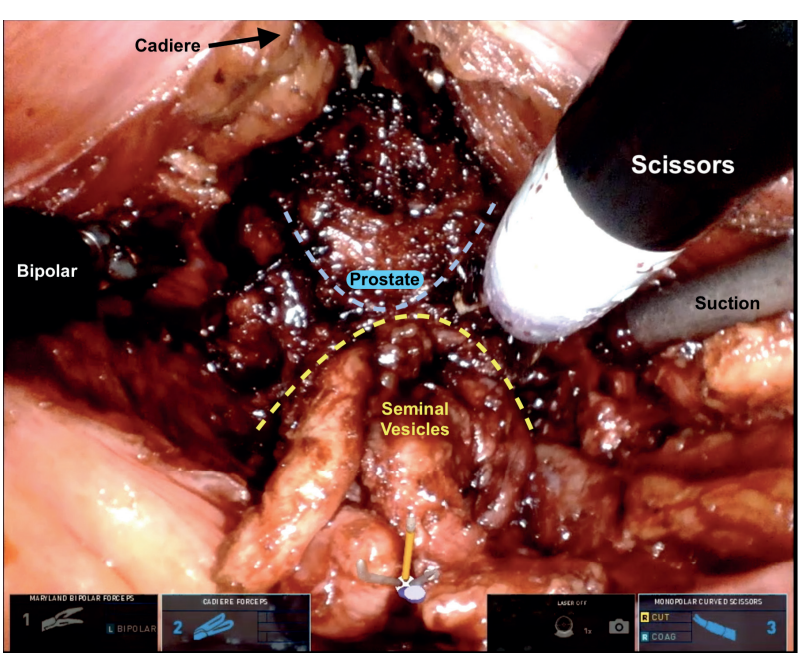
A GelPOINT mini (Applied Medical) or, or an SP Access kit is used to create the pneumoretroperitoneum, allowing visualization of the working space. We prefer using the SP access kit due to several advantages. The instruments can be visualized as they pass through the wound retractor, given the transparent balloon extending the insufflated working space. The docking port is extended with the port of entry naturally floated over the inflated access kit balloon.

Due to technological limitations and a resulting long learning curve, most surgical teams embarking on robotic prostatectomy chose the transperitoneal route, where the anatomy is more easily recognizable. The transperitoneal route, except in a "Retzius Sparing" approach requires a "bladder take down step" to access the prostate. The ease of creating a smaller working space for the multiport access will lead to more surgeons choosing the extraperitoneal route when using the SP. Additional instrumentations, and refinement of the single port robot will undoubtedly continue and lessen the invasiveness of surgical intervention which we all strive for.

Single Port Retzius-sparing

Retzius-sparing robotic radical prostatectomy has been originally described by Galfano et al. (16), to remove the prostate while preserving the periprostatic organs and structures including the bladder, the deep venous complex, the endopelvic fascia, the puboprostatic ligaments, and all the other structures in the anterior compartment (17). The technique has been associated with overall improved urinary continence rates compared to anterior approaches and immediate continence after catheter removal described up to 92% of patients (18, 19). The single port (SP) robotic platform has been designed to work in small, tunnel like spaces. Given its unique flexible camera, the proximal articulation, and the single--entry point of all the instruments, SP provides an exceptional possibility of working efficiently in "hard to reach" anatomic locations. Because of these peculiarities it might be uniquely suited to the anatomy of the recto-vesical pouch and Retzius sparing approach (Figure-4). Beside the already reported advantages in terms of decreased pain, shorter length of stay, and improved cosmesis, the SP might be able to facilitate

Figure 4 - SP Retzius-sparing: anterior bladder neck approach (Cadiere at 12 holding the bladder



the Retzius sparing technique and therefore adding advantages in terms of faster urinary continence recovery. A multicentric report of our initial experience with the single-port platform for a Retzius-sparing approach to radical prostatectomy is under review and proves safety, feasibility, and comparable oncological and functional outcome with the reported multiport results. Further studies are on the way to compare intra and perioperative outcomes of SP versus multiport Retzius sparing prostatectomy.

Single-port Transvesical Approach

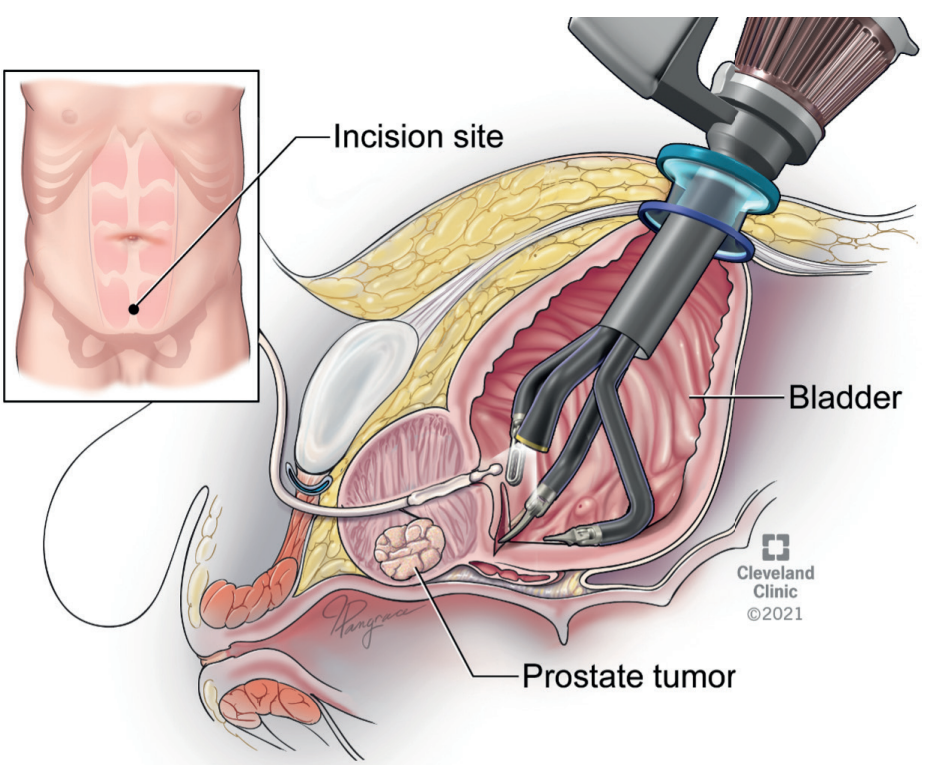
The single-port transvesical RARP approach was developed after we established our experience with SP transvesical robot-assisted simple prostatectomy and SP extraperitoneal RARP. Patients with localized prostate cancer and a history of extensive abdominal surgeries such as (20) colectomy with a colostomy or J-pouch creation, as well as those with NCCN (National Comprehensive Cancer Network) low to intermediate-risk disease were selected for this approach (21).

Patients are placed in a supine position; a 3.5 cm suprapubic midline incision is made two fingerbreadths cephalad to the symphysis pubis. After incising the fascia, splitting the rectus muscle, identifying the bladder, and placing 3-0 Vicryl stay sutures bilaterally, a 2 cm cystotomy is made. The white internal ring of the SP access port kit wound retractor (Intuitive Surgical, California, United States) is inserted into the bladder, the sliding ring is slid down to the skin level, and the rolling ring is rolled over the sleeve to reach the sliding ring and nest into it.

The 25 mm short entry guide is inserted into the access port. An 8 mm AirSeal port (Conmed Linvatec, Largo, Florida, USA) is inserted into the chamber seal. A remotely operated suction irrigation (ROSI) device (Vascular Technology, Nashua, NH, USA) is inserted. The bladder is insufflated to 12 mmHg pressure and the robot is docked (Figure-1). The Instruments are illustrated by Figure-5.

The posterior bladder neck is incised from 5 to 7 o'clock position while keeping a safe distance from the ureter orifices. The tips of seminal

Figure 5 - Single-port transvesical robot-assisted radical prostatectomy. The patient is kept in a supine position. The camera and instruments are introduced directly into the urinary bladder.



vesicles are clipped, and after lifting the seminal vesicles and vas deferens, Denonvilliers fascia is incised, and the posterior plane is developed between the prostate and rectum. The anterior wall of the bladder neck is then incised, and dissection is continued anteriorly.

In sequence, the endopelvic fascia is opened, puboprostatic ligaments are transected and the dorsal vein is ligated. Lateral prostatic fascia is opened bilaterally, and the vascular pedicles are identified. Pedicles are ligated then using Weck clips. The dorsal vein complex is transected, and any bleeding vein is oversewn. The urethra is divided just distal to the apex of the prostate. Once prostate dissection is completed, it is placed in the bladder. Limited lymph node dissection is performed for patients with >7% risk of lymph node involvement calculated using Briganti nomogram (22).

Next, the bladder insufflation pressure is decreased from 5 to 8 mmHg, and an 8 inch, dyed 3-0 V-Loc suture (Covidien, Mansfield, MA) is used for posterior reconstruction. The vesicourethral anastomosis is continued with the same suture in a running fashion. Another undyed suture is used for the contralateral side and both sutures are tied together at 12 o'clock. A new 20-Fr Foley catheter is inserted. The robot is undocked, and the bladder is closed in 2 layers. Fascia is closed with 0 Vicryl sutures.

SP transvesical radical prostatectomy is an alternative novel approach for patients with a hostile abdomen and those with low or intermediate-risk disease. Patients can be discharged home on the same day and benefit from the minimal opioid requirement, shorter catheter duration, and earlier return of continence without compromising intraoperative and oncological outcomes.

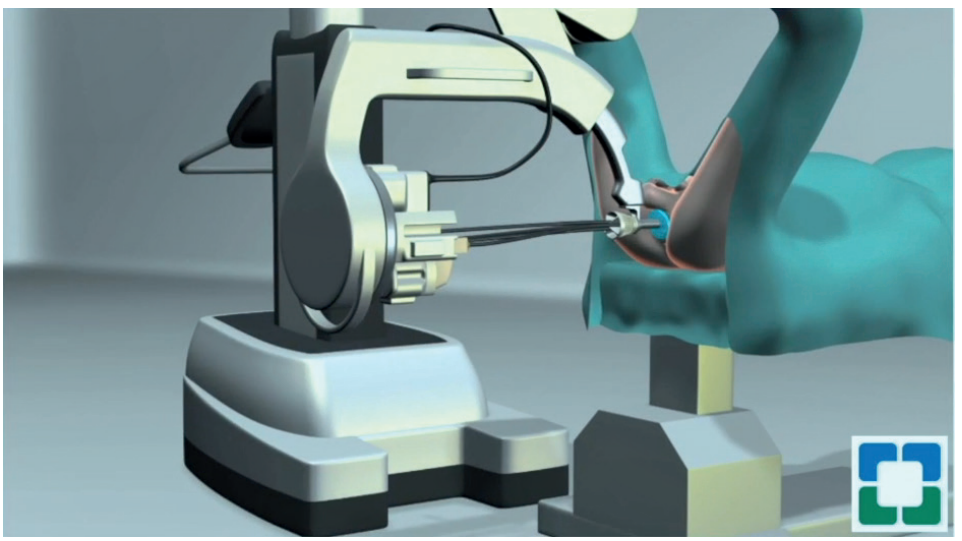
Single-Port Transperineal Approach

Due to its narrow profile, the purpose-built SP platform allows for procedures in narrow working spaces. SP-RARP using the perineal approach was developed and offered to patients who are not otherwise candidates for the traditional retropubic robotic approaches (23). Patients with extensive prior abdominal or pelvic surgeries such as total proctocolectomy and J-pouch, previous pelvic radiotherapy, or kidney transplants are offered the perineal approach to avoid working in a hostile abdomen.

