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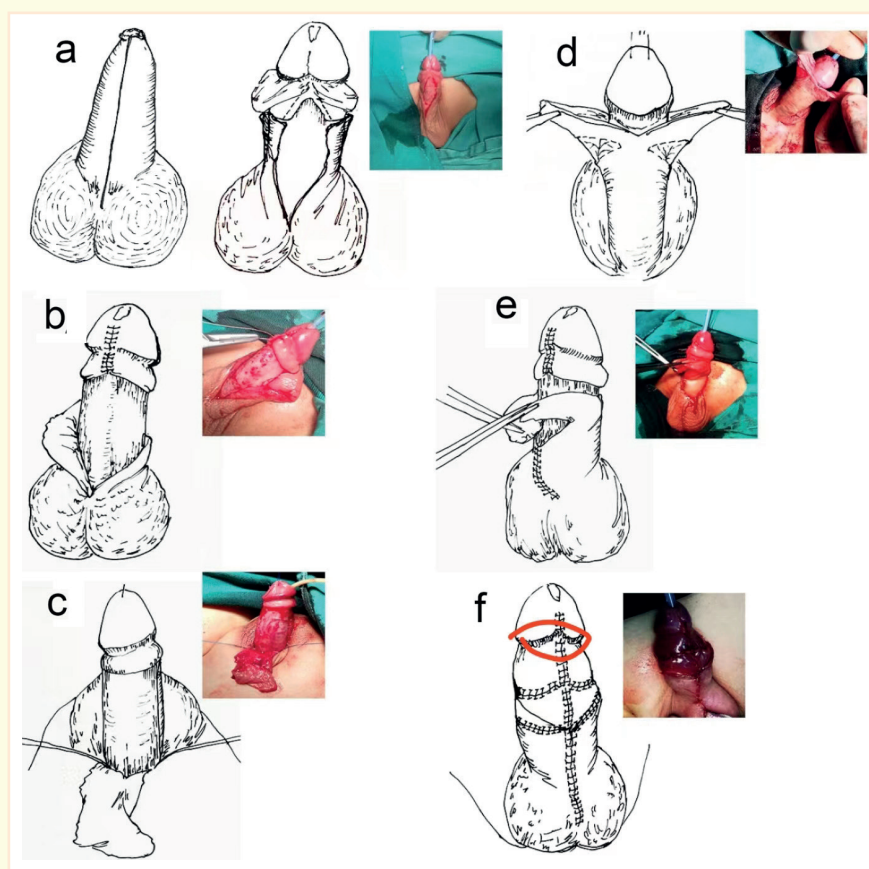


Diagram of surgical steps and Intraoperative picture. (Page 743)

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New perspectives of robotic surgery are the topic highlighteted in International Brazilian Journal of Urology

Luciano A. Favorito^{1,2}

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The Novermber-December number of *Int Braz J Urol* is the 25nd under my supervision. In this number the Int Braz J Urol presents original contributions with a lot of interesting papers in different fields: Robotic Surgery, Prostate Cancer, Bladder Cancer, Ureteral stones, UPJ obstruction, Bladder dysfunction, Concealed Penis, Renal cell Carcinoma, Systematic review and Metanalysis. The papers came from many different countries such as Brazil, USA, Spain, Iran, Italy, Germany and China, and as usual the editor's comment highlights some of them. The editor in chief would like to highlight some papers in this number, specially the papers about robotic surgery:

Dr. Belkovsky and colleagues from Brazil, presented in page 668 (1) a nice systematic review about expulsive therapy for distal ureteral stones with Tamsulosin and Tadalafil and concluded that Tadalafil has a higher stone expulsion rate than tamsulosin as a medical expulsive therapy for patients with distal stones from 5 to 10 mm without differences in side effects.

Dr. Moschovas and colleagues from USA, presented in page 677 (2) a important systematic review about the Outcomes of Salvage Robotic-assisted Radical Prostatectomy in the last decade and concluded that salvage robotic-assisted radical prostatectomy in patients with cancer recurrence after previous prostate cancer treatment is safe and feasible. The literature is based on retrospective studies with inherent limitations describing low rates of intraoperative complications and small blood loss. However, potency and continence rates are largely reduced compared to the primary RARP series, despite the type of the primary treatment. Better-designed studies to assess the long-term outcomes and individually specify each primary therapy impact on the salvage treatment are still needed. Future articles should be more specific and provide more details regarding the previous therapies and S-RARP surgical techniques.

Dr. Nunes and Colleagues from Brazil performed in page 688 (3) a nice study about the Association between rectal diameter and response to treatment with parasacral transcutaneous electrical nerve stimulation and behavioral changes in children and adolescents with bladder and bowel dysfunction and concluded that rectal diameter appears to be relevant in the evaluation of children with BBD, not only as a diagnostic tool but also as a predictor of treatment outcome.

Dr. da Silva and Colleagues from Brazil performed on page 700 (4) an interesting study about the Dynamic and static ultrasound (DSUS) features predictive of vesicoureteral reflux (VUR) and renal damage in children and adolescents with neurogenic bladder and concluded that DSUS predicts VUR and renal scarring in children with NB with fair to good accuracy, and all measurements exhibited a high negative predictive value (NPV). The increase in RPD during voiding or detrusor contractions proved to

be the most accurate parameter for indicating the presence of VUR in this study.

Dr. Chen and Colleagues from China performed on page 716 (5) a nice study about the Head-to-head comparisons of enhanced CT, 68Ga-PSMA-11 PET/CT and 18F-FDG PET/CT in identifying adverse pathology of clear-cell renal cell carcinoma and concluded that 68Ga-PSMA-11 PET/CT demonstrates distinct advantages in identifying aggressive pathological features of primary clear-cell renal cell carcinoma (ccRCC) when compared to enhanced CT and 18F-FDG PET/CT. Further research and assessment are warranted to fully establish the clinical utility of 68Ga-PSMA-11 PET/CT in ccRCC.

Dr. Bertolo and colleagues from Italy performed on page 732 (6) a nice comparative analysis of perioperative outcomes about “Single-Surgeon” versus “Dual-Surgeon” in Robot-Assisted Radical Prostatectomy (RARP) and Pelvic Lymph-nodes Dissection (PLND) and concluded that when RARP and PLND are split onto two surgeons, the operative time is shorter by 20 minutes compared to when a single surgeon performs RARP and PLND.

Dr. Jing and colleagues from China performed on page 740 (7) an study about a new treatment of concealed penis: symmetrical pterygoid flap surgery, this paper is the cover of the present edition. The authors concluded that the symmetrical pterygoid flap surgery is an effective surgical technique for the management of concealed penis in children producing predictable results and excellent satisfaction of the parents and patients.

Dr. Benzi and colleagues from Brazil performed on page 749 (8) a interesting translational study about the Fowler-Stephens surgery and concluded that the upper portion of the abdominal testis in human fetuses had a higher concentration of vessels than the lower portion. These results suggest that manipulation of the lower end of the testis during Fowler-Stephens surgery should be avoided in order to preserve the collateral circulation.

Dr. Ditunno and Colleagues from Italy performed on page 757 (9) a nice report about your experience in Single Port (SP) Robotic Pyeloplasty and concluded that the observed outcomes and potential benefits, combined with the adaptability of the SP platform, hold promising implications for the application of SP system in pyeloplasty treatment.

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

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CONFLICT OF INTEREST

None declared.

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Urological impact of race-free estimated glomerular filtration rate equations

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COMMENT

ForHistorically, estimated glomerular filtration rate (eGFR) have used equations that include a correction factor for race. This correction factor was introduced based on observed differences in serum creatinine levels between individuals of different races, with higher levels generally seen in people of African ancestry. However, in recent years there has been growing concern that the use of race as a factor in GFR calculations may not accurately reflect an individual's kidney function since we typically only use "Black" or "Non-black" as their racial categories and we know that this simplification does not reflect the real ethnic diversity of the global population (1).

In response to this context, the National Kidney Foundation and American Society of Nephrology Task Force recommended "race-free" eGFR calculations, and the two main formulas used to calculate the glomerular filtration rate – Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) – have been modified. The last CKD-EPI equation, adopted in 2021, does not include an adjustment for race and the MDRD has made the criterion "race" optional in calculating GFR. These changes carry substantial implications for Black African ancestry patients (2).

Although the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) opposes such a change in the calculation, the current race coefficient has been shown to be inapplicable to Black populations outside the USA, like in Europe, Africa, and Brazil. In these areas, the CKD-EPI equation without the race coefficient demonstrated better performance than the MDRD equation with the race coefficient (3, 4).

Most research studies to date that have evaluated the consequence of removing the race adjustment form the eGFR calculation formulas are simulations of alternative approaches that estimate the number of Black adults potentially affected by shifting eGFR across thresholds commonly used for clinical decision making. For CKD screening, it could increase the number of Black adults

meeting a threshold by 16% to >100% (local vs national studies) and the number of Black adults meeting eGFR <30 mL/min/1.73m² by up to 52%, with potential benefit or harm resulting from an increased diagnosis or overdiagnosis, respectively. It could also increase by 29%-52% the number of Black adults being eligible for Medicare's medical nutrition or kidney disease education benefit, vascular access referral, or transplant referral (5-7).

For patients with cancer, it would impact the cross-sectional imaging in diagnosing or staging and the type of urinary diversion following cystectomy, increasing the number of Black individuals ineligible for chemotherapy or those recommended to receive less than a full dose or a potentially less accurate dose adjustment (by 61%-163%) for several chemotherapies, which may lead to decreased quality of life and survival (8), thereby worsening the already prevalent racial disparities in healthcare. Furthermore, this might intensify the ongoing issue of underrepresentation by potentially increasing the exclusion of Black patients from clinical trials (9).

Another implication might be related to the disparity on potential kidney donors and qualification for renal transplantation, differences between race-based and race-free es-

timates might lead to disparate exclusion of donor candidates, increasing the exclusion of Black donor candidates (10).

Race-free eGFR equations have higher bias and lower agreement between measured and estimated GFR categories, compared to their predecessors. While the process for reporting race is not entirely clear, race can represent a genetically and socially heterogeneous group and race in eGFR equations bring a social and a biologic construct where race coefficients among the global ancestry proportions determines the genetic ancestry in percentage derived from genome-scale genetic data (11).

Considering the impact of the new guidelines on clinical decision making, we expect to see more data comparing old and new approaches. Is it time to review the treatment of patients who fit the old criteria? Or should we insist on adjusting GFR equations by exploring more ethnic diversity? Whatever the opinion, randomized trials are needed to compare patients who have changed classification with the new GFR equations and understand how they perform.

CONFLICT OF INTEREST

None declared.