Patients are positioned in a high lithotomy position. A 3cm semilunar perineal incision is made. After developing the subcutaneous space between the rectourethralis and levator ani muscles, the SP robot is docked using the GelPOINT (Applied Medical, California, USA) (Figure-6) (24). After exposing the levator ani muscle fibers, the Denovilliers are identified and incised, developing the posterior plane towards the base of the prostate. Next, lateral dissection is performed, and the vascular pedicle and neurovascular bundles are exposed and clipped using the robotic clip applier. The seminal vesicles and vas deferens are then identified and dissected. Using the tip of the seminal vesicle as a retractor. The release of the neurovascular bundle continues apically using sharp dissection, avoiding the use of electrocautery. Next, the membranous urethra is sharply divided starting from the posterior urethral plate. Care is required during this step since it is a common site for positive surgical margins. The dissection continues anterolaterally until the bladder is reached. Using the Foley balloon as a guide, the anterior bladder neck is opened and the dissection proceeds in a circumferential fashion and the prostate s freed from the last attachment. The robot is undocked to remove the specimen. In the perineal approach, lymph node dissection is performed in a caudal-to-cranial direction, as opposed to the conventional lymph node dissection. The obturator nerve and vein are identified first, and the dissection proceeds anterolateral to expose and dissect the obturator and external iliac lymph nodes. The vesicourethral anastomosis is completed using two 4-0 barbed running sutures in a water-tight fashion. Being the anastomosis above the camera in the perineal approach, it begins anteriorly and proceeds posteriorly. A pelvic drain is not placed in most of our cases.

The Perineal approach is considered an alternative but challenging therapeutic choice

Figure 6 - Single-port transperineal robot-assisted radical prostatectomy. An Illustration of the SP robot docked to the perineum, while the patient is in a high lithotomy position.



for patients with limited surgical options (frozen pelvis). It is associated with a shorter hospital stay, higher early continence rates due to the Retzius sparing approach, faster sexual recovery, and equivalent oncologic outcomes compared to the standard RARP (23, 25).

DISCUSSION

Before any comparisons with the multiport platform or between the SP centers, it is crucial to note that the current data has multiple confounding factors. All articles to date are based on retrospective data evaluation and their inherent risks of bias. In addition, we still don't have a standardized technique because all centers perform this surgery with different ways of trocar placement, several types of abdominal accesses, diverging surgical techniques, and distinctive postoperative routines. Furthermore, some centers adopted selection criteria for all patients, while other surgeons only selected patients in the first cases during the learning curve. Therefore, we have explained all crucial factors and technical details that are consensus among referral centers on SP surgery.

Every surgical innovation imposes challenges on surgeons, fellows, residents, and nurses. The new SP robot, with its unique structure and features, as well as the different surgical implementations, necessitates a new learning curve for its users. A previous study performed on SP extraperitoneal RARP learning curve, identified four different learning phases until the mastery level. Low PSM rate, postoperative complications, and BCR can take time to be achieved even for experienced robotic surgeons (26).

Different factors are associated with the SP learning curve (15). We believe that the best initial approach is to select cases with favorable BMI, prostate size, and tumor staging to reduce operative time and minimize positive surgical margins (PSM). Then, after achieving proficiency, despite the surgical technique, the surgeon should choose the best approach that fits the patient's needs in terms of cancer control and potential anatomical limitations to access the surgical field.

Finally, as previously explained, the SP robot is restricted to a few centers due to the short period in the market and some challenges posed by this platform in terms of modifications in the surgical approach and the new learning curve required. Therefore, we believe that sharing the experience of several referral centers is crucial to provide information to surgeons willing to perform a safe transition from the multiport to the SP approach. Therefore, we provided innovative

teaching material and illustrations with essential aspects from the implementation until the surgical technique variation.

CONCLUSIONS

Several techniques of SP-RARP are available in the literature, despite the short period of this robot in the market. We performed a multicentric collaboration describing and illustrating the most challenging steps of this surgery, from the technical implementation to the learning curve in different approaches. We believe that the details provided in this article are useful teaching material for new centers willing to adopt the SP technology. The available data describes feasible and safe procedures with acceptable perioperative and short-term outcomes. However, the SP literature is based on retrospective data, which carries the inherent risks of bias. In this scenario, better-designed studies with long-term follow-up are still awaited.

COMPLIANCE WITH ETHICAL STANDARDS

According to the International Committee of Medical Journal Editors conflict of interest (ICMJE), the authors declare that they have no conflict of interest or competing financial interests related to the manuscript. Dr. Vipul Patel is a consultant for Active Surgical. Dr. Jihad Kaouk is a speaker Bureau for Intuitive Surgical. Dr. Simone Crivellaro is consultant for Intuitive Surgical.

*On behalf of Society of Robotic Surgery (SRS)

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Yates DR, Vaessen C, Roupret M. From Leonardo to da Vinci: the history of robot-assisted surgery in urology. BJU Int. 2011;108:1708-13; discussion 1714.
2. Kaouk JH, Haber GP, Autorino R, Crouzet S, Ouzzane A, Flamand V, et al. A novel robotic system for single-port urologic surgery: first clinical investigation. Eur Urol. 2014;66:1033-43.
3. Lai A, Dobbs RW, Talamini S, Halgrimson WR, Wilson JO, Vigneswaran HT, et al. Single port robotic radical prostatectomy: a systematic review. Transl Androl Urol. 2020;9:898-905.
4. Jones R, Dobbs RW, Halgrimson WR, Vigneswaran HT, Madueke I, Wilson J, et al. Single port robotic radical prostatectomy with the da Vinci SP platform: a step by step approach. Can J Urol. 2020;27:10263-9.
5. Covas Moschovas M, Bhat S, Rogers T, Onol F, Roof S, Mazzone E, et al. Technical Modifications Necessary to Implement the da Vinci Single-port Robotic System. Eur Urol. 2020;78:415-23.
6. Covas Moschovas M, Bhat S, Rogers T, Noel J, Reddy S, Patel V. Da Vinci Single-Port Robotic Radical Prostatectomy. J Endourol. 2021;35(S2):S93-S99.
7. Moschovas MC, Seetharam Bhat KR, Onol FF, Rogers T, Ogaya-Pinies G, Roof S, et al. Single-port technique evolution and current practice in urologic procedures. Asian J Urol. 2021;8:100-4.
8. Covas Moschovas M, Bhat S, Rogers T, Thiel D, Onol F, Roof S, Sighinolfi MC, Rocco B, Patel V. Applications of the da Vinci single port (SP) robotic platform in urology: a systematic literature review. Minerva Urol Nephrol. 2021;73:6-16.
9. Moschovas MC, Helman T, Bhat S, Sandri M, Rogers T, Noel J, et al. Does type of robotic platform make a difference in the final cost of robotic-assisted radical prostatectomy? J Robot Surg. 2022;28. Epub ahead of print. Erratum in: J Robot Surg. 2022; 25.
10. Covas Moschovas M, Bhat S, Onol FF, Rogers T, Roof S, Mazzone E, et al. Modified Apical Dissection and Lateral Prostatic Fascia Preservation Improves Early Postoperative Functional Recovery in Robotic-assisted Laparoscopic Radical Prostatectomy: Results from a Propensity Score-matched Analysis. Eur Urol. 2020;78:875-84.
11. Martini A, Falagario UG, Villers A, Dell'Oglio P, Mazzone E, Autorino Ret al. Contemporary Techniques of Prostate Dissection for Robot-assisted Prostatectomy. Eur Urol. 2020;78:583-91.
12. Basourakos SP, Kowalczyk K, Moschovas MC, Dudley V, Hung AJ, Shoag JE, et al. Robot-Assisted Radical Prostatectomy Maneuvers to Attenuate Erectile Dysfunction: Technical Description and Video Compilation. J Endourol. 2021;35:1601-9.
13. Moschovas MC, Patel V. Nerve-sparing robotic-assisted radical prostatectomy: how I do it after 15.000 cases. Int Braz J Urol. 2022;48:369-70.
14. Moschovas MC, Patel V. Neurovascular bundle preservation in robotic-assisted radical prostatectomy: How I do it after 15.000 cases. Int Braz J Urol. 2022;48:212-9.

15. Covas Moschovas M, Kind S, Bhat SK, Noel J, Sandri M, Rogers TP, et al. Implementing the da Vinci SP® without increasing positive surgical margins: experience and pathological outcomes of a prostate cancer referral center. J Endourol. 2021;29. Epub ahead of print.
16. Galfano A, Ascione A, Grimaldi S, Petralia G, Strada E, Bocciardi AM. A new anatomic approach for robot-assisted laparoscopic prostatectomy: a feasibility study for completely intrafascial surgery. Eur Urol. 2010;58:457-61.
17. Bassett JC, Salibian S, Crivellaro S. Single-Port Retzius-Sparing Robot-Assisted Radical Prostatectomy: Feasibility and Early Outcomes. J Endourol. 2022;12. Epub ahead of print.
18. Menon M, Dalela D, Jamil M, Diaz M, Tallman C, Abdollah F, et al. Functional Recovery, Oncologic Outcomes and Postoperative Complications after Robot-Assisted Radical Prostatectomy: An Evidence-Based Analysis Comparing the Retzius Sparing and Standard Approaches. J Urol. 2018;199:1210-7.
19. Galfano A, Di Trapani D, Sozzi F, Strada E, Petralia G, Bramerio M, et al. Beyond the learning curve of the Retzius-sparing approach for robot-assisted laparoscopic radical prostatectomy: oncologic and functional results of the first 200 patients with ≥ 1 year of follow-up. Eur Urol. 2013;64:974-80.
20. Kaouk J, Valero R, Sawczyn G, Garisto J. Extraperitoneal single-port robot-assisted radical prostatectomy: initial experience and description of technique. BJU Int. 2020;125:182-9.
21. Kaouk J, Beksac AT, Abou Zeinab M, Duncan A, Schwen ZR, Eltemamy M. Single Port Transvesical Robotic Radical Prostatectomy: Initial Clinical Experience and Description of Technique. Urology. 2021;155:130-7.
22. Gandaglia G, Ploussard G, Valerio M, Mattei A, Fiori C, Fossati N, et al. A Novel Nomogram to Identify Candidates for Extended Pelvic Lymph Node Dissection Among Patients with Clinically Localized Prostate Cancer Diagnosed with Magnetic Resonance Imaging-targeted and Systematic Biopsies. Eur Urol. 2019;75:506-14.
23. Lenfant L, Garisto J, Sawczyn G, Wilson CA, Aminsharifi A, Kim S, et al. Robot-assisted Radical Prostatectomy Using Single-port Perineal Approach: Technique and Single-surgeon Matched-paired Comparative Outcomes. Eur Urol. 2021;79:384-92.
24. Lenfant L, Kim S, Aminsharifi A, Sawczyn G, Kaouk J. Floating docking technique: a simple modification to improve the working space of the instruments during single-port robotic surgery. World J Urol. 2021;39:1299-305.
25. Tuğcu V, Akça O, Şimşek A, Yiğitbaşı İ, Şahin S, Yenice MG, et al. Robotic-assisted perineal versus transperitoneal radical prostatectomy: A matched-pair analysis. Turk J Urol. 2019;45:265-72.
26. Lenfant L, Corrigan D, Beksac AT, Schwen Z, Kaouk J. Learning curve analysis of single-port robot-assisted extraperitoneal prostatectomy using the cumulative sum (CUSUM) method. BJU Int. 2021;128:688-91.

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SURGICAL TECHNIQUE

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Orchio-Septopexy: A new technique to cover and fix detorsed testis undergoing fasciotomy of tunica albuginea

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ABSTRACT

Purpose: Compartment Syndrome (CS) has been recognized as a potential factor that worsens testicular viability after detorsion, especially in borderline cases of prolonged ischemia. Fasciotomy of the testicular tunica albuginea to relieve the pressure associated with CS has been proposed to accommodate edema after detorsion, embracing the raw fasciotomy area with tunica vaginalis flap (TVF) or graft. Fashioning the TVF can be tedious in cases of severe scrotal edema. Herein we present a technique that facilitates and expedites the procedure, maintaining the fasciotomy area decompressed.
Materials and Methods: In testicular torsion, where the testis remains with dark coloration and questionable viability after detorsion a longitudinal releasing incision is made in the tunica albuginea (fasciotomy) to decrease compartmental pressure. If signs of parenchymal recovery (bleeding points, better color) are seen an orchio-septopexy is performed, suturing the incised albuginea's edges to the septum with a running suture, avoiding CS as well as re-torsion.
Results: Orchio-septopexy was performed in 11 cases with a mean age of 11.9 years (3-17). All cases had clinic follow-up and testicular Doppler US with a mean of 9.5 months (6-24). 6/11 cases (54%) were salvaged, with good vascularity in the Doppler US and maintained more than 50% testicular volume compared to the contralateral side.
Conclusion: Orchio-septopexy after testicular fasciotomy is a simple and fast technique that can be utilized in cases of prolonged testicular ischemia and questionable viability. More than half of the testes recovered, encouraging us to propose its utilization as well as its validation by other surgeons.

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INTRODUCTION

Testicular torsion (TT) is a common emergency condition encountered by Pediatric urologist with annual incidence of 3.8 per 100,000 pediatric patients (1). The clinical management of TT is critical, relying on prompt assessment and surgical exploration (2). The testicle viability is time sensitive to ischemia, with rate of orchiectomy reaching 80- 90% when ischemia time exceeds 24 hours (3). Different methods were used aiming to improve the salvage rate of testis post torsion, namely: educational material for health care takers, initial care of TT

cases, clinical guidelines to decrease time from emergency department door to operating room (4), manual detorsion maneuver prior to exploration (5) and incision in the testicular albuginea (TA) to relieve potential compartmental pressure and improve testicular vascularization (6). The conceptualization of testicular compartment syndrome (CS) following TT with fasciotomy to tunica albuginea to relieve that pressure has been previously validated for the management of TT with prolonged ischemia time, mobilizing a tunica vaginalis flap (TVF) to cover the fasciotomy site and to maintain lower intra testicular pressure (7, 8). Although the construction of TVF is a relatively simple procedure, it can be time-consuming and associated with bleeding, especially if scrotal edema and inflammatory reaction is present. We designed a technique that expedites the procedure, maintaining the fasciotomy area covered and decompressed. We hypothesized that fixing the testis and attaching the fasciotomy area to the septum facilitates the technique and decompress the parenchyma, avoiding CS and improving vascularization. The objective of this report is to present a novel technique for testicular fixation in cases of torsion and to confirm usefulness of previously validated fasciotomy of tunica albuginea (7-9). Herein we describe the procedure and our preliminary results.

MATERIAL AND METHODS

We performed a retrospective review of all cases with testicular torsion that underwent scrotal exploration between January 2018 and 2020. Patients with unilateral intravaginal TT and a minimum of one documented follow up visit have been included. Perinatal TT, torsion of undescended testis, TT in patients with single gonad and documented contra-lateral testicular abnormality were excluded. Patient's demographics as well as time of evolution was noted.

Surgical technique

The scrotum is explored via midline incision, identifying and preparing the testicular septum as well as exposing the affected side first in order to confirm the diagnosis of TT. The testicle is untwisted and kept covered with gauzes soaked with warm saline. Attention is then driven to the contralateral testicle that is pexed to avoid future torsion. Then the affected side is re-assessed. If it recovers normal colour it is then pexed with monofilamentar non absorbable 5/0 sutures. If it remains darker after detorsion a generous incision in TA is made, aiming decompression and improvement of vascularization. If parenchyma remains dark and with bleeding points it is assumed that irreversible necrosis have ocurred and orchiectomy is warranted. If color improves and bleeding points appear in the parenchyma an orchio-septopexy is performed via running suture of polydioxanone 5.0 sutures , starting at the lower edges of the fasciotomy (Figure-1). For additional technical details we invite the reader to view a video following the link: <https://intbrazjurol.com.br/videos/20220128_Pippi-Salle_et_al.mp4>

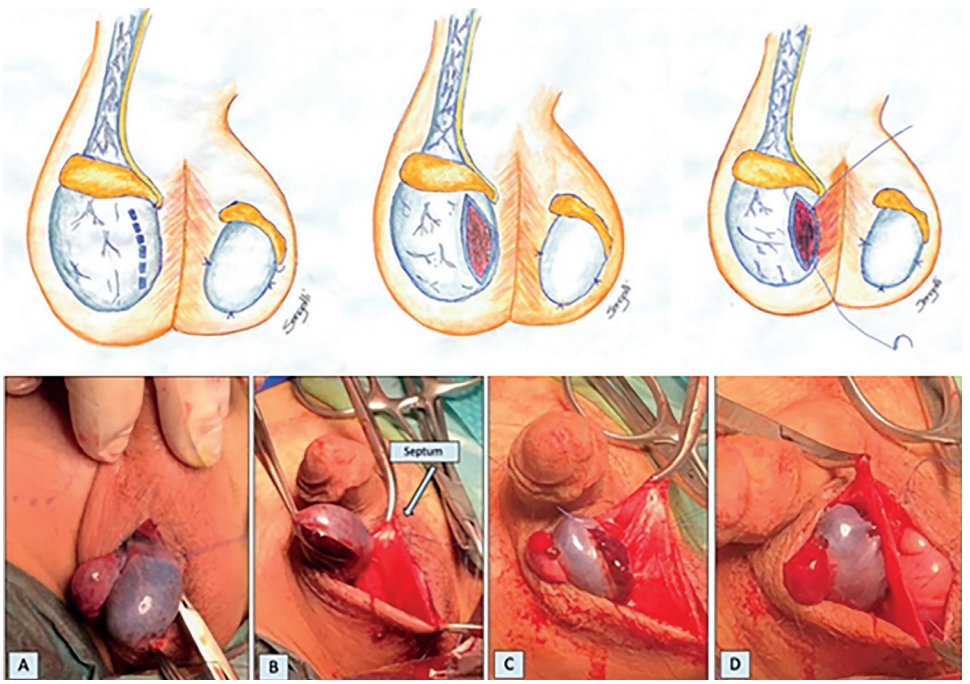
The summary of intra-operative approach of TT as shown in Figure-2.

Post-operative physical examination as well as Doppler US were performed at least 6 months after surgery. The definition of post-operative testicular salvageability is having adequate blood flow on Doppler US, maintaining at least of 50% testicular volume compared to the contralateral side.

RESULTS

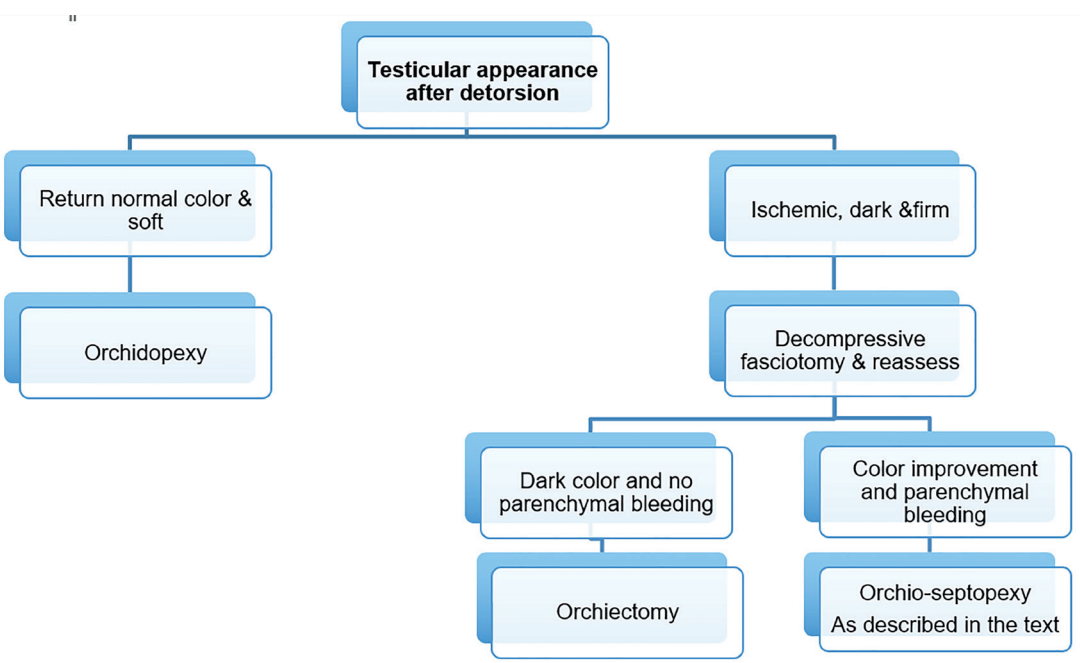
Between January 2018 and 2020, 21 patients underwent scrotal exploration for TT. The age of patients ranged from 3 to 17 years old. Left sided was slightly more affected than right (12 cases, 57.14%). Five cases (23.8%) improved with detorsion alone and underwent routine bilateral orchiopexy. In 16 patients the color did not improve after detorsion and underwent fasciotomy. Dark coloration with necrotic looking parenchyma remained in 5 cases and these patients underwent orchiectomy. Eleven testicles improved the color, having points of parenchyma bleeding and underwent orchio-septopexy. All patients who underwent orchio-septopexy

Figure 1 - Orchio-Septopexy technique.



A) Testis with persistent discoloration after de-torsion; B) Aspect of the testis after fasciotomy of tunica albuginea (improved coloration and with some bleeding points); C) Running suture of the lower edges of incised albuginea to midline scrotal septum; D) Orchio-septopexy completed.

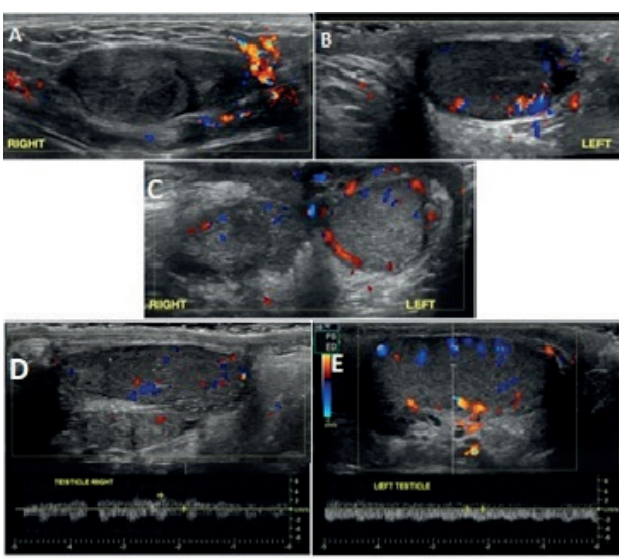
Figure 2 - illustrates our algorithm for management of TT.



Summary of intra-operative approach for testicular torsion.

after fasciotomy had clinic follow-up and testicular Doppler US with a mean of 9.5 months (6-24) and 6 of 11 (54%) were salvaged, having good flow, maintaining more than 50% testicular volume compared to the contralateral as illustrated in Figure-3. Interestingly, 4 patients (66.7%) with 12 hours or less history of pain, who underwent orchio-septopexy had viable testis post operatively and also 2 (40%) with prolonged ischemia time (>12H) recovered after this procedure (Table-1).

Figure 3 - Pre and post testicular ultrasounds in a 14-year old boy with borderline viable testis after detorsion who underwent right orchio-septopexy.



A, B) Pre-op Doppler in patient with right testicular torsion and prolonged ischemia: no flow in the parenchyma; C) Doppler 2 weeks after right orchio-septopexy showing recovery of flow; D, E) Doppler at 1 year follow-up: maintenance of good flow and more than 50 % of right testicular volume compared by left side.