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Tamsulosin vs. Tadalafil as medical expulsive therapy for distal ureteral stones: a systematic review and meta-analysis

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ABSTRACT

Purpose: Medical expulsive therapy (MET) is recommended for distal ureteral stones from 5 to 10 mm. The best drug for MET is still uncertain. In this review, we aim to compare the effectiveness of tadalafil and tamsulosin for distal ureteral stones from 5 to 10 mm in terms of stone expulsion rate (SER), stone expulsion time (SET) and the side effect profile.

Materials and methods: A comprehensive literature search was conducted on MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Scopus and Web of Science, from inception until April 2023. Only randomized controlled trials were included in the analysis.

Results: Eleven publications with 1,330 patients were included. We observed that tadalafil has a higher SER (OR 0.55, CI 95% 0.38;0.80, p=0.02, I²=52%) and the same efficacy in SET (MD 1.07, CI 95% -0.25; 2.39, p=0.11, I²=84%). No differences were found when comparing side effects as headache, backache, dizziness, and orthostatic hypotension.

Conclusion: Tadalafil has a higher stone expulsion rate than tamsulosin as a medical expulsive therapy for patients with distal stones from 5 to 10 mm without differences in side effects.

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INTRODUCTION

Nephrolithiasis is one of the most common diagnosed urinary diseases that mostly affects individuals between the ages of 20–40 years. The clinical presentation may include colic pain, urinary symptoms, nausea, and vomiting. Ureteral stones account for 22% of nephrolithiasis cases, with 68% being distal ureteral stones (1).

Medical Expulsive Therapy (MET) is recommended for distal stones measuring 5 to 10 mm to reduce the risk of surgical intervention and reduce the stone expulsion time (2). MET involves the use of medications that facilitate stone passage by relaxing smooth muscle, with α -blockers, phosphodiesterase inhibitors (PDEIs), and calcium channel blockers among the commonly employed drugs (3). Nowadays, α -blockers, such as tamsulosin, are the preferred option for MET. This recommendation, however, is based on conflicting evidence that shows limited benefits (4–6).

Network meta-analysis compared multiple alternatives for MET and, interestingly, silodosin, also an α -blocker, seems to have the best performance as monotherapy. However, these analyses are restricted to limited number of outcomes, usually only stone expulsion rate (SER) and stone expulsion time (SET) and leave uncertain the safety profile of this interventions (7, 8).

Tadalafil, a more accessible drug, but a PDEI, has also been proposed as a viable alternative for MET. Studies and meta-analysis that compared tadalafil and tamsulosin for the treatment of distal ureteral stones from 5 to 10 mm have shown conflicting results (9, 10). The last meta-analysis about this subject was published in 2017 with 565 patients. Bai et al. (11) observed that tadalafil outperforms the tamsulosin without differences in side effects.

Given that subsequent trials (1, 12–15) have been conducted since the publication of the meta-analysis, we aim to explore the effects of tadalafil compared to tamsulosin considering new evidence. The purpose of this meta-analysis is to provide an updated assessment of the efficacy and safety of tadalafil versus tamsulosin as medical expulsive therapy for distal ureteral stones measuring 5 to 10 mm.

MATERIALS AND METHODS

Registration and databases search

This study was registered at Prospero CRD42023417044 (Prospero register). A search was conducted at PubMed/MEDLINE, Embase, Web of Science, Scopus, and Cochrane databases from its inception to April 2023 to identify randomized controlled trials reporting the comparison of tadalafil and tamsulosin as medical expulsive therapy for distal stones from 5 to 10mm. Our outcomes of interest were stone expulsion rate, stone expulsion time, pain episodes, analgesic use, and side effects.

Search strategy

Tadalafil and tamsulosin and (stone or stones or nephrolithiasis or calculi or calculus) and (“randomized controlled trial” or “controlled trial” or randomized or placebo or “drug therapy” or randomly or trial or groups).

Screening

EndNote Online™ was utilized to remove any duplicate studies. Two independent researchers conducted a screening of titles and abstracts to eliminate irrelevant studies. Following this process, the full text was reviewed to select the included articles. Any disagreements were solved by a third reviewer.

Data Extraction and Quality Assessment

Data was independently extracted from the included studies by two authors. Any discrepancies among the extracted data were resolved by discussion with a third reviewer. The Rob2 score (16) was used to assess the quality of the RCTs.

Statistical Analyses

The meta-analysis was performed by the Review Manager, version 5.4. Continuous outcomes are presented as a mean difference (MD) with 95% confidence interval (CI). Dichotomous data are presented as odds ratio (OR) with 95% CI. Pooled estimates were calculated with the random-effect model, considering that the pa-

tients came from different populations. We also performed a subgroup analysis of different doses of tadalafil. For all statistical analyses, a two-sided value of $P < 0.05$ was considered statistically significant.

RESULTS

The search retrieved 201 articles. After screening 11 were included in this study (Fig-

ure-1). In total, 1,330 patients were included. Most of the studies followed patients up to 4 weeks. The dosage of tamsulosin was the same across the studies (0.4mg), but 8 studies used 10mg of tadalafil and 3 studies used 5mg. Four studies lacked gender distribution (Table-1).

Stone expulsion

Overall, tadalafil was more efficient regarding our primary outcome (SER) than tamsu-

Figure 1 - Prisma flow diagram.

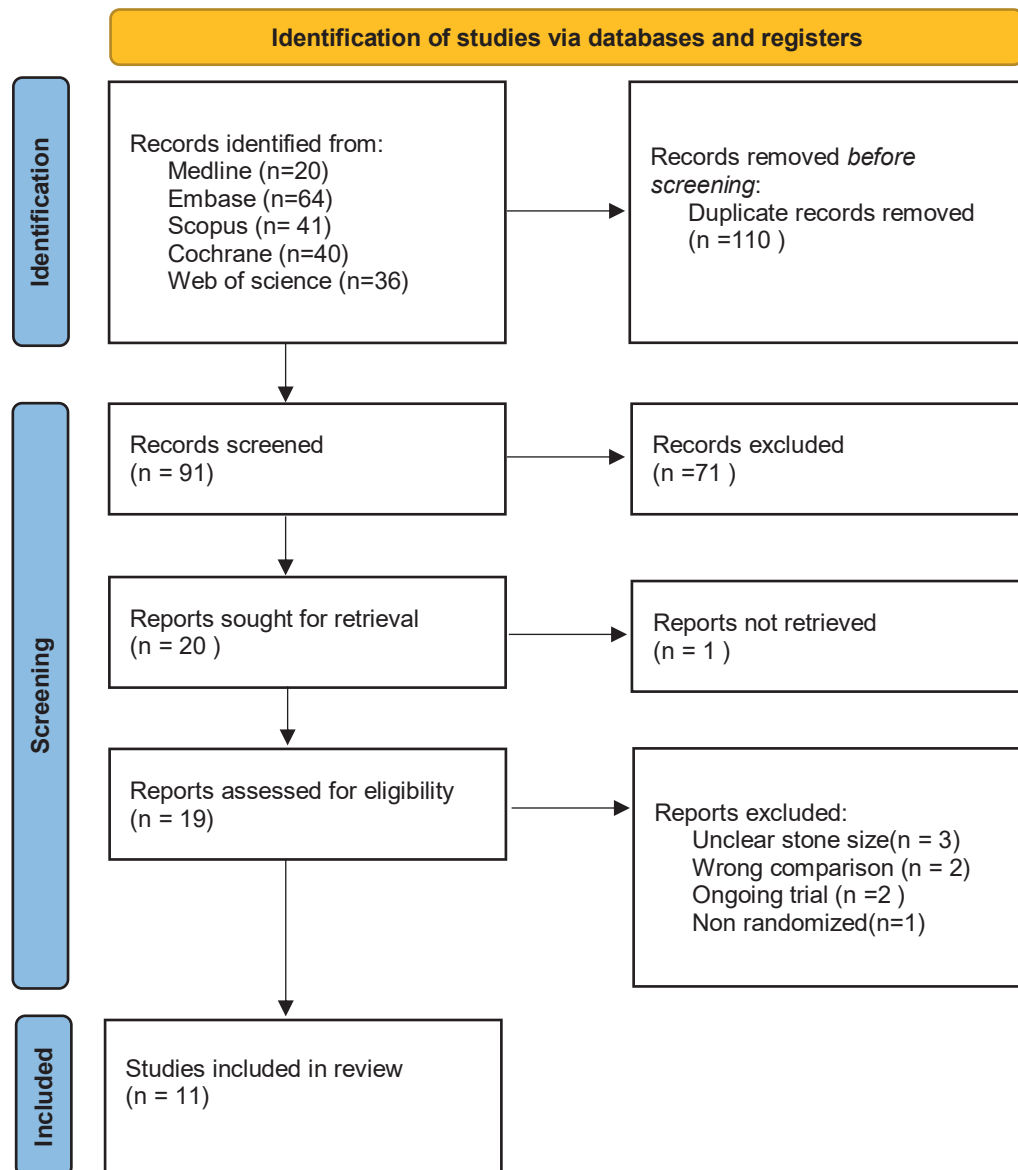


Table 1 - Baseline characteristics of included studies.

Study	Tamsulosin dose (mg)	Tadalafil dose (mg)	Number of patients, Tamsulosin/Tadalafil	Mean age(y)±SD, Tamsulosin/Tadalafil	Males (%), Tamsulosin/Tadalafil	Mean stone size (mm)±SD, Tamsulosin/Tadalafil	Duration (weeks)
Abdelaal et al., (15) 2023	0.4	5	50/50	38.7/41.9 ^c	70/68	6.7±1.3/6.9±1.5	4
Abishek et al., (20) 2015 ^b	0.4	10	50/50	NA	NA	NA	NA
Aggarwal et al., (21) 2017 ^b	0.4	10	109/109	NA	NA	NA	4
Falahatkar et al., (1) 2021	0.4	10	44/44	37.0±11.3/37.3±12	54.5/47.7	6.9±1.5/6.9±1.7	4
Goyal et al., (12) 2018	0.4	10	61/62	42.1±13.9/42.6±14.9	70.5/66.1	7.5±1.1/7.6±0.9	4
Gur et al., (13) 2021	0.4	5	48/46	41±15.9/39.0±12 ^a	100/100	6.2±2.2/6.1±1.6 ^a	NA
KC et al., (22) 2016	0.4	10	41/44	31.4±12/32.1±13.3	65.9/54.5	7.1±1.2/7.1±1.5	2
Khouni et al., (14) 2022 ^b	0.4	5	42/40	NA	NA	NA	6
Kumar et al., (23) 2015	0.4	10	90/90	36.4±10/37.5±13.5	68.9/74.4	7.4±1.2/7.8±1.4	4
Puvvada et al., (24) 2016	0.4	10	100/100	37.5±12.7/36.3±11.3	67/65	7.2±1.3/7.1±1.4	4
Raza et al., (25) 2016 ^b	0.4	10	30/30	NA	NA	NA	4

^a Estimated from median and interquartile range using the Cochrane estimator; ^b Conference abstract; ^c The article did not provided information about age dispersion; RCT: randomized controlled trial; NA: not available.

losin (OR 0.55, CI 95% 0.38;0.80, p=0.02, I2=52%), but no difference was observed in SET (MD 1.07, CI 95% -0.25; 2.39, p=0.11, I2=82%) (Figure-2).