DISCUSSION

Compartment syndrome (CS) is a well-known and important initiator of post ischemic insult to various organs constrained by natural envelops, including but not limited to orthopedics and trauma, being well documented in the literature (10). The increase of intra compartmental pressure leads to vicious cycle of hypoxia, accumulation of lactate due to anaerobic metabolism, edema, further deterioration in the intra compartmental pressure and decrease in capillary flow (11). Similarly, the concept can be applied to testis which is constrained by the non-elastic layer of tunica albuginea. An increase in the intra-testicular blood volume due to venous congestion of the spermatic cord, in addition to tissue changes following ischemia reperfusion injury, are likely the pathophysiology of testicular CS (12). Therefore, the concept of testicular fasciotomy via incising the tunica albuginea has been introduced to break the pathological vicious cycle of testicular CS following torsion. The concept of covering the raw fasciotomy area with tunica vaginalis flap or graft (TVF) aims to maintain a low compartment pressure inside the testicle, preventing high intra testicular compartment pressure (9). However, construction of a TVF in edematous and inflamed scrotal tissue can be tedious due to blood oozing. Our technique, attaching the raw parenchymal directly to the septum instead of covering with TVF facilitates and expedites

Table 1 - The correlation of the duration of pain with different surgical outcome.

Duration of pain	Bilateral Orchiopexy (Viability %)	Orchiectomy (Viability %)	Orchio-septopexy (Viability %)
6 hours or less	4	0	0
7-12 hours	1	0	6 (4 cases 66.70%)
More than 12 hours	0	5	5 (2 cases 40%)
Total (21 cases)	**5 (100%)**	**5(NA)**	**11 (6 cases 54.5%)**

the surgery, usually done in emergency conditions, therefore useful in such conditions. This procedure was successful in 54.5% of patients with questionable viability testis after detorsion.

Although we did not measure the time spent to perform orchio-septopexy or compare with other techniques, it seems faster and easier than the TVF technique, done previously by the senior author. This modification, with a follow-up of 9.5 months, confirms the results published in previous paper from Toronto, a similar experience with 11 patients who had TVF after fasciotomy, obtaining 54% of testicular viability on Doppler US at 7.9 months mean follow-up (8).

Orchio-septopexy seems to be particularly useful in patients with prolonged clinical evolution. Our study confirms the impression of Chu, et al. who retrospectively reviewed a cohort of 182 patients who 49, 36, and 97 underwent orchiectomy, TVF and orchiopexy alone, respectively (13). In their study TVF was particularly useful in patients with prolonged ischemia but less than 24 hours evolution where 33% of testis remained viable. In our study 6 of the 11 testis treated with orchio-septopexy remained viable (54%), including 2 with more than 12h history 6 months post operatively, confirming that, recovery is possible even in severely compromised testicles treated by orchio-septopexy (Table-1). It's worth mentioning that, 81% (17 cases) of our patients had more than 6 hours history of acute scrotal pain and that explain the higher rate of fasciotomy of TA (52%) among our cases to relieve the CS associated with prolonged ischemia.

Our study has limitations: it is retrospective and reviews a small number of patients with relatively short follow-up. In addition, in order to confirm our impression that the proposed technique is faster and easier to perform, it should be ideally done in a randomized fashion with the established utilization of TVF to cover the fasciotomy area, measuring the duration of the procedures with both techniques as well as the outcomes. However, its simplicity and the encouraging early results stimulate us to propose its utilization and possible validation by other surgeons.

In conclusion, orchio-septopexy after fasciotomy of tunica albuginea is a simple and fast technique that can be utilized in cases of prolonged testicular ischemia with questionable viability. More than half of the testis recovered, encouraging us to propose it as alternative to treat testis jeopardized by compartment syndrome after detorsion.

ETHICAL STATEMENT

IRB cirteria was met and approval granted (protocol no. 1661699).

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Zhao LC, Lautz TB, Meeks JJ, Maizels M. Pediatric testicular torsion epidemiology using a national database: incidence, risk of orchiectomy and possible measures toward improving the quality of care. J Urol. 2011;186:2009-13.
2. Mäkelä E, Lahdes-Vasama T, Rajakorpi H, Wikström S. A 19-year review of paediatric patients with acute scrotum. Scand J Surg. 2007;96:62-6.
3. Visser AJ, Heyns CF. Testicular function after torsion of the spermatic cord. BJU Int. 2003;92:200-3.
4. Afsarlar CE, Ryan SL, Donel E, Baccam TH, Jones B, Chandwani B, et al. Standardized process to improve patient flow from the Emergency Room to the Operating Room for pediatric patients with testicular torsion. J Pediatr Urol. 2016;12:233.e1-4.
5. Dias Filho AC, Oliveira Rodrigues R, Riccetto CL, Oliveira PG. Improving Organ Salvage in Testicular Torsion: Comparative Study of Patients Undergoing vs Not Undergoing Preoperative Manual Detorsion. J Urol. 2017;197(3 Pt 1):811-7.
6. Arda IS, Ozyaylali I. Testicular tissue bleeding as an indicator of gonadal salvageability in testicular torsion surgery. BJU Int. 2001;87:89-92.
7. Kutikov A, Casale P, White MA, Meyer WA, Chang A, Gosalbez R, et al. Testicular compartment syndrome: a new approach to conceptualizing and managing testicular torsion. Urology. 2008;72:786-9.
8. Figueroa V, Pippi Salle JL, Braga LH, Romao R, Koyle MA, Bägli DJ, et al. Comparative analysis of detorsion alone versus detorsion and tunica albuginea decompression (fasciotomy) with tunica vaginalis flap coverage in the surgical management of prolonged testicular ischemia. J Urol. 2012;188(4 Suppl):1417-22

9. Kutikov A, Casale P, White MA, Meyer WA, Chang A, Gosalbez R, et al. Testicular compartment syndrome: a new approach to conceptualizing and managing testicular torsion. Urology. 2008;72:786-9.
10. Balogh ZJ, Butcher NE. Compartment syndromes from head to toe. Crit Care Med. 2010;38(9 Suppl):S445-51.
11. Mars M, Hadley GP. Raised compartmental pressure in children: a basis for management. Injury. 1998;29:183-5.
12. Anaya-Prado R, Toledo-Pereyra LH, Lentsch AB, Ward PA. Ischemia/reperfusion injury. J Surg Res. 2002;105:248-58.
13. Chu DI, Gupta K, Kawal T, Van Batavia JP, Bowen DK, Zaontz MR, et al. Tunica vaginalis flap for salvaging testicular torsion: A matched cohort analysis. J Pediatr Urol. 2018;14:329.e1-329.e7.

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EXPERT OPINION

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Recommendations for prostate cancer diagnosis and treatment during COVID-19 outbreak were not followed in Brazil

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COMMENT

In Brazil, the COVID-19 outbreak has spawned two intertwined massive waves of hospital admissions, which have exposed the long-acquainted public health care shortcomings in our country. Before the end of October 2021, Brazil had reached 21.680.488 confirmed severe acute respiratory syndrome cases due to coronavirus 2 (SARS-Cov-2), accounting for over 604.000 deaths, ranking Brazil the second in number of fatalities worldwide, only behind the United States with over 732.000 reported deaths. This significant overload in hospital admissions and intensive care unit need has resulted in incredible stress to hospitals across the country and compounded deep underlying problems in the Brazilian public health system. In this complex scenario, the health care structure should be prepared to respond to the SARS-Cov-2 increase of cases and other usual emergencies and other chronic conditions that require adequate diagnosis, workup, and treatment.

Several studies have demonstrated a decrease in non-COVID-related hospital admissions, including reductions in elective procedures (1-5). In Germany, non-COVID overall inpatient admissions decreased by 35% after the lockdown announcement, with even admissions for critical care conditions such as cancer treatment significantly reduced (4). A cross-sectional study in Brazil observed a significant reduction in hospital admissions related to cancer and cardiovascular, metabolic, and musculoskeletal diseases from January to June 2020 compared to the same period over the last three years. This study has observed a reduction as high as 35% in neoplasm inpatient admissions (6).

Non-melanoma skin cancer aside, Prostate Cancer (PCa) figures as the most prevalent neoplasm in men (7, 8). In Brazil, according to GLOBOCAN, there were 97.278 PCa new cases in the year 2020, accounting for 16.4% of all neoplasm diagnoses in the same year (7). There are private and public health services in Brazil. The Public Health System (SUS) is responsible for the care of nearly 70% of all Brazilians. It is one of the largest Public Health Systems in the World. PCa burdens the health care system not only for its elevated prevalence but also because of disease characteristics. It demands populational screening with multiple clinic visits, prostate biopsies, imaging for staging, and finally, the treatment that comprehends surgery, radiotherapy, androgen deprivation therapy (ADT), and chemotherapy (9).

Some studies have demonstrated the impact of the COVID-19 pandemic on hospital admissions in chronic conditions and non-covid related emergencies (2-5). In Brazil, many health care institutions had their non-urgent procedures and elective surgeries suspended for months to concentrate economic and human resources to respond to the COVID-19

outbreak waves (10). With that, guidelines and suggestions have been provided to categorize urological diseases into risk groups and recommendations for follow-up during the COVID-19 outbreak in the management of numerous neoplasms (11, 12).

In a cross-sectional evaluation obtained from the Brazilian Public Health Information system (DATASUS), we observed that the number of hospital admissions for PCa increased during the last years until 2019. An average increment of 3.718% for PCa admissions was observed throughout Brazil from 2013 to 2019. However, we observed a significant reduction in the absolute number of hospital admissions for PCa between March 2020 and February 2021 compared to the previous year (Figure-1, p <0.0001). There was an 18.7% reduction (6.236 fewer cases) in hospital admissions if compared to the previous year, and a 23.8% reduction (7.916 cases) if considered the projected increment according to the historic increase (Table-1). Hospital admissions for a diagnosis of PCa were also lower during 2020 than in 2019 in all 27 states of Brazil (Figure-2). There was a significant reduction in the number of prostate biopsies performed in 2019, with 11.763 fewer biopsies performed in 2020 (p <0.0001, Table-1). This reduction was accompanied by a deficit of over 1.700.000 PSA tests performed in 2020 compared to 2019 (p <0.001) (Table-1; Figure-3).

Comparing to the previous year, 2.089 fewer men underwent radical prostatectomies in Brazil (p <0.0001). There was also a significant reduction in the number of men who underwent radiotherapy. There were 2.174 fewer radiotherapies for PCa in 2020 than in 2019. In May 2020, there was an increment of 33.6% in the number of procedures, but in the following months, there was a reduction of up to 15% in the number of procedures compared to 2019. Excluding May, there was a significant reduction of radiotherapies for PCa (p=0.0079). There was also a substantial reduction in ADT for PCa in 2020 compared to previous years, and 23.615 fewer doses of ADT were applied (p <0.0001, Figures-1).

Figure 1 - Number of patients in the Public Health System with a diagnosis of PCa in Brazil, from 2017 to 2020 and effects of the COVID-19 outbreak: A) Number of PSA tests (2017 to 2020); B) number of prostate biopsies (2017 to 2020); C) number of PCa diagnoses (2017 to 2020); D) number of hospital admissions with a diagnosis of PCa (2017 to 2020); E) number of radical prostatectomies performed (2017 to 2020); F) ADT for a diagnosis of PCa (2017 to 2020); *=p<0.05.