Pain episodes and analgesic use

Only 4 RCT assessed pain episodes, with 292 patients in the tamsulosin group, and 296 patients in the tadalafil group. No statistical significance was observed when comparing pain episodes (OR 0.20 CI 95% -0.38; 0.78, p=0.51, I=94%) or analgesic use (MD 44.46, CI 95% -29.10; 118.01, p=0.24, I=91%) (Figure-3). Regarding analgesic use, all authors used oral diclofenac as analgesic, only KC et al. used aceclofenac.

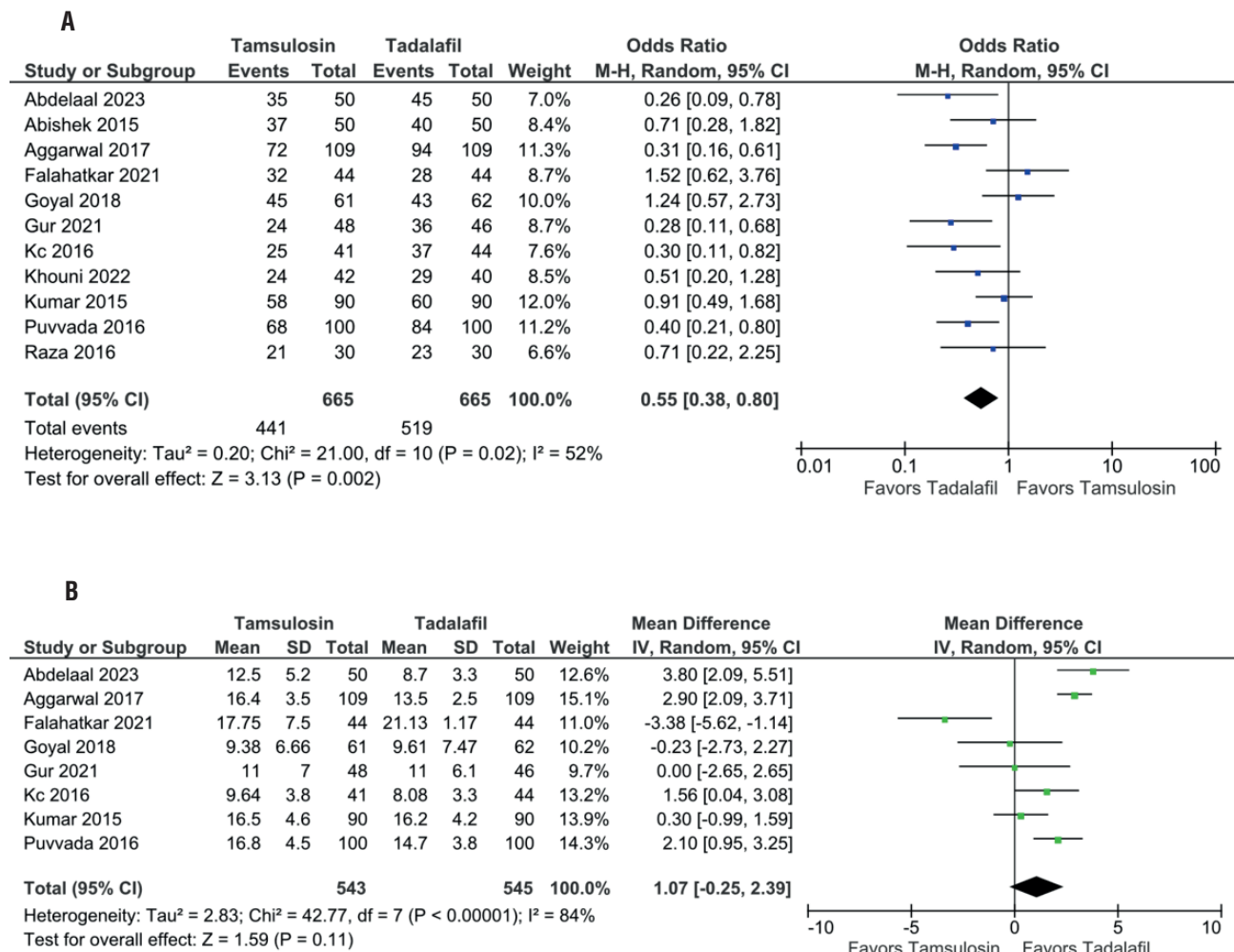
Side effects

No difference was observed among all the assessed side effects. Six studies reported headache (OR 0.68, CI 95% 0.44;1.03, p=0.92, I2=0%), backache (OR 0.83, CI 95% 0.47; 1.45, p=0.51, I2=30%), and orthostatic hypotension (OR 1.23, CI 95% 0.65;2.35, p=0.53, I2=30%) as side effects while only five reported dizziness (OR 0.79, CI 95% 0.49;1.29, p=0.35, I2=0%) (Figure-4).

Subgroup analyses

We performed a subgroup analysis of SER and SET among different doses of tadalafil (5mg and 10 mg) (Appendix-1). We found that the

Figure 2 - Tadalafil vs tamsulosin stone expulsion, higher SER, no difference in SET.



(A) Forest plot of stone expulsion rate. (B) Forest plot of stone expulsion time, CI, confidence interval; SD, standard deviation.

subgroup receiving a 5mg showed a higher benefit in terms of SER (OR 0.34, CI 95% 0.19;0.59, $p=0.0001$, $I^2=0\%$) compared to the subgroup receiving a 10mg dose (OR 0.65, CI 95% 0.42;1.00, $p=0.05$, $I^2= 56\%$). No differences were observed when comparing SET within both subgroups, 5mg (MD 2.04, CI95% -1.67;5.75, $p=0.28$, $I^2=82\%$) and 10mg (MD 0.76, CI95% -0.76;2.27, $p=0.33$, $I^2=86\%$).

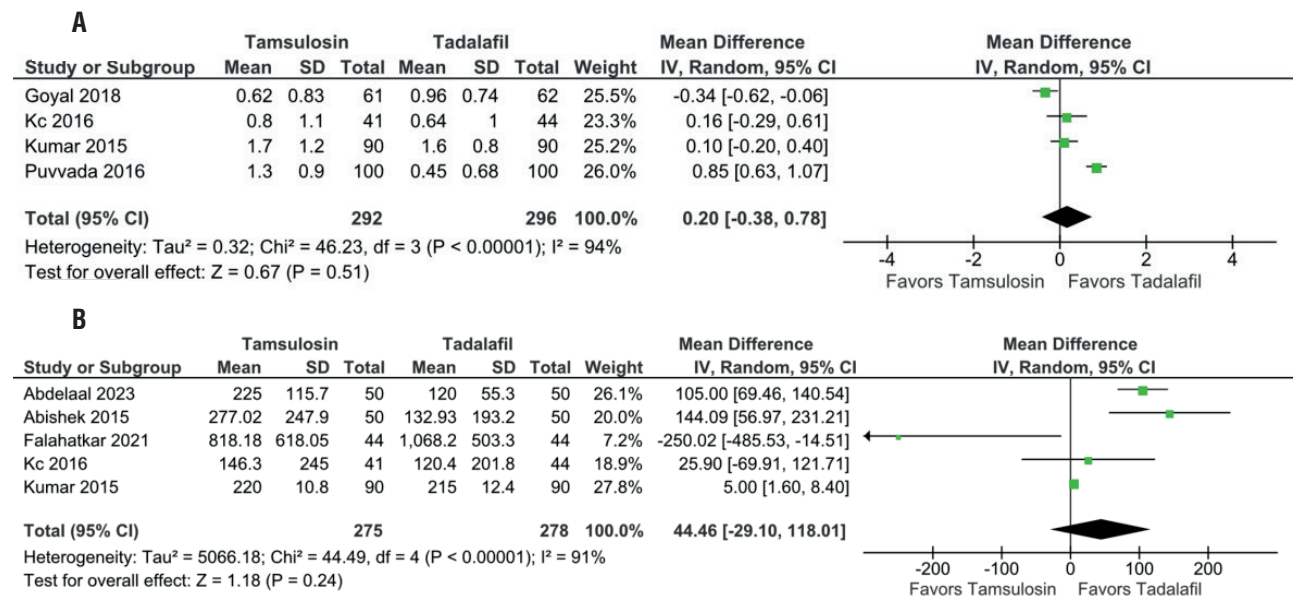
DISCUSSION

Our meta-analysis included 1330 patients from 11 RCTs comparing tamsulosin and tadalafil

in cases with distal ureteral stones from 5 to 10mm. We observed that tadalafil has the same SET and even a greater SER than tamsulosin, without differences in side effects (headache, dizziness, backache, and orthostatic hypotension).

Medical expulsive therapy (MET), typically using α -blockers, is an off-label recommendation, supported by urological societies, to facilitate the passage of distal ureteral stones sized 5-10 mm (2, 3). This recommendation is based on a pooled analysis on 27 studies that shows a SER of 77.3% of α -blockers, compared to 54.4% of placebo (2). However, this recommendation is contentious due to contradictory evidence from randomized con-

Figure 3 - Tadalafil vs tamsulosin no difference in pain episodes or analgesic use.



(A) Forest plot of pain episodes (B) Forest plot of analgesic use. CI, confidence interval; SD, standard deviation.

trolled trials, demonstrating limited benefits of this therapy (4-6). In this regard, tadalafil, has also been suggested as a potential alternative, with concerns about adverse events and uncertainties about its efficacy (17).

The largest previous meta-analysis, conducted by Bai et. al. (11), included 565 patients from 4 RCTs. Bai et. al. described that tadalafil outperforms tamsulosin not only when comparing SER (without differences in side effects) but also when comparing analgesic use and SET. Indeed, the last two comparisons were made applying the fixed effect model. This model is a controversial approach in statistics that increases the chance of false positive results (18). In our study all the comparisons were done using the random effects model.

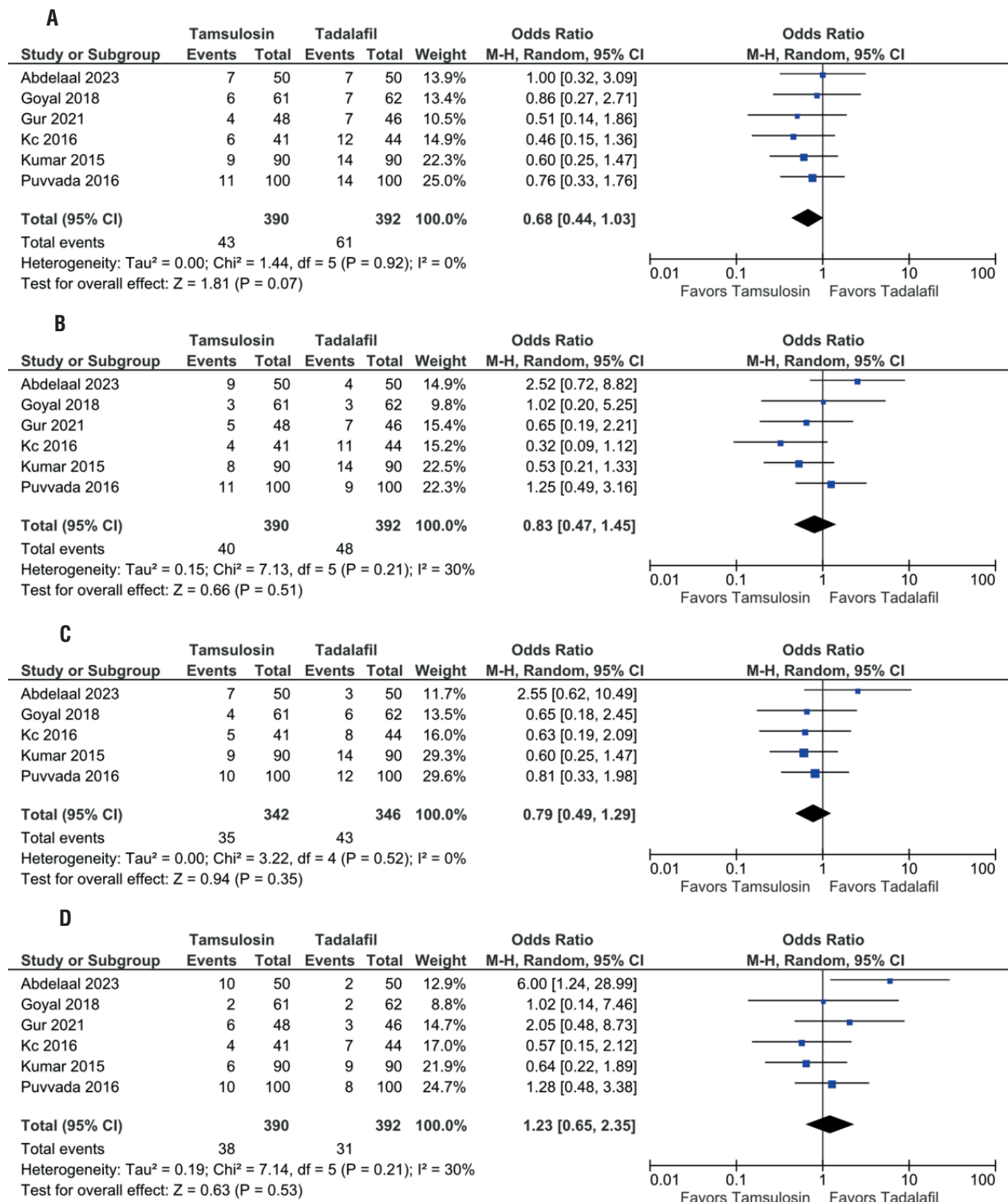
Curiously lower doses of tadalafil seem to be more effective. Even if a statistical artifact seems to be the most reasonable explanation to this finding, as it goes against the dose-response principle, it is also biologically plausible that excessive smooth muscle relaxation can hinder the stone expulsion process, as observed in some studies comparing antispasmodics with placebo (8).

A more modern approach to establish the best MET is the use of network meta-analysis (NMA) (7, 8). The most recent was conducted by Sharma et. al. in 2021 (7). This NMA compared 50 RCTs involving various interventions such as α -blockers, PDEi, and CCB (calcium channel blockers). The outcomes were exclusively SER and SET.

Even if it claimed that the two most effective options for MET are a combination of naftodipil and steroids (resulting in the highest SER) or a combination of tadalafil and silodosin (resulting in the shortest SET) the absence of side effect assessment limits its clinical significance (7). It also included patients with stones smaller than 5mm, which represents a subgroup where the benefits of MET are not clearly established (2, 3). Additionally, the exclusion of conference abstracts from the analysis raises concerns about potential publication bias.

Based on our clinical experience dealing with patients with urological conditions in an ambulatory setting, in Brazil, we observe that MET with tadalafil has a lower cost than MET with tamsulosin and we believe that it could be true for other centers, which strengthens our recommen-

Figure 4 - Tadalafil vs tamsulosin no difference in side effects.



(A) Forest plot of headache episodes. (B) Forest plot of backache episodes. (C) Forest plot of dizziness episodes. (D) Forest plot of the number of orthostatic hypotension episodes. CI, confidence interval; SD, standard deviation.

dation. However, our study lacks a cost-effective analysis as this information was not provided by the included studies.

Our study has limitations. Included articles lacked information regarding time from beginning of the symptoms to introduction of MET, and regarding use of additional medications that could affect the efficacy of the treatment. As a confounding factor, the impact of tadalafil on fre-

Finally, our study leaves unanswered questions as the safety and efficacy of combined therapy with tamsulosin and tadalafil for distal ureteral stones and the ideal dosage of tadalafil for MET.

CONCLUSIONS

Tadalafil has a higher stone expulsion rate than tamsulosin as a medical expulsive therapy

Figure 5 - Risk of bias of the included studies.

<u>Unique ID</u>	<u>D1</u>	<u>D2</u>	<u>D3</u>	<u>D4</u>	<u>D5</u>	<u>Overall</u>		
Abdelaal 2023	+	!	+	+	+	+	+	Low risk
Abishek 2015	!	!	+	+	+	!	!	Some concerns
Aggarwal 2017	!	!	+	+	+	!	-	High risk
Falahatkar 2021	+	!	+	+	+	+		
Goyal 2018	!	!	+	+	+	!	D1	Randomisation process
Gur 2021	!	!	+	+	+	+	D2	Deviations from the intended interventions
Kc 2016	+	!	+	+	+	+	D3	Missing outcome data
Khouni 2022	!	!	+	+	+	!	D4	Measurement of the outcome
Kumar 2015	+	!	+	+	+	+	D5	Selection of the reported result
Puvvada 2016	+	!	+	+	+	+		
Raza 2016	!	!	+	+	+	!		

quency of sexual intercourse, which also have a potential role in the stone expulsion, was not assessed either (19). Although articles presented low bias, the absence of description of the allocation concealment in all included trials may result in some undetected bias (Figure-5).

for patients with distal stones from 5 to 10 mm without differences in side effects.

CONFLICT OF INTEREST

None declared.

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Outcomes of Salvage Robotic-assisted Radical Prostatectomy in the last decade: systematic review and perspectives of referral centers.

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ABSTRACT

Purpose: Salvage robotic-assisted radical prostatectomy (S-RARP) has gained prominence in recent years for treating patients with cancer recurrence following non-surgical treatments of Prostate Cancer. We conducted a systematic literature review to evaluate the role and outcomes of S-RARP over the past decade.

Material and Methods: A systematic review was conducted, encompassing articles published between January 1st, 2013, and June 1st, 2023, on S-RARP outcomes. Articles were screened according to PRISMA guidelines, resulting in 33 selected studies. Data were extracted, including patient demographics, operative times, complications, functional outcomes, and oncological outcomes.

Results: Among 1,630 patients from 33 studies, radiotherapy was the most common primary treatment (42%). Operative times ranged from 110 to 303 minutes, with estimated blood loss between 50 to 745 mL. Intraoperative complications occurred in 0 to 9% of cases, while postoperative complications ranged from 0 to 90% (Clavien 1-5). Continence rates varied (from 0 to 100%), and potency rates ranged from 0 to 66.7%. Positive surgical margins were reported up to 65.6%, and biochemical recurrence ranged from 0 to 57%.

Conclusion: Salvage robotic-assisted radical prostatectomy in patients with cancer recurrence after previous prostate cancer treatment is safe and feasible. The literature is based on retrospective studies with inherent limitations describing low rates of intraoperative complications and small blood loss. However, potency and continence rates are largely reduced compared to the primary RARP series, despite the type of the primary treatment. Better-designed studies to assess the long-term outcomes and individually specify each primary therapy impact on the salvage treatment are still needed. Future articles should be more specific and provide more details regarding the previous therapies and S-RARP surgical techniques.

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INTRODUCTION

Since the first robotic platform was cleared by the FDA (Food and Drug Administration) in 2000, robotic surgery has expanded and improved in multiple fields with the use of different consoles in urologic surgeries. Currently, radical prostatectomy (RP) is the most common urologic procedure performed with robotic assistance, and it is the gold-standard surgical treatment for localized prostate cancer (PCa) in centers with access to robotic surgery (1). However, despite these technological advancements, other less-invasive therapies and technologies have also been described, and the surgical approach is not the only option available for treating PCa.

Concurrent with robotic surgery development, the armamentarium for treating prostate cancer without surgery is vast in the current literature, including several modalities of radiation therapy (RT) (2, 3) and different techniques of focal therapy (FT) (4, 5). However, the best management for the local cancer recurrence after a non-surgical primary treatment is still under discussion, and despite the variety of non-surgical treatments for localized PCa, every therapy causes anatomical modifications and consequences that will impact the outcomes of a subsequent salvage robotic-assisted radical prostatectomy (S-RARP).

As a minimally invasive surgical approach, due to increased experience by robotic surgeons, S-RARP has rapidly gained momentum over the last decade, transforming the landscape of prostate cancer salvage therapy. Unlike traditional open surgeries, robotic-assisted techniques employ advanced technology, enabling surgeons to achieve unparalleled dexterity and visual magnification. This revolution in surgical technology has allowed for greater preservation of critical anatomical structures, leading to reduced rates of postoperative complications and improved functional outcomes. However, even with robotic surgery advantages, S-RARP is still a challenging procedure for surgeons and patients. Therefore, we performed a systematic literature review assessing the outcomes and the robotic surgery role in the past decade to approach salvage radical prostatectomy.