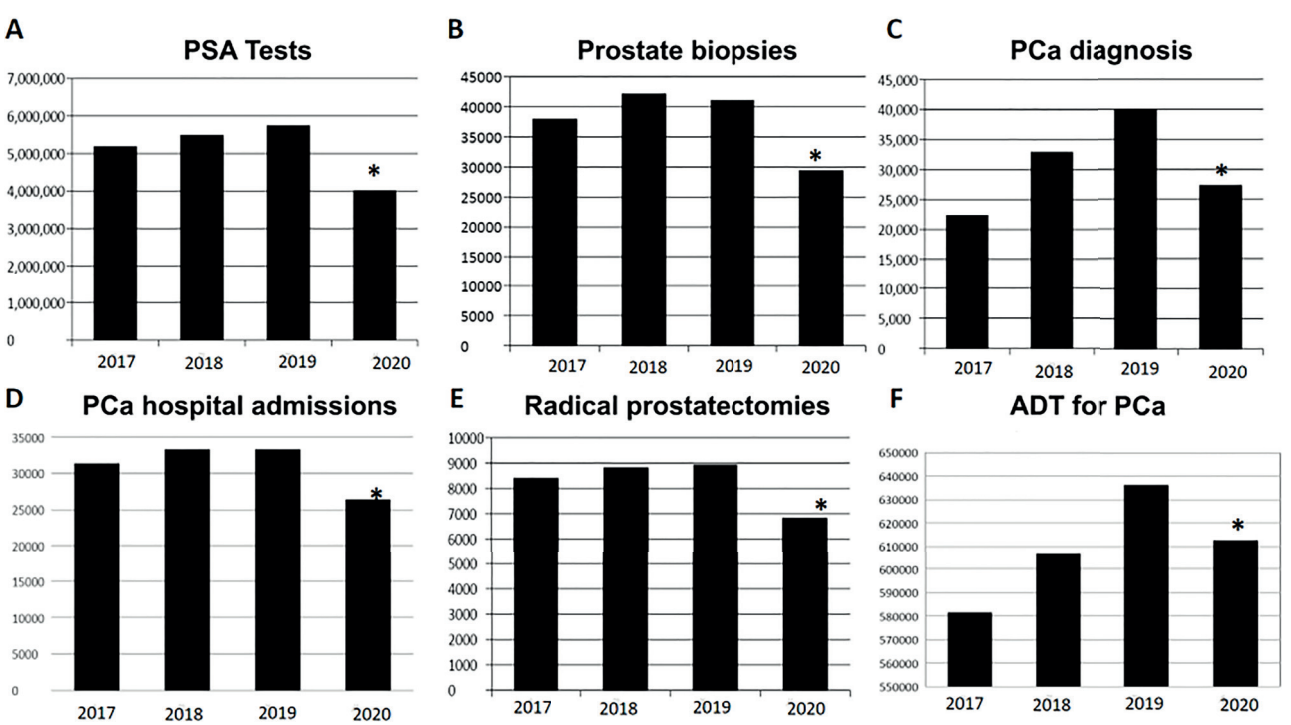


Table 1 - Effect of the COVID-19 pandemic on Prostate Cancer in Brazil. The impact was the reduction of the diagnosis and procedure involved in this neoplasm compared to previous years and projection.

	2017	2018	2019	2020	Average (2017-2019)	Projection	Déficit* (2019)	Deficit ** (2017-2019)	Deficit *** (projection)	P value
PSA tests	5.193.632	5.495.131	5.751.854	4.020.851	5.480.206	6.053.165	-1.731.003	-1.459.355	-2.032.314	<0.0001
PCa diagnosis	22.396	32.930	39.953	27.358	31.760	53.609	-12.595	-4.402	-26.251	<0.0001
Prostate biopsies	38,23	42.218	41.166	29.403	40.469	42.924	-11.763	-11.066	-13.521	<0.0001
PCa hospital admissions	31,369	33.312	34.680	26.428	33.120	34.344	-8.252	-6.692	-7.916	<0.0001
Radical prostatectomies	8,429	8,829	8.942	6.853	8.733	9.211	-2.089	-1.880	-2.358	<0.0001
Radiotherapy for PCa	-	-	19.824	17.650	19.824	-	-2.174	-2.174	-2.174	0.0079
ADT for PCa	581,544	606,562	636.340	612.725	608.149	665.648	-23.615	4.576	-52.923	<0.0001

*2020 vs. 2019
** 2020 vs. Mean 2017, 2018 and 2019
*** 2020 vs. Historic growth projection

Figure 2 - The number of hospital admissions for PCa increased during the last years until 2019, an average increment of 3.718% for PCa admissions was observed throughout Brazil from 2013 to 2019. But with the COVID-19 outbreak the hospital admissions for a diagnosis were also lower during 2020 than in 2019 in all twenty-seven states of Brazil.

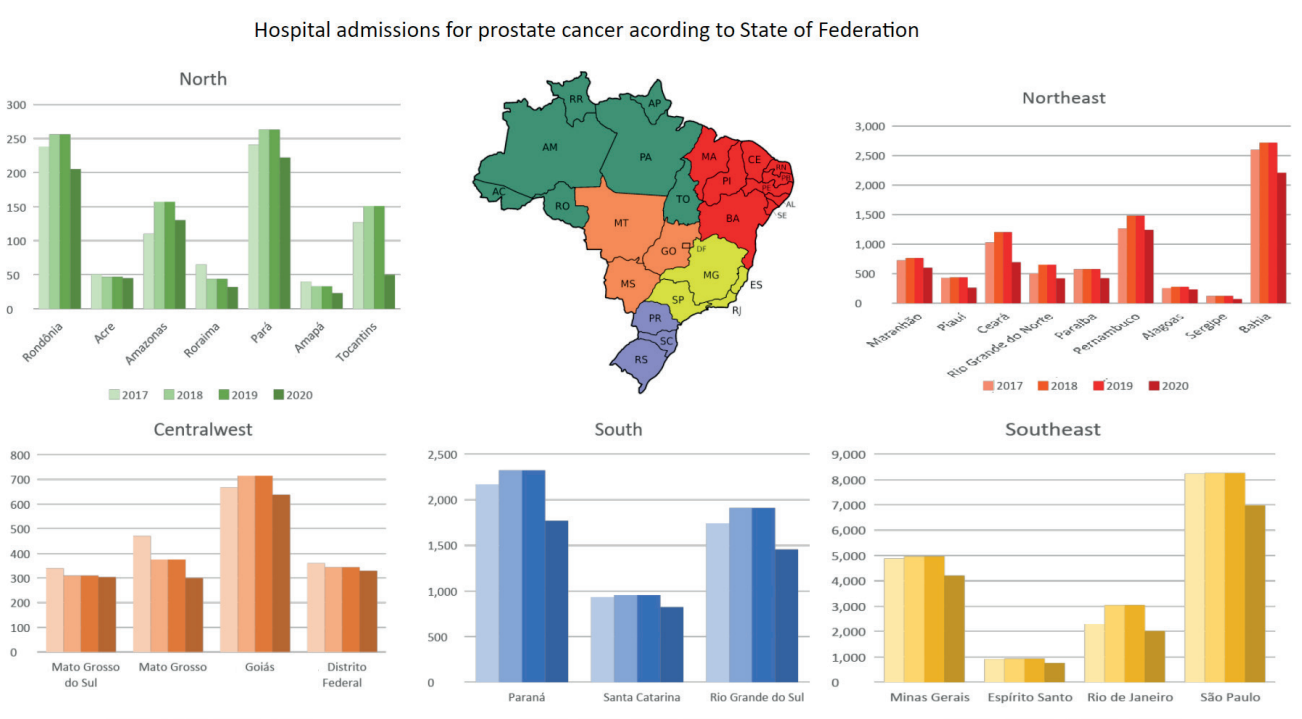
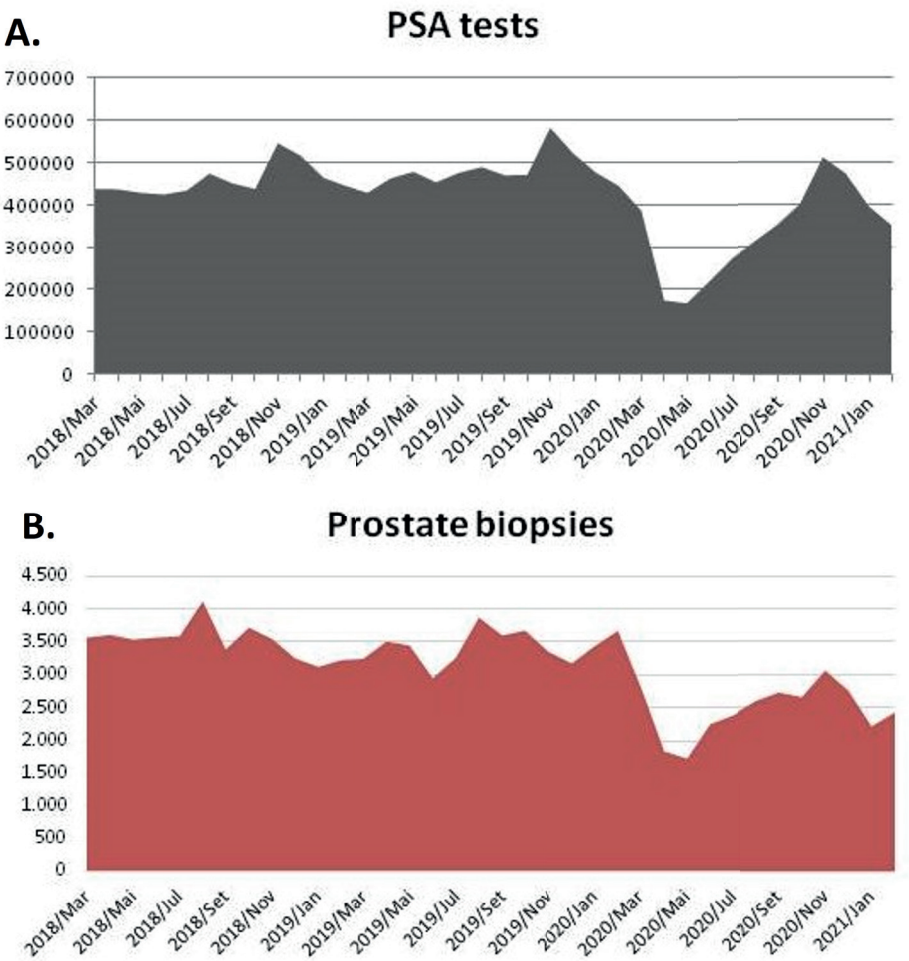


Figure 3 – Number of PSA tests and Prostate Biopsies at the last three years, with a decrease during the COVID-19 outbreak.



We observed a significant reduction in prostate biopsies, hospital admissions, surgical treatments, and radiotherapy treatments for PCa from March 2020 to February 2021 compared to the three previous years in Brazil. There were fewer treatments for localized disease (surgery and radiotherapy) and advanced disease (ADT). The collapse of the Public Health System and social distancing measures may have been associated with this reduction. As previously mentioned, social distancing measures impacted cancer care with the suspension of elective surgeries, procedures, and clinic visits (13). Several urologic and oncologic associations have proposed guidelines for the treatment of PCa during the COVID pandemic (14-19). In May 2020, the National Comprehensive Cancer Network (NCCN) produced a guideline that encouraged postponing investigation, staging, and treatment of all patients with very low to favorable-intermediate risk PCa. This guideline also recommended that even patients diagnosed with unfavorable intermediate-risk PCa should have their workup deferred until deemed safe. Evidence from a John's Hopkins retrospective cohort of over 2.300 patients supports this treatment deferral. It showed no association with unfavorable outcomes for patients who have waited for radical prostatectomy for up to six months to treat unfavorable intermediate to very-risk PCa (20).

There was a significant reduction in Radical Prostatectomies (RP) performed in Brazil, and 2.089 fewer procedures were performed during

2020. (p <0.0001) (Table-1). The American College of Surgeons (ACS), the American Society of Anesthesiologists (ASA), and the American Society of Clinical Oncology have advocated making surgical decisions by a leadership team represented by surgery anesthesiology and nursing departments. Therefore, in April 2020, EAU has produced a list for the triage of urologic surgeries and stated that most RP should indeed be delayed in the face of the aggravation of the pandemic (21). Following other associations such as NCCN and Canadian Framework, EAU recommended that only surgery for high-risk patients be considered. However, given the availability of other treatments, it was suggested that RP received lower prioritization than other urological surgeries (14, 19, 21). In this scenario, it is possible to understand that the 25% reduction in RP in 2020 when compared to 2019 might be the result of a combination of aspects compounded by the COVID-19 outbreak in Brazil: health system overload with the scarcity of hospital beds; decrease in PCa screening and diagnosis; and lower prioritization of RP in the face of other urological surgeries with redirecting patients to other treatment options. The latter might be implicated in a radiotherapy increase in Brazil's early stages of the COVID-19 outbreak.