EVIDENCE ACQUISITION

Literature Search Strategy

We performed a systematic literature review (PROSPERO number CRD42023429052) of articles published in the last ten years (from January 1st, 2013 to June 1st, 2023), assessing the available studies describing outcomes of salvage robotic-assisted radical prostatectomy (S-RARP). The literature screening included PubMed®, Web of Science, and Cochrane using the terms “salvage robotic-assisted radical prostatectomy, salvage robotic laparoscopic prostatectomy, and salvage robotic radical prostatectomy.”

Afterward, two investigators (M.C.M and C.B) independently screened and checked all articles using standardized data extraction forms. In case of any discrepancy about eligibility, the article was evaluated by a third author (P.D). The review was performed according to preferred reporting items for Systematic reviews and Meta-analyses (PRISMA) guidelines (6, 7).

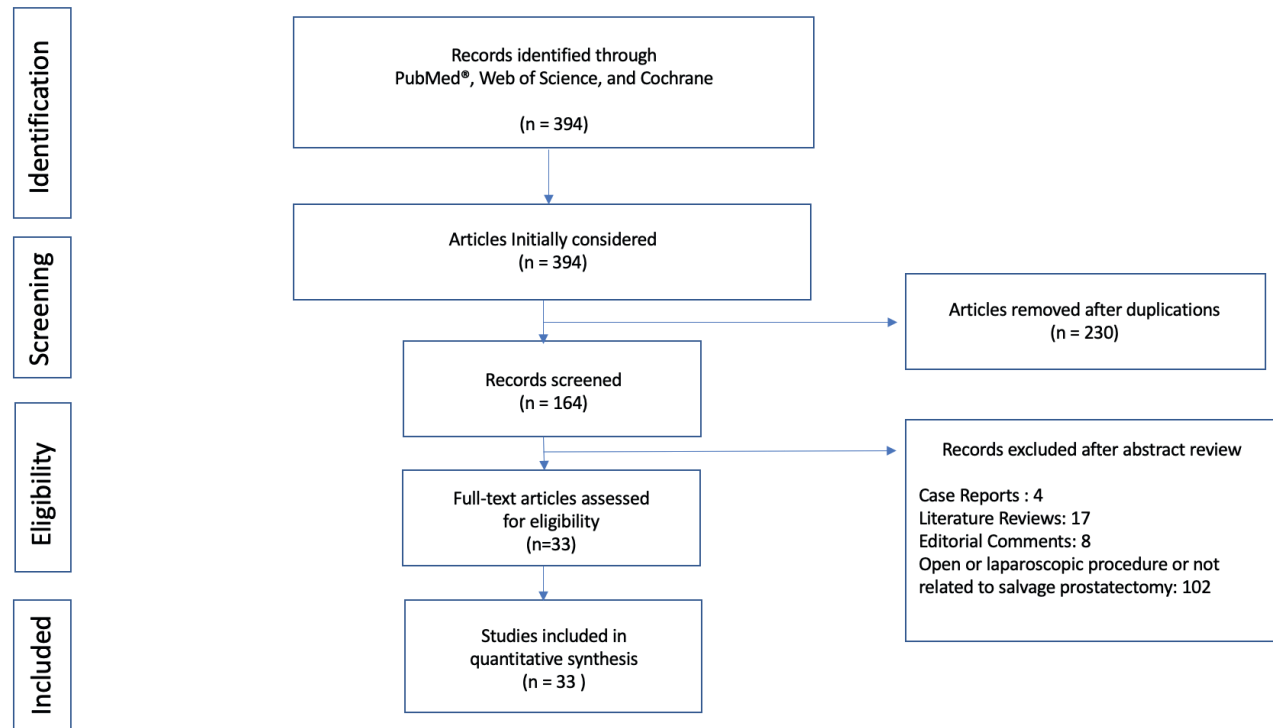
Inclusion and exclusion criteria

We selected articles written in English describing research and studies in humans. When finding studies from the same institution with overlapping patients and outcomes, we considered only the most recent data. We also excluded previous literature reviews, studies mixing the data of different approaches (open, laparoscopic, and robotic) without specifying the robotic surgery outcome, conference abstracts, and case reports of techniques previously described in the literature. When evaluating studies with different groups of S-RARP, we considered only the robotic surgery data. Figure-1 illustrates a flowchart with the selection criteria used. References were manually reviewed and reported according to the PubMed® citation format.

Variables and outcomes definition

We included relevant data regarding the year of the article publication: number of patients undergoing S-RARP in the study, type of primary therapy, total operative time (TOT), console time (CT), intraoperative complications (IOC), estimated blood loss (EBL), postoperative complications

Figure 1 - Flowchart illustrating the literature search with exclusion criteria until reaching the number of articles used in the review.



(POC), positive surgical margins (PSM), continence recovery rates, potency recovery rates, biochemical recurrence (BCR), and median follow-up (MFU).

The primary endpoint of our review is to evaluate and report complication rates, functional and oncological outcomes of S-RARP.

EVIDENCE SYNTHESIS

Summary of the studies

Similar to the primary intervention, the salvage treatment for prostate cancer can be performed with different approaches, such as surgery, RT, HIFU, Cryo, EBRT, and androgen deprivation. However, in this section, we will describe the literature specific on the surgical treatment with salvage robotic-assisted radical prostatectomy (S-RARP).

Overall, we identified 394 articles that fulfilled our search criteria, of which 230 were duplications. From 164 remaining articles, we excluded 131 after the abstract review. In summary,

33 articles were selected containing the robotic surgery approach to patients who underwent previous non-surgical treatment for prostate cancer (Figure-1) (8-40).

Overall, we identified a total of 33 articles with a median follow-up that ranged from 7 to 44 months. Table-1 illustrates the articles from 2013 to 2019, while Table-2 illustrates articles from 2020 to 2023. The tables include the data collected on each study, including the year of publication, the number of patients of each study, type of primary therapy, total operative time (TOT), console time (CT), intraoperative complications (IOC), estimated blood loss (EBL), postoperative complications (POC) according to Clavien-Dindo (Clv), positive surgical margins (PSM), continence, potency, biochemical recurrence (BCR), and median follow-up (MFU) in months.

Primary therapy for PCa before S-RARP

Overall, in the past 10 years, a total of 1630 patients reported in the literature underwent S-RARP, with radiotherapy being the most com-

Table 1 - Articles included from 2013 to 2019.

Author	Year	N. of patients	Primary Therapy	TOT/CT (minutes)	IOC (%)	EBL (mL)	POC in 90 days (%) Clavien range	PSM (%)	Continence/Potency (%)	BCR (%)	MFU months
Kaffenberger et al. (8)	2013	34	BRC-19 RT-11 HIFU-4	NA/ NA	3 rectal	NA	30 (Clv 1-3)	26	39/21	18	16
Zugor et al. (9)	2014	13	EBRT-7 BRC-6	154/ NA	0	130	30 (Clv 1-3)	0	54/23	23	22.8
Yuh et al. (10)	2014	51	BRC-23 Cryo- 3 EBRT- 18 HIFU-1 PB-6	179/ NA	5	175	47 (Clv1-5)	31	45/23	43	36
Vora et al. (11)	2015	6	RT	NA/ NA	0	NA	16.7	NA	83.4/ NA	16.7	7.2
Kenney et al. (12)	2016	20	RT	303/ NA	5	381	30 Clv ≥ 3	15	NA/ NA	22	9.5
Ozu et al. (13)	2016	1	HIRT	244/ 189	0	100	0	0	NA/NA	0	10
Peretsman et al. (14)	2017	9	HIFU (Sonablate)	130/ NA	0	125	NA	NA	100/20	NA	NA
Orré et al. (15)	2017	7	BCR	148/ NA	0	NA	14 Clv ≥ 3	14	50/ 66	14	24
Ou et al. (16)	2017	14	RT-11 CKR-2 HIFU-1	NA/ 134	7	100	21	21.4	71.4/ 66.7	21	32.4
Nunes-Silva et al. (17)	2017	22	FT	134/ NA	9.1	465	NA	4.5	53.8/ NA	31.8	12
Ogaya-Pinies et al. (38)	2018	60	EBRT-35 BCR-10 PB-6 Cryo-7 HIFU-2	131/ NA	0	130	5 Clv 1-2	NA	50 / NA	NA	12
Bonet et al. (22)	2018	80	RT-63 ABL-17 EBRT-37 BCR-14 BCR+EBRT-13 CYK-3	NA/ NA	0	NA	NA	NA	53.7/ 16.6	31	22.5
Ogaya-Pinies et al. (40)	2018	96	PB-1 Cryo-18 HIFU-7 Others 4	125/ NA	0	100	26 Clv 1-4	16.7	57.3/ 55	15	14

			HIFU-57								
			Cryo-16								
Marconi et al. (18)	2019	82	IRE-4	NA/ NA	0	400	6.1 Clv 1-3b	13.4	83/ 14	41.5	13
			VTP-3								
			PRX302-2								
			RT-121								
			BCR-55								
Gontero et al. (19)	2019	209	Cryo-14	228/ NA	0.48	222	34.9 Clv1-4	NA	63.9/ 8.1	NA	28.8
			HIFU-9		rectal						
			Others-10								
Onol et al. (20)	2019	126	RT-94	129/84	0	106	20 Clv 1-4	17	51.3/ 13	17	32
			ABL-32	122/84	0	93	9 Clv 1-3a	43.8	87.5/ 27	18	29

Clv (Clavien-Dindo); EBL (estimated blood loss); PSM (positive surgical margins); TOT (total operative time); CT (console time); IOC (intraoperative complication); POC (postoperative complications); NA (not available); MFU (median follow up); PB (proton beam); Cryo (cryotherapy); CYK (Cyberknife); BCR (biochemical recurrence on the period of the study); Primary Therapy: RT (radiotherapy); HIRT (heavy iron radiotherapy therapy); BRC (Brachytherapy); HIFU (high intensity focused ultrasound); FT (focal therapy); EBRT (external-beam radiotherapy); ABL (ablation); IRE (Irreversible Electroporation) VTP (vascular-targeted photodynamic therapy); PRX302 (Topsalysin)

mon primary treatment (42%), followed by HIFU (18%), brachytherapy (10%), and cryotherapy (5%). The remaining patients (25%) underwent other therapies or a combination of therapies as primary treatment for PCa.

Surgical Performance and Complications

The total operative time range was from 110 to 303 minutes (reported by most articles), and the console time ranged from 84 to 199 minutes (reported by few studies).(12,20,23,36) Estimated blood loss ranged from 50 to 745 mL.(23,30) Intra- and postoperative complications ranged from 0 to 9,1% and 0 to 90%, respectively (Clavien 1 to 5). Rectal injury ranged from 0.48 to 3%. (8, 19, 25, 37).