There was an increment during May 2020 compared to May 2019 (from 1.053 to 1.407) in the number of radiotherapies performed for PCa treatment. A possible explanation for the initial increment was the re-management of many patients who were to undergo surgery in the initial phases of the outbreak. But after July 2020, a consistent and significant (p=0.0079) decrease in the number of radiotherapies performed might be an effect of the decline in PCa diagnosis. During the pandemic, the European Association of Urologists (EAU) and NCCN recommended that neoadjuvant androgen-deprivation therapy (ADT) might be considered before external beam radiotherapy (EBRT) for up to 6 months for patients with unfavorable intermediate- to high-risk patients, with 6-month ADT formulations being preferred over 1-month medications (18). Our data showed a decrease in radiotherapy alongside an increase in adjunctive ADT from May to December 2020 compared to the same period in 2019. This might indicate that patients were preferably sent to neoadjuvant ADT just as recommended by the guidelines during the COVID pandemic.

Of note is the significant reduction of prostate biopsies. In comparison with 2019, there were 11.763 fewer biopsies performed in the year 2020 (Table-1, Figure-1). Indeed, the Canadian Framework and NCCN recommended that patients with elevated prostatic antigen (PSA) or abnormal digital rectal exam (DRE) might have further testing, and biopsies postponed to the end of pandemic (14, 19). Interestingly, our data has shown that a concomitant decrease in the number of PSA tests occurred alongside the reduction in the number of prostate biopsies, especially from March to May 2020, as the COVID-19 outbreak in Brazil deepened its impact (Figure-3).

The reduction in 1.5-2.0 million PSA tests and 11.000-13.000 prostate biopsies during the last year is similar to what happened in the USA after the USPSTF recommendation against PCa screening between 2008-2012 (22). As a consequence, an increment in metastatic disease was observed during the following years. According to previous studies, for low- and intermediate-risk PCa, a delay in diagnosis and treatment seems to bring little harm in outcomes. However, for high-risk and advanced diseases, treatment delays might have adverse consequences (23).

Additionally, an economic crisis is currently taking place in Brazil as a consequence of the COVID-19 outbreak. Reduced public expenditure on health care and unemployment are expected. This might result in even higher cancer mortality rates (24). As a consequence of the significant reduction in diagnostic tests and therapeutic procedures for prostate cancer in Brazil, a cumulative number of patients are expected, and many advanced diseases might be observed during the following years.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Prezotti JA, Henriques JVT, Favorito LA, Canalini AF, Machado MG, Brandão TBV, et al. Impact of COVID-19 on education, health and lifestyle behaviour of Brazilian urology residents. Int Braz J Urol. 2021; 47:753-76.
2. De Filippo O, D'Ascenzo F, Angelini F, Bocchino PP, Conrotto F, Saglietto A, et al. Reduced Rate of Hospital Admissions for ACS during Covid-19 Outbreak in Northern Italy. N Engl J Med. 2020; 383:88-89.
3. Baldi E, Sechi GM, Mare C, Canevari F, Brancaglione A, Primi R, et al. Out-of-Hospital Cardiac Arrest during the Covid-19 Outbreak in Italy. N Engl J Med. 2020; 383:496-8.
4. Kapsner LA, Kampf MO, Seuchter SA, Gruendner J, Gulden C, Mate S, et al. Reduced Rate of Inpatient Hospital Admissions in 18 German University Hospitals During the COVID-19 Lockdown. Front Public Health. 2021; 8:594117.
5. Korkes F, Smaidi K, Salles MP, Lopes AC Neto, Heilberg IP, Glina S. COVID-19: The impact on urolithiasis treatment in Brazil. Int Braz J Urol. 2022; 48:101-9.
6. Maselli-Schoueri JH, de Carvalho LEW, Rezende LFM, Fonseca FLA, Ferrari G, Adami F. Hospital Admissions Associated With Noncommunicable Diseases During the COVID-19 Outbreak in Brazil. JAMA Netw Open. 2021; 4:e210799.
7. GLOBOCAN 2020: Global Cancer Statistics - Cancer Incidence and Mortality Worldwide: IARC CancerBase. Vol. 278. 2020. p. 1–2.
8. Tourinho-Barbosa RR, Pompeo AC, Glina S. Prostate cancer in Brazil and Latin America: epidemiology and screening. Int Braz J Urol. 2016; 42:1081-90.
9. Mottet N, Bellmunt J, Briers E, Bergh RCN van den, Bolla M, Casteren NJ van, et al. EAU - EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer 2020.
10. Castro EIB, Secchi GL, Gómez CD, Gómez JT, Clark O, Alonso IAM, et al. COVID-19: Measures to prevent hospital contagion. What do urologists need to know? Int Braz J Urol. 2020; 46 (suppl.1):113-9.
11. Esperto F, Pang KH, Albisinni S, Papalia R, Scarpa RM. Bladder Cancer at the time of COVID-19 Outbreak. Int Braz J Urol. 2020; 46 (suppl.1):62-68.
12. Rodríguez-Covarrubias F, Castillejos-Molina RA, Autrán-Gómez AM. Summary and considerations in genitourinary cancer patient care during the COVID-19 Pandemic. Int Braz J Urol. 2020; 46 (suppl.1):98-103.
13. [No authors]. COVID Surg Collaborative. Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans. Br J Surg. 2020; 107:1440-9.
14. [No authors]. NCCN. Recommendations of the NCCN Managing of Prostate Cancer During the COVID-19 Pandemic:1–4. [Internet]. Available at. <https://caunet.org/wp-content/uploads/2020/04/NCCN_PCa_COVID_guidelines.pdf.pdf>
15. Sanchez LR, Cathelineau X, Pinto AMA, Borque-Fernando Á, Gil MJ, Yee CH, et al. Clinical and Surgical Assistance in Prostate Cancer during the COVID-19 Pandemic: Implementation of assistance protocols. Int Braz J Urol. 2020; 46 (suppl.1):50-61.
16. Obek C, Doganca T, Argun OB, Kural AR. Management of prostate cancer patients during COVID-19 pandemic. Prostate Cancer Prostatic Dis. 2020; 23:398-406.
17. Detti B, Ingrosso G, Becherini C, Lancia A, Olmetto E, Alì E, et al. Management of prostate cancer radiotherapy during the COVID-19 pandemic: A necessary paradigm change. Cancer Treat Res Commun. 2021; 27:100331.
18. Ribal MJ, Cornford P, Briganti A, Knoll T, Gravas S, Babjuk M, European Association of Urology Guidelines Office Rapid Reaction Group: An Organisation-wide Collaborative Effort to Adapt the European Association of Urology Guidelines Recommendations to the Coronavirus Disease 2019 Era. Eur Urol. 2020; 78:21-8.
19. Kokorovic A, So AI, Hotte SJ, Black PC, Danielson B, Emmenegger U, et al. A Canadian framework for managing prostate cancer during the COVID-19 pandemic: Recommendations from the Canadian Urologic Oncology Group and the Canadian Urological Association. Can Urol Assoc J. 2020; 14:163-8.
20. Gupta N, Bivalacqua TJ, Han M, Gorin MA, Challacombe BJ, Partin AW, et al. Evaluating the impact of length of time from diagnosis to surgery in patients with unfavourable intermediate-risk to very-high-risk clinically localised prostate cancer. BJU Int. 2019; 124:268-74.
21. Stensland KD, Morgan TM, Moinzadeh A, Lee CT, Briganti A, Catto JWF, et al. Considerations in the Triage of Urologic Surgeries During the COVID-19 Pandemic. Eur Urol. 2020; 77:663-6.
22. Hu JC, Nguyen P, Mao J, Halpern J, Shoag J, Wright JD, et al. Increase in Prostate Cancer Distant Metastases at Diagnosis in the United States. JAMA Oncol. 2017; 3:705-707. Erratum in: JAMA Oncol. 2017; 3:709.

23. Wallis CJD, Novara G, Marandino L, Bex A, Kamat AM, Karnes RJ, et al. Risks from Deferring Treatment for Genitourinary Cancers: A Collaborative Review to Aid Triage and Management During the COVID-19 Pandemic. Eur Urol. 2020; 78:29-42.

24. Maruthappu M, Watkins J, Noor AM, Williams C, Ali R, Sullivan R, et al. Economic downturns, universal health coverage, and cancer mortality in high-income and middle-income countries, 1990-2010: a longitudinal analysis. Lancet. 2016; 388:684-95.

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Pembrolizumab as a promising intervention for advanced penile cancer

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COMMENT

Penile cancer (PeCa) as a rare neoplasm has an incidence of 0.1 to 0.9 per 100,000 men in Europe and the USA. Some factors related to this epidemiologic difference include HPV infection status, smoking history, poor hygiene, and lack of infant circumcision. Most patients show an initial period of local growth, followed by regional node compromise and, finally, distant spread. Unfortunately, patients who show at advanced stages have a grim prognosis. Studies have shown one-third of patients who have regional recurrences are alive at five years, and none with distant metastases live longer than two years (1, 2).

Standard treatments used in penile cancer patients with recurrence and metastatic disease include schemes with paclitaxel, ifosfamide, and cisplatin (TIP). Disappointingly, the efficacy of these agents has been recently contested (3) and overall survival rates do not exceed twelve months (2). Since its approval in 2014 (4) and its further indication as salvage therapy in certain penile SCC (5), pembrolizumab has been considered as a relevant therapeutic option.

Considering that there are no clinical trials to guide systemic therapy recommendations, we aimed to discuss the effectiveness and safety of pembrolizumab in patients with locally advanced or metastatic penile SCC.

When searching the vast literature through most databases, we found scarce information regarding this topic. Only two studies accomplished this criteria: Hahn et al. (6) and Chahoud et al. (7).

Regarding the general characteristics of people requiring immunotherapy, we might highlight that they are usually older patients with advanced stage penile cancer. Patients commonly show mass sensation, non-healing penile lesions, bloody discharge, and inguinal lymphadenopathies. Furthermore, they have T2-3 disease, N0-3, recurrent or even metastatic, squamous cell carcinoma (SCC) with a moderate to poor differentiation.

Consequently, patients undergo a multimodal therapy. A partial or radical penectomy, and bilateral and pelvic lymph node dissection are their initial and stepped surgical approach. Consolidation surgery may comprise a wide hemipelvectomy resection with acetabular reconstruction. Among patients, commonly used chemotherapeutic schemas included cisplatin/gemcitabine/ifosfamide and paclitaxel/ifosfamide/cisplatin, and they also use radiation therapy.

Although, patients may share interesting features regarding the biomarker expression, these are heterogeneous. PD-L1 expression and tumor

mutational burden (TMB) are present in almost all patients. Moreover, tumor proportion score (TPS) is around 10%, and there is a combined positive score (CPS) of 1, 80 and 130. Furthermore, microsatellite instability (MSI) might be stable or high, and the tumor-infiltrating score (TIL) score may be consistent with few and moderate lymphocytic infiltration. Finally, there might be between three and 14 mutations per mega-base; however, there is no report of mismatch repair deficiency. There are other molecular alterations found using Foundation One that might be essential for future analysis (Supplementary Table-1).

Supplementary Table 1 - Molecular disturbances.