Functional Outcomes

Functional outcomes are illustrated in Tables 1 and 2. The continence rates ranged from 0 to 100% (14, 24, 33, 34), and the studies diverge regarding the definition of continence. Twenty-one studies defined continence as no pads use (10, 12, 15-22, 25, 26, 30, 31, 33, 35-40), five studies considered up to one pad (8, 9, 23, 28, 32), one study evaluated continence using EPIC-26 questionnaire 24, and one study considered the ICIQ-

score questionnaire (29). We were not able to find continence definition in five studies (11, 13, 14, 27, 34).

Potency rates ranged from 0 to 66.7% (16, 21, 30) and most studies defined potency as the capacity to have intercourse with or without phosphodiesterase 5 (PDE-5) inhibitors (8-10, 14-16, 18-22, 25, 26, 31, 33, 37, 39,40). One study evaluated potency recovery using the EPIC-26 questionnaire 24, and two studies using the IIEF-5 (29, 36). In some studies, we were not able to find data on potency (11-13, 17, 23, 27, 28, 30, 32, 34, 35, 38), continence, or BCR. Finally, most authors described the number of events in the follow-up period and failed to demonstrate functional outcomes in Kaplan-Meier curves (time to event) to estimate early potency or continence following surgery.

Pathological and Oncological Outcomes

Tables 1 and 2 describe the oncological outcomes. Positive surgical margins after S-RARP reached up to 65.6%(28), while biochemical recurrence ranged from 0 to 57% (32). All studies reported BCR according to RTOG-ASTRO Phoenix Criteria (1). However, in most studies, BCR in five years was not available due to the short-term fol-

Table 2: Articles included from 2020 to 2023.

Author	Year	N. of patients	Primary Therapy	TOT/CT (minutes)	IOC (%)	EBL (mL)	POC (Clavien) In 90 days (%)	PSM (%)	Continence/Potency (%)	BCR (%)	MFU months
Thompson et al. (21)	2020	45	HIFU	NA/ 140	0	200	17.8 Clv 1-3	44.4	65.5/ 0	5.3	17.7
Bonet et al. (39)	2020	120	RT ABL	127/ 84	0	103	14.2 Clv1-4	22.5	55,8/ 19.2	32.5	44
De Groote et al. (35)	2020	106	HIFU-59 RT-27 BRC-10 Others -10	142/NA	0	200	8 Clv 1-3	39	50/ 5	13	25
Madi et al. (23)	2021	*RS (20) Usual (6)	EBRT-18 BRC-4 Cryo-2 CYK-2	NA/ 141 NA/ 199	0 0	50 100	10 Clv 1-3 16,7 Clv 3	30 33	100/NA 44/NA	20 33,3	18
Cathcart et al. (24)	2021 (RCT)	23	Cryo (4) HIFU (17) Electro (1)	NA	0	NA	4 (Clv 1)	35	100/52	18	12
Martinez et al. (25)	2021	26	BRC (3) EBRT (19) IMRT (3)	NA	3.8 rectal	150	11.5(Cliv 3-5)	26,9	90.9/4.5	39.1	47
Nathan et al. (26)	2021	135	N/A	165/NA	0.8 rectal	200	13.3 (Clv 1-5)	37.8	78.8/5.2	22.2	43
Nunes-Silva (27)	2021	*RS (12)	EBRT (10) BRC (2)	NA/138	0	81	8.3(Cliv 3)	25	91.6/NA	16.6	12
Kowalczyk et al. (28)	2021	*RS (40)	EBRT (21) BRC (12) HIFU (7)	NA/130	2.5	100	12.5 (Clv 1-5)	57.5	54.1/10	23.1	23
Kowalczyk et al. (28)	2021	32	EBRT (16) BRC (9) Cryo (5) RT (2)	NA/175	0	150	28.1(Cliv 1- 3)	65.6	6.3/12.5	37.5	36
Spitznagel et al. (29)	2021	13	HIFU	260/NA	0	230	46.2 (Clv 1-3)	7.7	NA/NA	0	12
Bozkurt et al. (30)	2021	10	PTB	230/NA	0	745	90 (Clv 1-4)	20	12.5/0	10	31.8
Bhat et al. (31)	2021	53	FT	NA/121	0	100	21 (Clv1-2)	40	56/13	17	36.3

Schuetz et al. (32)	2021	*RS (21)	RT (8) HIFU (9) BRC (2) Cryo (1) FT (1)	228/NA	0	300	NA	19	19/NA	14.3	12
Schuetz et al. (32)	2021	7	RT (4) HIFU (1) BRC (2)	252/NA	0	500	NA	57,1	0/NA	57,1	36
Blazevski et al. (33)	2022	15	FT	NA/NA	0	200	NA	7	100/60	0	22
Mortensen et al. (34)	2022	5	EBRT	205/NA	0	120	60 (Clv 1-3)	60	0/NA	20	13
Nathan et al. (37)	2022	100	HIFU (92) Cryo (5) IRE (2)	170/NA	0	200	9 (Clv 1-3)	25	84,7/21	23	16,5
De Luca et al. (36)	2022	11	HIFU	110/NA	0	NA	20 (Clv 1)	27	81/18	0	12

Clv (Clavien-Dindo), EBL (estimated blood loss), PSM (positive surgical margins), TOT (total operative time), CT (console time), IOC (intraoperative complication), POC (postoperative complications), NA (not available), MFU (median follow up), PB (proton bean), Cryo (cryotherapy), CYK (Cyberknife), BCR (biochemical recurrence on the period of the study). Primary Therapy: RT (radiotherapy), HIRT (heavy iron radiotherapy therapy), BRC (Brachytherapy), HIFU (high intensity focused ultrasound), FT (focal therapy), EBRT (external-bean radiotherapy), IRE (Irreversible Electroporation), Electro (Electroporation), IMRT (Intensity-modulated radiotherapy), *RS (Retzius-sparing), PTB (proton bean).

low-up. Most authors described BCR as the number of events in the follow-up period with percentages and failed to demonstrate it in Kaplan-Meier curves (time to event) to estimate the recurrence time following surgery in a better fashion.

Retzius-Sparing (RS) approach to S-RARP

Only four articles, comprising 93 patients, described the RS approach to S-RARP. In these studies, PSM ranged from 23.8 to 57.5% and continence from 19 to 100%. None of the studies described or compared early continence following RS. Potency was available in only one study (10%) (28). BCR ranged from 14.3 to 23.1% (23, 27, 28, 32).

DISCUSSION

We have summarized the past decade of all studies describing outcomes of salvage robotic-assisted radical prostatectomy for prostate cancer recurrence after primary treatment. Reporting and comparing the outcomes of S-RARP is challeng-

ing because the available data is based on retrospective studies with a small number of patients and all its inherent risks of bias. The current literature is inconsistent, and most studies reported the overall outcomes adding different primary therapies without specifying or separating the patients and results according to the primary approach. Furthermore, the surgeries were performed by several surgeons with diverse levels of experience and techniques, which also impacts the outcomes of each patient (39). In addition, most studies failed to report the primary therapy details, such as radiation dose and fractions, type of energy used on the focal approach (full or partial ablation), side and histology of the primary tumor, and details of preoperative hormone treatment, which may impact in the positive surgical margins rates. In this scenario, due to the multifactorial risks of bias and inconsistencies, avoiding misleading conclusions regarding S-RARP, we reported and evaluated the current articles individually instead of conducting a meta-analysis.

Recent studies described the importance of selection criteria for S-RARP to optimize operative outcomes (41). According to the European Association of Urology (EAU), candidates for S-RARP should have low comorbidity, life expectancy of at least 10 years, PSA lower than 10, International Society of Urological Pathology (ISUP) grade group $\leq 2/3$, no lymph node involvement on pre-operative imaging exam, and clinical stage T1 or T2. Callaris and colleagues described significant differences and benefits for patients selected according to these variables. Unfortunately, being a recent study and guideline by EAU, most articles included in our review were published before 2022 and violated at least one criterion for selecting candidates for S-RARP (41). Therefore, we believe that outcomes of Robotic-assisted Salvage Prostatectomy should improve in the following years when selecting patients according to these guidelines.

Only one randomized clinical trial (RCT) was reported with a small number of patients (23), describing 100% continence rates after 12 months and 58% of potency recovery in patients treated with previous Focal Therapy (24). The largest series of S-RARP to date was published by Gontero et al., reporting the outcomes of 18 tertiary centers comparing open and robotic groups of salvage prostatectomy. In this retrospective study, 209 patients underwent S-RARP, and the author reported up to 34.9% of postoperative complication rates, with 0.48% of rectal injuries. Potency and continence for the robotic group reached 8.1% and 57.5%, respectively. PSM and BCR were not assessed in this study (19). Even with a relatively high number of patients reported by this study, evaluating functional and oncological outcomes in S-RARP is challenging due to several factors that impact surgical results. From this article, it is reasonable to conclude that intraoperative complications and rectal injury have low rates, but continence and potency recovery are suboptimal and challenging to perform a critical analysis of due to a lack of data on the preoperative function of these patients. In a subsequent study, the same group published a cohort of 414 patients describing the oncological outcomes. However, we excluded this data from our review because open

and robotic results were mixed and not reported individually (42).

Some studies have assessed the S-RARP outcomes of patients selected according to the primary therapy. Two of them reported and compared the results of S-RARP following ablation and radiation. The authors had similar conclusions in terms of functional outcomes between the therapies (20, 35). In both articles, potency and continence rates were higher in patients who underwent primary ablations. However, the results are still suboptimal, even in the ablation group, which in theory had only partial damage on the prostate during the primary treatment. Kenney et al. also described the S-RARP in patients with previous radiation and reported complications with Clavien-Dindo ≥ 3 reaching up to 30%, while PSM and BCR reached 15% and 22%, respectively (12). In another study, Orré M et al. reported 14% of PSM and 14% of BCR in patients with previous brachytherapy (15). However, even with compatible results presented by these studies, PSM and BCR are also influenced by several factors such as tumor histology, previous hormone treatment, radiation fractions and dose, brachytherapy technique, and surgeon's experience.

Furthermore, nine articles including 374 patients exclusively reported the S-RARP following Focal Therapy (14, 17, 18, 21, 26, 29, 31, 33, 36). The complication rates ranged from 6.1 to 46.2%, PSM from 4.5% to 44%, and BCR from 0 to 41.5%. In these series, it is also challenging to stratify the patients due to a lack of information regarding the type of energy used in the Focal therapy (Focal One or Sonablate), whole or partial gland ablation, initial tumor histology and stage, preoperative potency, and continence. In this context, Bhat and colleagues described worse functional and oncological outcomes of S-RARP post Focal Therapy compared to primary radical prostatectomy, showing that focal ablations often cause contralateral prostate damage and also impact functional outcomes (31).

The Retzius-sparing approach to S-RARP has also been described in 4 studies comprising 93 patients (23, 27, 28, 32). The results were compatible with other series of S-RARP with intraoperative complications ranging from 0 to 2.5%,

biochemical recurrence from 14.3 to 23%, continence from 19 to 100%, and most studies did not describe potency recovery rates. In one study, continence rates were 100% for the RS versus 44% for the conventional approach (27). However, due to the small number of cases reported and some missing data on outcomes in the literature, we still need more studies evaluating outcomes of this approach in salvage settings. The RS approach to S-RARP is feasible and safe when performed by experienced surgeons. We believe the challenge lies in the tumor recurrence and lack of landmarks posed by the primary treatment, not in the RS technique.

Among all possible intraoperative complications in patients undergoing S-RARP, rectal injury is one of the most feared by surgeons. Due to the technical challenges and lack of anatomic landmarks posed by the primary treatment, posterior adhesions between the prostate and rectum are common in this type of surgery. In addition, the primary therapy aggression on the rectum, especially radiation, usually makes the intestinal tissue more susceptible to dehiscence and fistula after an eventual repair. Evaluating the current articles in the literature, intraoperative complications ranged from 0 to 9%, and only three studies described rectal injury, being one patient with local staging pT4 disease (8,19,25). However, it is important to note that the literature on salvage prostatectomy is based on retrospective studies with great potential for selection bias, and we believe that the percentage of rectal injuries could be underestimated and underreported. In this scenario, patients and surgeons should be aware of the increasing risks of rectal injuries in these cases, and we recommend always having a general surgeon consultation and backup before operating on these patients.

Despite its strengths, our study is not devoid of limitations. First, as previously described, the current literature is based on retrospective studies and all its inherent limitations, especially selection bias. Second, most articles grouped different primary therapies and reported the outcomes without individualizing the primary approach with more details, such as radiation fractions and dose, previous hormone treatment and type of regimen (agonist or antagonist), type of ablation (whole

or focal gland), and initial tumor histology and staging before primary treatment. Third, the articles have some inconsistencies in the definitions and reports of the trifecta (potency, continence, and BCR). Also, some studies reported only part of these outcomes. Fourth, most articles reported the overall rates of biochemical recurrence without specifying the time to recurrence on Kaplan-Meier curves and the next steps on the treatment after recurrence following S-RARP. However, despite the literature limitations on S-RARP, we believe we could summarize the most important aspects of this challenging procedure, adding valuable inputs from experts in this field.

CONCLUSIONS

In the last decade, salvage robotic-assisted radical prostatectomy in patients with cancer recurrence after previous prostate cancer treatment was safe and feasible. The literature is based on retrospective studies with inherent limitations describing low rates of intraoperative complications and small blood loss. However, potency and continence rates are largely reduced compared to the primary RARP series, despite the type of the primary treatment. In this scenario, patients should be aware and counseled about technical and anatomical challenges posed by the primary therapy and potential risk of rectal injury during the procedure. Better-designed studies to assess the long-term outcomes and individually specify each primary therapy impact on the salvage treatment are still needed. Future articles should be more specific and provide more details regarding the previous therapies and S-RARP surgical techniques.

CONFLICT OF INTEREST

None declared.

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Association between rectal diameter and response to treatment with parasacral transcutaneous electrical nerve stimulation and behavioral changes in children and adolescents with bladder and bowel dysfunction

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ABSTRACT

Purpose: Parasacral Transcutaneous Electrical Stimulation (TENS) is one of the treatments for children with Bladder and Bowel Dysfunction (BBD). Some studies showed that children with increased Rectal Diameter (RD) have more Functional Constipation (FC). However, RD prediction in maintenance of BBD after treatment was never evaluated. Our aim is to evaluate the association between RD and response to treatment in children and adolescents with BBD.

Materials and Methods: This study evaluated patients from 5-17 years old with BBD. Dysfunctional Voiding Scoring System (DVSS), Rome IV criteria, and the Constipation Score were used. RD was measured using abdominal ultrasound before treatment according to the technique established by Klijn et al. and was considered enlarged when $>3\text{cm}$. No laxatives were used during treatment. Descriptive analysis and binary regression were performed and the area under the ROC curve was calculated.

Results: Forty children were included (mean age 8.4 ± 2.8 years, 52.5% male). Before treatment, RD was enlarged in 15 children (37.5%) (mean diameter $3.84 \pm 0.6\text{cm}$), with FC persisting post-treatment in 11/15 (73.3%). Those patients also required more laxatives following treatment and had more severe FC. Binary regression showed pre-treatment RD to be an independent predictor of the persistence of FC post-treatment ($\text{OR}=9.56$; 95%CI:2.05-44.60). In ROC curve analysis, the sensitivity was 100% (95%CI: 0.49-1.0) and specificity 77.14% (95%CI:0.60-0.90) for rectal diameter $>3\text{ cm}$. The likelihood ratio was 4.38 (95%CI:2.40-8.0) for the persistence of BBD following treatment.

Conclusion: RD appears to be relevant in the evaluation of children with BBD, not only as a diagnostic tool but also as a predictor of treatment outcome.

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INTRODUCTION

Bladder and Bowel Dysfunction (BBD) is characterized by the presence of Lower Urinary Tract Symptoms (LUTS) associated with Functional Constipation (FC). The physiopathology of BBD lies with anatomical, embryological, and functional interactions(1-3). The presence of a large fecal mass in the rectum that eventually affects bladder capacity, lack of coordination in the pelvic floor muscles/sphincters, central nervous system abnormalities, and cross-organ sensitization between the bladder and the rectum have been implicated in the development of this dysfunction (2, 4-9).

BBD is associated not only with important clinical consequences related to the urinary tract such as urinary infections and possible renal sequelae but also with emotional and behavioral problems (10). The social stigma of fecal and urinary incontinence is a common challenge faced

by children with BBD and can lead to issues such as self-esteem, embarrassment, loneliness, a decline in school performance, aggressiveness, and other behavioral issues (10). Early diagnosis and quick management of constipation are considered crucial in achieving an improvement in urinary symptoms (4, 11, 12).

In this context anticholinergics medications can be used to improve symptoms of urinary urgency and daytime incontinence, but exert a negative effect on colonic transit, making FC worse (2). In turn, Parasacral Transcutaneous Electrical Nerve Stimulation (TENS) has been used as an alternative treatment for children with LUTS refractory to behavioral changes in urinary and bowel habits, and this treatment has also been reported to exert an effect on FC, improving urinary and intestinal symptoms in more than 80% of children with BBD when associated with behavioral changes (13).

Measurement of the transverse diameter of the rectum, rectal diameter (RD), has been used as an ancillary tool in the diagnosis of FC in children, with an association already demonstrated between fecal incontinence and enlarged RD (14). RD seems to be a noninvasive exam and a reliable alternative to digital rectal examination in constipated children (15); therefore, it's an easy method and can be particularly useful for diagnosing and treating fecal impaction (16).

Identifying outcome predictors in BBD is essential when planning treatment. According to Hoffman et al., the presence of enuresis in children with an overactive bladder, a clinical condition commonly linked to FC, is a factor associated with a poor response to treatment (17). Furthermore, the persistence of FC itself is associated with the persistence of urinary symptoms (4). Therefore, determining the influence of enlarged RD on treatment outcome can be particularly useful. Indeed, RD is easily obtainable and unrelated to subjective complaints, making it a potential prognostic marker that could help identify the best treatment approach for BBD in children and adolescents.

To the best of our knowledge, no study has yet been conducted to evaluate RD as a predictor of treatment outcome; therefore, the objective of this study was to analyze whether enlarged RD plays any role in the persistence of urinary symptoms and FC in children and adolescents submitted to treatment for BBD. In addition, the study aimed to evaluate the association between RD and response to treatment in children and adolescents with BBD.

MATERIAL AND METHODS

This cohort study was nested within a randomized clinical trial previously approved by the institute's review board under protocol number 683884517.5.0000.5544 and registered in the Brazilian Clinical Trials Registry as RBR-58c63h (13). The study was conducted by the principles laid out in the Declaration of Helsinki and in compliance with the requirements of Resolution 466/12 of the Brazilian National Health Council (CNS) that regulates research involving human beings. The participation of all the individuals enrolled in the

main study was completely voluntary and confidential, with patients being identified exclusively as alphanumerical codes, thus preserving their privacy. All the parents/guardians of the participants in the main study provided written informed consent with guarantees of confidentiality.

Study setting

The study was conducted between January 2017 and December 2019 in a referral center for the treatment of childhood urinary disorders. Children and adolescents from 5 to 17 years of age diagnosed with BBD and submitted to treatment with behavioral changes associated or not with Parasacral TENS were included. Patients with a diagnosis of anatomic or neurological alterations of the gastrointestinal or urinary tract, such as neurogenic bladder, were excluded from the study.

Instruments

The Dysfunctional Voiding Scoring System (DVSS) (Supplementary File-1), translated and validated for use in Brazilian Portuguese (18), was used to evaluate urinary symptoms before and following treatment. Bowel symptoms were evaluated using the Rome IV criteria (19) for children and adolescents 4 to 18 years of age. Patients who fulfilled at least two Rome IV criteria were considered constipated.

The Constipation Scoring System (Supplementary file 2) was also used to evaluate the severity of FC (20).

The symptoms referring to items 3, 4, 5, and 7 (feeling of incomplete evacuation, abdominal pain, time in lavatory per attempt, and unsuccessful attempts for evacuation per 24 hours) were also evaluated individually, with scores ≥ 2 being considered abnormal. Concerning item 6 (use of some type of assistance to defecate), scores ≥ 1 were considered abnormal. The Bristol Stool Scale was used to analyze the shape of the stool (7).

Treatment of BBD and rectal diameter measurement

Patients were previously randomized into two groups using sealed envelopes containing four sequential numbers. The control group was submitted to behavioral changes plus sham while

the treatment group was submitted to behavioral changes plus Parasacral TENS. Both groups were submitted to treatment for 20 sessions in an intention-to-treat analysis. Behavioral changes consist of the following recommendations: not to wait longer than three hours between voids; to avoid coffee, tea, carbonized drinks, chocolate, and citric fruits during treatment; to void before going to sleep; to drink more fluids during the day (around 5 to 8 X 200 mL glasses/day depending on age); with those complaining of enuresis to avoid drinking fluids at least 2-3 hours before going to sleep. In addition, instructions were also given regarding the appropriate intake of high-fiber foods. However, neither fiber supplements nor specific nutritional diets were recommended for either group. All patients were instructed to sit appropriately on the toilet for 5-10 minutes three times a day after their main meals.