PTCH1 S1203fs*52 (VAF 19.2%)
EP300 N419fs*12 (VAF 20.3%)
FAT1 S1669* (VAF 33.1%)
HSD3B1 G171R (VAF 1.2%)
MLL2 L4921fs*74 (VAF 21.9%)
MLL2 P2354fs*30 (VAF 22.9%)
QKI K134fs*14 (VAF 24.4%)
MYD88 L265P (VAF 1.5%)
NFE2L2 W24R (VAF 36.4%)
SMARCA4 M1233I (VAF 8.9%)
TERT promoter 146C>T (VAF 18.7%)
TP53 R280G (VAF 18.3%)

Specifically, for pembrolizumab usage, we found that patients receive between two and nine cycles with a total time on treatment of 1.7 to 8.1 months (6). Authors also reported adverse effects such as Grade 2 hypothyroidism, maculopapular rash, and anorexia (6), and hypothyroidism (7).

Pembrolizumab use must follow the RECIST 1.1 criteria to evaluate the outcomes. Hahn et al. (6) documented that only one patient (out of three) had a 34% decrease from baseline, consistent with a partial response. Despite this, Chahoud et al. (7) reported that one of their patients had a complete response while the other had a partial response. They followed patients from 18 to 38 months, without having disease progression.

Despite all the described data, there was a multicenter phase II trial that started in 2016 and enrolled six patients. However, it was ended prematurely by poor accrual and no results were published.

Accordingly, the FDA approved Pembrolizumab to treat many tumor types that are MSI high, MMR deficient, or TMB high (4). In penile SCC, The National Comprehensive Cancer Network (NCCN) guidelines consider it as a salvage therapy option for those patients with TMB ≥10 (8) and MSI high tumors (5); despite this, it is still not clear when it is the best fit for these patients. Heterogeneity of tumor tissue and its dynamic nature over disease course, render another obstacle to getting uniform information (9). Higher TMB means that there is a higher frequency of gene mutations per coding area of a tumor's genome (10). In the past years, there have been several efforts to assess biomarkers that predict response; however, results have not been consistent, and we could not fulfill the need for an ideal accurate biomarker.

Overall, 40-62% penile SCC express ≥1% PD-L1 on tumor or infiltrating immune cells (5); consequently, pembrolizumab might be a reasonable intervention. Still, with the currently available information, it is not possible to determine if this is completely accurate for penile SCC patients. Some authors have hypothesized that benefits occur irrespective of PD-L1 expression (11). Albeit statistically insufficient, this information supports previous evidence gathered from other urologic cancers. Other reports argue that high rates of MSI probably are related to DNA polymerase epsilon (POLE) and delta 1 (POLD) mutations rather than dMMR (12). To date, there is an unmet need for an ideal biomarker that predicts response to checkpoint inhibitors. We need to measure PD-L1 expression consistently and establish if TBM is a good surrogate marker for evaluating microsatellite instability. Furthermore, we could determine if POLE and POLD mutations are relevant.

In conclusion, we found a very scarce data, specifically only a few reports, but showing promising results for using pembrolizumab in advanced penile cancer patients. More trials need to be done to establish objective response and progression-free survival.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Montes Cardona CE, García-Perdomo HA. Incidence of penile cancer worldwide: systematic review and meta-analysis. Rev Panam Salud Publica. 2017;41:e117.
2. Thomas A, Necchi A, Muneer A, Tobias-Machado M, Tran ATH, Van Rompuy AS, et al. Penile cancer. Nature Reviews Disease Primers. Nature Research; 2021;7:1-24.
3. Azizi M, Aydin AM, Hajiran A, Lai A, Kumar A, Peyton CC, et al. Systematic Review and Meta-Analysis-Is there a Benefit in Using Neoadjuvant Systemic Chemotherapy for Locally Advanced Penile Squamous Cell Carcinoma? J Urol. 2020;203:1147-55.
4. Marabelle A, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. 2020;21:1353-65.
5. Udager AM, Liu TY, Skala SL, Magers MJ, McDaniel AS, Spratt DE, et al. Frequent PD-L1 expression in primary and metastatic penile squamous cell carcinoma: potential opportunities for immunotherapeutic approaches. Ann Oncol. 2016;27:1706-12.
6. Hahn AW, Chahoud J, Campbell MT, Karp DD, Wang J, Stephen B, et al. Pembrolizumab for advanced penile cancer: a case series from a phase II basket trial. Invest New Drugs. 2021;39:1405-10.
7. Chahoud J, Skelton WP 4th, Spiess PE, Walko C, Dhillon J, Gage KL, et al. Case Report: Two Cases of Chemotherapy Refractory Metastatic Penile Squamous Cell Carcinoma With Extreme Durable Response to Pembrolizumab. Front Oncol. 2020;10:615298.
8. Subbiah V, Solit DB, Chan TA, Kurzrock R. The FDA approval of pembrolizumab for adult and pediatric patients with tumor mutational burden (TMB) ≥10: a decision centered on empowering patients and their physicians. Ann Oncol. 2020;31:1115-8.
9. Gu W, Zhu Y, Ye D. Beyond chemotherapy for advanced disease-the role of EGFR and PD-1 inhibitors. Transl Androl Urol. 2017;6:848-54.
10. Ahmed ME, Falasiri S, Hajiran A, Chahoud J, Spiess PE. The Immune Microenvironment in Penile Cancer and Rationale for Immunotherapy. J Clin Med. 2020;9:3334.
11. Buonerba C, Scafuri L, Costabile F, D'Ambrosio B, Gatani S, Verolino P, et al. Immune checkpoint inhibitors in penile cancer. Future Sci OA. 2021;7:FSO714.
12. Sardana R, Mishra SK, Williamson SR, Mohanty A, Mohanty SK. Immune checkpoints and their inhibitors: Reappraisal of a novel diagnostic and therapeutic dimension in the urologic malignancies. Semin Oncol. 2020;47:367-79.

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UPDATE IN UROLOGY

UROANATOMY

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Editorial Comment: Penile Transplantation: Lessons Learned and Technical Considerations

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COMMENT

Penile amputation is an extremely serious and crippling condition with terrible repercussions for patients. Reconstruction techniques are little studied in the literature due to the limited number of cases and the results are not very reproducible (1, 2). Penile transplantation is a very good option although there are few reports of success. The present paper is very important and shows a very nice review about penile transplantation. During the paper we can observe the great importance of penile anatomy knowledge for this surgery. The paper has amazing original schematic drawings about penile vascular anatomy.

This paper shows the penile arteries collateral circulation and the vascularization of the perineal skin - key points to the success of penile transplantation. The authors show the vascular anastomosis of the 4 cases of penile transplantation in literature in a very beautiful figure.

The paper concludes that penile allotransplantation represents a revolutionary technique in the management of penile loss. The inclusion of external pudendal artery anastomoses appears to have prevented any form of penile skin necrosis and anastomosis of the corpora cavernosa appears sufficient for restoration of erectile function independent of the cavernous artery.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Wang P, Luo Y, Li YF, Zhang Y, Bi G, Jin DC, et al. Microscopic Replantation of Complete Penile Amputation With Video Demonstration. Urology. 2022:S0090-4295(22)00225-4.
2. Wu Q, Liu L, Yang Z, Ma N, Wang W, Li YQ. Significance and Surgical Options for Nontranssexual Phalloplasty: A Retrospective Single-Center Analysis of 166 Patients. Ann Plast Surg. 2022;88:440-5.

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UPDATE IN UROLOGY

UROANATOMY

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Editorial Comment: Validity of a patient-specific percutaneous nephrolithotomy (PCNL) simulated surgical rehearsal platform: impact on patient and surgical outcomes

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COMMENT

In the past the endocast model confection was the most important method to study the intra-renal anatomy in humans and in anatomic models (1-4). Technological Advances in last year's provide a great advance in the development of simulators for surgical training and recently in the Int Braz J Urol some papers studied this kind of translational anatomical studies (5).

Percutaneous nephrolithotomy training using simulation is very important to the young urologists and to all surgeons who can have multiple attempts and opportunity for trial-and-error learning. In the present paper the authors evaluate the impact of preoperative high-fidelity patient-specific percutaneous nephrolithotomy hydrogel simulations on surgical and patient outcomes using amazing figures.

This paper shows the importance of the translational research and anatomy for urological practice and for the training of urologists. The authors conclude that patient-specific procedural rehearsal

is effective reducing the experience curve for a complex endourological procedure, resulting in improved surgical performance and patient outcomes.

The paper concludes that penile allotransplantation represents a revolutionary technique in the management of penile loss. The inclusion of external pudendal artery anastomoses appears to have prevented any form of penile skin necrosis and anastomosis of the corpora cavernosa appears sufficient for restoration of erectile function independent of the cavernous artery.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Sobrinho ULGP, Albero JRP, Becalli MLP, Sampaio FJB, Favorito LA. Three-dimensional printing models of horseshoe kidney and duplicated pelvicalyceal collecting system for flexible ureteroscopy training: a pilot study. Int Braz J Urol. 2021;47:887-9.
2. Marroig B, Favorito LA, Fortes MA, Sampaio FJ. Lower pole anatomy and mid-renal-zone classification applied to flexible ureteroscopy: experimental study using human three-dimensional endocasts. Surg Radiol Anat. 2015;37:1243-9.
3. Marques-Sampaio BP, Pereira-Sampaio MA, Henry RW, Favorito LA, Sampaio FJ. Dog kidney: anatomical relationships between intrarenal arteries and kidney collecting system. Anat Rec (Hoboken). 2007;290:1017-22.
4. Pereira-Sampaio M, Favorito LA, Henry R, Sampaio FJ. Proportional analysis of pig kidney arterial segments: differences from the human kidney. J Endourol. 2007;21:784-8.
5. Marroig B, Fortes MA, Pereira-Sampaio M, Sampaio FJ, Favorito LA. Two-part silicone mold. A new tool for flexible ureteroscopy surgical training. Int Braz J Urol. 2016;42:850-1.

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VIDEO SECTION

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Corporoplasty: A simplified technique for clitoroplasty

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ABSTRACT

Introduction: Clitoroplasty constitutes an important step in feminizing surgery for congenital adrenal hyperplasia (CAH) (1). In this video we present a technique that aims to preserve clitoral sensitivity and engorgement while minimizing the risk of neurovascular lesion.
Materials and methods: We present a video of a three-year-old girl with history of CAH classical form, PRADER-III, who underwent clitoroplasty. After an initial endoscopic evaluation of the urogenital sinus, the clitoris was degloved and a rectangular incision was made on the ventral corpora cavernosa 15mm above the corpora bifurcation and 0.5 mm below the coronal sulcus. The cavernous tissue was partially resected. The upper and lower borders of the rectangular gap were closed by a 5-0 PDS running suture similar to the Mikulicz technique. Next, the edge of the glans was deepithelialized to reduce its size. For improved clitoral positioning, the clitoris was sutured to the pubic fat. From that point onward the procedure followed that of a standard vaginoplasty using the en-bloc technique (2-4). Thus far we have performed this technique in 33 patients, with 31 of them being girls with CAH and 2 being women with clitoral hypertrophy.
Conclusion: Corporoplasty is a simplified technique for clitoroplasty, with the advantage being that is faster and safer than the technique that involves the dissection of the neurovascular bundle. In addition, corporoplasty has the possible benefit of preserving the cavernosal blood flow that permits the engorgement of the clitoris during sexual arousal.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. J. M. Hutson, R. W. Voigt, Meera Luthra, J. H. Kelly, R. Fowler. Girth-reduction clitoroplasty — a new technique: experience with 37 patients. Pediatric Surgery International 1991, 6:336-340.
2. Gonzalez R, Fernandes ET. Single-stage feminization genitoplasty. J Urol. 1990; 143:776-8.
3. Ludwikowski B, Oesch Hayward I, González R. Total urogenital sinus mobilization: expanded applications. BJU Int. 1999; 83:820-2.
4. Rink RC, Adams MC. Feminizing genitoplasty: state of the art. World J Urol. 1998; 16:212-8.

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VIDEO SECTION

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Da Vinci SP radical prostatectomy: a multicentric collaboration and step-by-step techniques

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ABSTRACT

Introduction: Several techniques of robotic-assisted radical prostatectomy (RARP) using the da Vinci SP (SP) have been described since its clearance by the FDA (Food and Drug Administration) in 2018 (1, 2). Even with the expanding literature about this robot, the SP technology has been restricted to a few centers in the US and Asia due to the recent release of this robot in the marked.3 In this scenario, we provided, in this video compilation, a consensus of SP referral centers describing the current approaches and techniques of da Vinci SP Radical prostatectomy (SP-RARP).
Surgical Technique: We have illustrated five different techniques, including transperitoneal, extraperitoneal, Retzius-sparing, transvesical, and transperineal (4-6). Each surgery demonstrated crucial steps from the trocar placement until anastomosis. All approaches follow anatomic concepts and landmarks to minimize positive surgical margins, optimize oncological outcomes and promote optimal functional recovery. The trocar placement and the use of an assistant port were selected according to the operative technique of each institution. None of these surgeries had intra- or postoperative complications, and the pain management until discharge was controlled without using narcotics. All patients were discharged in less than 16 hours of surgery.
Conclusion: Robotic-assisted radical prostatectomy performed with the da Vinci SP is feasible and safe with optimal perioperative outcomes. Five different approaches were described in this video compilation, and we believe that the technical details provided by this multicentric collaboration are crucial for centers willing to initiate the SP approach to radical prostatectomy.

COMPLIANCE WITH ETHICAL STANDARDS

Dr. Jihad Kaouk is a speaker Bureau for Intuitive Surgical. Dr. Simone Crivellaro is consultant for Intuitive Surgical.

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CONFLICT OF INTEREST

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REFERENCES

1. Covas Moschovas M, Bhat S, Rogers T, Thiel D, Onol F, Roof S, et al. Applications of the da Vinci single port (SP) robotic platform in urology: a systematic literature review. Minerva Urol Nephrol. 2021;73:6-16.
2. Moschovas MC, Seetharam Bhat KR, Onol FF, Rogers T, Ogaya-Pinies G, Roof S, et al. Single-port technique evolution and current practice in urologic procedures. Asian J Urol. 2021;8:100-4.
3. Garisto J, Bertolo R, Reese SW, Bove P, Kaouk J. Minimizing minimally invasive surgery: Current status of the single-port robotic surgery in Urology. Actas Urol Esp (Engl Ed). 2021;45:345-52. English, Spanish.
4. Covas Moschovas M, Kind S, Bhat SK, Noel J, Sandri M, Rogers TP, et al. Implementing the da Vinci SP® without increasing positive surgical margins: experience and pathological outcomes of a prostate cancer referral center. J Endourol. 2021;29. Epub ahead of print.
5. Bassett JC, Salibian S, Crivellaro S. Single-Port Retzius-Sparing Robot-Assisted Radical Prostatectomy: Feasibility and Early Outcomes. J Endourol. 2022; 12. Epub ahead of print.
6. Kaouk J, Sawczyn G, Wilson C, Aminsharifi A, Fareed K, Garisto J, et al. Single-Port Percutaneous Transvesical Simple Prostatectomy Using the SP Robotic System: Initial Clinical Experience. Urology. 2020;141:173-7.

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LETTER TO THE EDITOR

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Re: Can Concomitant Bladder Neck Incision and Primary Valve Ablation Reduce Early Re-admission Rate and Secondary Intervention?

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To the editor,

Is it necessary to perform a bladder neck incision (BNI) in patients with a posterior urethral valve (PUV)? In this edition of the International Brazilian Journal of Urology, Abdelhalim et al. (1) addresses this question and thereby adds data to the literature concerning this topic.

Some studies have demonstrated that PUV ablation + BNI can be more effective than ablation alone (2, 3). In a randomized control trial by Singh et al, PUV ablation + BNI was more effective than PUV ablation alone in terms of achieving maximal urinary flow and the reduction of post-void residual but was similar not only regarding other urodynamic parameters such as compliance, bladder capacity, and detrusor overactivity but also in the resolution of vesicoureteral reflux (2). Kajbafzadeh et al., in a study regarded by the authors as prospective, found a lower rate of reintervention, less use of anticholinergics, and less need for CIC in the group with PUV ablation + BNI compared with the PUV ablation alone group. (2) The study by Kajbafzadeh et al, however, does not make clear what were the selection criteria for one treatment or the other.

The major limitation of the two studies is the fact that the group undergoing PUV ablation alone did not systematically use alpha1-blockers. In the study by Singh et al, only about 20% of patients used alpha-blockers in the control group (PVU ablation alone) (2), while in the study by Kajbafzadeh et al et al this information is not given, though it seems clear that the use of alpha-blockers was not part of the study protocol (3).

On the other hand, Abdelhalim et al. (1) have shown that there is no need to perform BNI together with PUV ablation, since patients who underwent BNI had the same reoperation rate as those who underwent PUV alone. Other studies have not shown a significant difference in urodynamic improvement in the BNI + PUV ablation group (4).

The main reason for not performing BNI together with PUV ablation is the lack of studies that have been completed that compare this procedure with the use of alpha 1 blockers of the bladder neck. Since there is no current study that shows the superiority of BNI over alpha-blockers, this procedure should not be used routinely. As an example, Androulakakis et al. reported on 5 patients with underactive bladder secondary to PUV being treated successfully, one by BNI and 4 with alpha-blockers, which demonstrates the efficacy of this medication (5). Others have reported satisfactory results with alpha-blockers in patients with VUP (6).

We routinely use alpha-blockers such as doxazosin, 1mg, even before a patient's first year of life; however, this does not mean that BNI is contraindicated. Some patients will not respond well to this medication and will exhibit high post-voiding residue, recurrent urinary tract infection, or worsening renal function. These are the cases in which we opted for BNI at the same time as we performed a cystoscopy to review a possible valve persistence.

Patients with a posterior urethral valve most often have a hypertrophied bladder neck. The justification for not performing BNI, which concerns the risk of retrograde ejaculation or urinary incontinence, does not seem to be supported by medium-term studies (5, 6). BNI is a well-tolerated procedure without any significant increased risk of bleeding, increased postoperative pain, longer hospital stays, or significant cost increases.

In conclusion, based upon the interpretation of the literature, PUV ablation can be performed alone without additional procedure; however, the valve bladder must be aggressively treated with alpha-blockers and oxybutynin most of the time. In the future, BNI may be necessary in cases of unfavorable evolution.

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CONFLICT OF INTEREST

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REFERENCES

1. Abdelhalim A, Hashem A, Abouelenein EE, Atwa AM, Soltan M, Hafez AT, et al. Can Concomitant Bladder Neck Incision and Primary Valve Ablation Reduce Early Re-admission Rate and Secondary Intervention? Int Braz J Urol. 2022;48:485- 92.
2. Singh SK, Sharma V, Singh A. Urodynamic Changes after Valve Fulguration Alone and Valve Fulguration with Bladder Neck Incision. J Indian Assoc Pediatr Surg. 2019;24:31-5.
3. Kajbafzadeh AM, Payabvash S, Karimian G. The effects of bladder neck incision on urodynamic abnormalities of children with posterior urethral valves. J Urol. 2007;178:2142-7; discussion 2147-9.
4. Sarin YK, Sinha S. Efficacy of bladder neck incision on urodynamic abnormalities in patients with posterior urethral valves. Pediatr Surg Int. 2013;29:387-92.
5. Androulakakis PA, Karamanolakis DK, Tsahouridis G, Stefanidis AA, Palaeodimos I. Myogenic bladder decompensation in boys with a history of posterior urethral valves is caused by secondary bladder neck obstruction? BJU Int. 2005;96:140-3.
6. Combs, Andrew J, Horowitz, Mark, Glassberg, Kenneth I. Secondary bladder neck obstruction in boys with a history of posterior urethral valve: revisited. J Urol. 2009; 4(suppl): 171.

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LETTER TO THE EDITOR

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Re: Percutaneous tibial nerve stimulation versus electrical stimulation with pelvic floor muscle training for overactive bladder syndrome in women: results of a randomized controlled study

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To the editor,

I thank the authors of "Percutaneous tibial nerve stimulation versus electrical stimulation with pelvic floor muscle training for overactive bladder syndrome in women: results of a randomized controlled study (1)." I support the importance you attribute to intravaginal electrical stimulation (IVES) and percutaneous tibial nerve stimulation (PTNS) in the management of idiopathic overactive bladder (OAB). The authors stated that PTNS is more effective than IVES in women with idiopathic OAB. Women with antimuscarinic naive OAB were included in this study (1). However, it is known that many patients with idiopathic OAB receive pharmacological treatment before reaching a conservative treatment option such as IVES. As the authors stated, in common practice, antimuscarinic agents are frequently used as an initial treatment although burdened by a low adherence, and these patients need protracted treatment with periodic controls.

First-line or third-line?

What is the ranking of IVES and PTNS among the treatment options in patients with idiopathic OAB? Some authors listed the treatment options in idiopathic OAB as follows; first-line - behavioral therapy (lifestyle modifications, pelvic floor muscle training, bladder training, timed voiding), second--line - pharmacologic (antimuscarinic, beta-3 agonists), and third-line - neuromodulation/chemodenervation (PTNS, sacral neuromodulation, intradetrusor botulinum toxin). IVES is involved in pelvic floor muscle training as a first-line treatment option (2). On the contrary, some authors stated that "the first-line treatment of idiopathic OAB includes behavior modification and physical therapy, and neuromodulation methods are used as third-line therapy in cases refractory to first-line and second-line (pharmacological) treatment. IVES, PTNS, and sacral neuromodulation are included as neuromodulation options" (3, 4). Furthermore, as you know, some studies included subjects not using antimuscarinics within the last 4 weeks or antimuscarinic-naive patients with OAB (1, 5), while some included patients with OAB who were unresponsive or intolerant to antimuscarinics (3).

As a result, IVES and PTNS appear to be effective therapies used both as first-line treatment, as well as in managing refractory patients with idiopathic OAB. This needs to be expressed more clearly. Would it be more effective on the first line or the third line? or in other words; is there a difference in response to IVES and PTNS in antimuscarinic naive and refractory patients with OAB? Clarification

of the ranking of both PTNS and IVES among treatment options in patients with OAB will be possible with the increase of qualified studies addressing this issue. This would make it easier to understand the rankings of IVES and PTNS among treatment options in patients with idiopathic OAB.

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CONFLICT OF INTEREST

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REFERENCES

1. Scaldazza CV, Morosetti C, Giampieretti R, Lorenzetti R, Baroni M. Percutaneous tibial nerve stimulation versus electrical stimulation with pelvic floor muscle training for overactive bladder syndrome in women: results of a randomized controlled study. Int Braz J Urol. 2017; 43:121-6.
2. Kasman A, Stave C, Elliott CS. Combination therapy in overactive bladder-untapped research opportunities: A systematic review of the literature. Neurourol Urodyn. 2019; 38:2083-92.
3. Wang S, Lv J, Feng X, Lv T. Efficacy of Electrical Pudendal Nerve Stimulation versus Transvaginal Electrical Stimulation in Treating Female Idiopathic Urgency Urinary Incontinence. J Urol. 2017; 197:1496-1501.
4. La Rosa VL, Platania A, Ciebiera M, Garzon S, Jedra R, Ponta M, et al. A comparison of sacral neuromodulation vs. transvaginal electrical stimulation for the treatment of refractory overactive bladder: the impact on quality of life, body image, sexual function, and emotional well-being. Prz Menopauzalny. 2019; 18:89-93.
5. Firinci S, Yildiz N, Alkan H, Aybek Z. Which combination is most effective in women with idiopathic overactive bladder, including bladder training, biofeedback, and electrical stimulation? A prospective randomized controlled trial. Neurourol Urodyn. 2020; 39:2498-508.

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