Parasacral TENS consists of placing self-adhesive electrodes on the parasacral region between S2 and S4, with the patient in the ventral decubitus position. The electrodes were connected to an electrical stimulation device with a frequency of 10 Hz and pulse width of 700 μ s, three times a week for a total of 20 sessions, with intensity varying according to the patient's tolerance level and without reaching the motor threshold. Sham treatment was performed identically but with no electrical activity, thus functioning as a placebo. None of the patients included in the study used laxatives during treatment.

RD was measured by abdominal ultrasound, performed twice on each patient by the same experienced professional and with the patient in the dorsal decubitus position. A 7-MHz probe was placed on the abdominal wall, two centimeters above the symphysis. To measure RD, bladder capacity should be between 30% and 70% of the expected capacity for age calculated as: $(\text{age} + 1 \times 30)$ (21). Before the sonographic measurements were obtained, all the children were asked whether they needed to defecate, and the examination was not performed on those who stated that they did or with urge to defecate. Measurement was performed according to the technique established by Klijn et al. (21). Rectal diameters were considered enlarged when ≥ 3 cm for all patients, as demonstrated in Figure-1, regardless of age, since there

Figure 1 - Increased rectal diameter in trans-abdominal ultrasound.



Source: Personal archive.

is no significant difference in this cut-off in older children and adolescents (21).

Sample size

This paper is a nested study of a randomized clinical trial (13) which included 40 patients through sample size calculation. We evaluated the area under the ROC curve (AUC) with that number of patients, finding an accuracy of 74.5% with a power of 80% ($1 - \beta$) and a type I error of 0.05, making it feasible to evaluate the rectal diameter with that number of patients. The sample size was calculated using MedCalc, version 19.5 (MedCalc Software Ltd., Ostend, Belgium; <https://www.medcalc.org>; 2020).

Statistical Analysis

Independent categorical variables were described using numbers and percentages and the numerical variables as means and standard deviations (SD) when normally distributed or as medians and interquartile range (IQR) if the distribution was not normal. The normality of the distribution of the variables was tested using the Kolmogorov-Smirnov test.

Clinical characteristics of the study population were described and compared using numerical and categorical variables. Numerical variables were expressed as means and SD or as medians and IQR and compared using Student's t-test or the Mann-Whitney test depending on their distribution. The categorical variables were described using absolute and relative frequencies and compared using Fisher's exact test.

Variables with p-values <0.1 were then selected for inclusion in a multivariate analysis and those subsequently found to have differences with a p-value <0.05 were included in the final multivariate model. Those that were statistically significant in this model were used to analyze the accuracy of the final model. The discrimination ability was analyzed based on the area under the receiver operating characteristic (ROC) curve, adopting a confidence interval of 95% (95%CI). The Hosmer-Lemeshow test was performed to evaluate the goodness of fit.

P-values <0.05 were considered statistically significant. Data for analysis were stored and processed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA), version 25.0 for Windows, and MedCalc, version 19.5 (MedCalc Software Ltd., Ostend, Belgium; <https://www.medcalc.org>; 2020).

RESULTS

Forty patients with a diagnosis of BBD and a mean age of 8.4 ± 2.8 years were evaluated. Of these, 52.5% were male. Enlarged Rectal Diameter was detected in 15 patients (37.5%) before treatment, with a mean diameter of 3.84 ± 0.6 cm.

Analysis of the association between the transverse diameter of the rectum before treatment and lower urinary tract symptoms (LUTS), FC and its effect on treatment outcome

Patients with Overactive Bladder and Voiding Postponement were included. No association was found between LUTS and enlarged pretreatment rectal diameter. In addition, there was no association between rectal diameter and the bowel symptoms associated with FC. However, children and adolescents with an enlarged

rectal diameter had a significantly higher constipation score (Table-1).

Evaluation of the measurement of rectal diameter before treatment and of urinary and bowel symptoms following treatment showed that 11 constipated patients (73.3%) with an enlarged pretreatment rectal diameter continued to have bowel dysfunction following the intervention. Of these 11 patients, 9 had been treated with behavioral changes alone and 2 with behavioral changes plus Parasacral TENS. After treatment, these patients also required laxatives and had more severe FC (Table-2).

Patients that underwent different treatments were analyzed as a single group (enlarged RD). Regarding the type of treatment, there was no difference between the two groups (control and treatment groups) concerning to pretreatment rectal diameter or to the frequency of enlarged rectal diameter. In the control group, 9/10 patients (90%) in whom rectal diameter was enlarged continued to have FC following treatment, while 5 patients (50%) in whom rectal diameter was normal had FC following treatment ($p=0.51$). In the treatment group, 2/5 patients (40%) in whom the rectal diameter was enlarged continued to have FC following treatment ($p=0.2$). Moreover, 12 (80%) patients with enlarged rectal diameter remained with enuresis ($p=0.05$).

In the binary regression performed to evaluate whether sex, age or enlarged pretreatment rectal diameter played any role in the persistence of BBD, the model containing enlarged pretreatment rectal diameter was statistically significant [$X^2(1) 9.66 = 0.002$; R^2 Nagelkerke = 0.368]. Enlarged pretreatment rectal diameter was the only independent predictor (OR=9.56; 95%CI: 2.05-44.60) in the model found to affect the persistence of BBD following treatment.

The accuracy of rectal diameter as a predictor of response to treatment

Rectal diameter was included in the model to generate the ROC Curve (Figure-2). Rectal diameter >3.09 cm had an area under the curve of 0.83 (95%CI: 0.68-0.91) ($p<0.0001$) for predicting the persistence of constipation and urinary incontinence following treatment. In the association

Table 1 - Association between rectal diameter and the presence of lower urinary tract symptoms and bowel symptoms associated with functional constipation before treatment.

Parameters	Rectal diameter before treatment		p-value
	< 3 cm (n=25)	≥ 3 cm (n=15)	
DVSS, median (IQR)	13 (10-16)	14 (11-17)	0.54†
Urinary urgency, n (%)	25 (100)	14 (93.3)	0.19*
Daytime incontinence, n (%)	23 (92)	12 (80)	0.27*
Holding maneuvers, n (%)	20 (80)	13 (86.7)	0.59*
Daytime urinary frequency, n (%)	14 (56)	9 (60)	0.80*
Nocturia, n (%)	8 (32)	3 (20)	0.33*
Enuresis, n (%)	18 (72)	14 (93.3)	0.10*
Lower urinary tract dysfunction, n (%)	23 (92)	14 (93.3)	0.87*
Constipation score, median (IQR)	9 (6-11)	11 (10-16)	0.01†
Feeling of incomplete evacuation, n (%)	13 (52)	7 (46.7)	0.74*
Time in lavatory per attempt >5 minutes, n (%)	14 (56)	12 (80)	0.12*
Assistance to evacuate, n (%)	3 (12)	2 (13.3)	0.90*
Unsuccessful attempt to defecate, n (%)	18 (72)	14 (93.3)	0.10*
Abdominal pain, n (%)	14 (56)	11 (73.3)	0.27*
Bristol Stool Scale: Types 1 and 2, n (%)	12 (48)	5 (33.3)	0.36

IQR = interquartile range; n: number; * = Fisher's exact test; †Mann Whitney test.

analysis, for rectal diameter >3.09 cm sensitivity was 100% (95%CI: 0.48 - 1.0) and specificity 77.14% (95%CI: 0.60 - 0.90). The likelihood ratio was 4.38 (95%CI: 2.40 - 8.0) for the persistence of constipation and urinary incontinence following TENS treatment.

DISCUSSION

Previous studies have described rectal diameter as a tool for diagnosing FC since this ultrasound measurement is enlarged in constipated children compared to children with no bowel dysfunction (14, 21, 22). Nevertheless, evaluation of the association between pretreatment rectal diameter and the persistence of BBD following treatment showed that the children in whom rectal diameter was greater were more likely to remain constipated and less likely to achieve a successful outcome. This finding is important since, in our perspective, no studies in the literature have evaluated the value of rectal diameter in predict-

ing treatment outcomes in children and adolescents with BBD. Our study also used an objective finding to evaluate the response to treatment, less subject to bias.

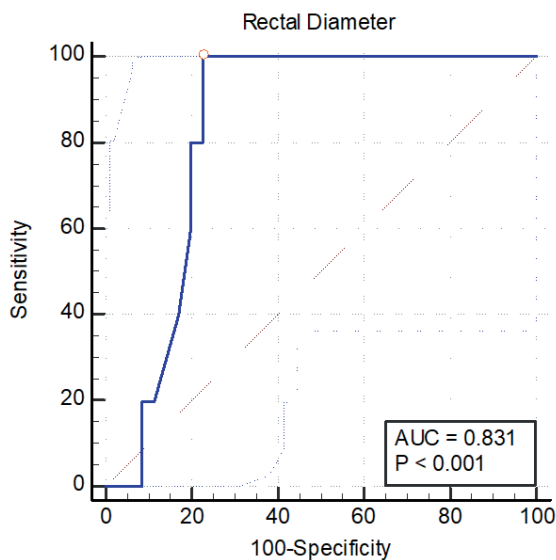
The present study found no association between enlarged pretreatment rectal diameter and LUTS, the severity of LUTS or bowel complaints. However, an association was found between this measurement and higher constipation scores, with the rectal diameter being greater in children with more severe constipation. Therefore, the use of rectal diameter could increase the accuracy of a diagnosis of BBD.

There is still controversy in the literature regarding the use of rectal diameter as a tool with which to diagnose FC in children, with a diagnosis of this dysfunction remaining essentially of a clinical nature and based on the Rome IV criteria. However, an association between rectal diameter >3 cm and the presence of FC has been reported, particularly when fecal impaction is present, and rectal diameter is greater in constipated chil-

Table 2 - Comparison between rectal diameter before treatment and the persistence of lower urinary tract symptoms and functional constipation following treatment.

Parameters	Rectal diameter before treatment		p-value
	<3 cm (n=25)	≥ 3 cm (n=15)	
Δ DVSS, median (IQR)	- 9.4	- 6.2	0.09†
Urinary urgency, n (%)	6 (24%)	8 (53.3)	0.06*
Daytime incontinence, n (%)	8 (32)	7 (46.5)	0.35*
Holding maneuvers, n (%)	5 (20)	7 (46.7)	0.08*
Daytime urinary frequency, n (%)	2 (08)	4 (26.7)	0.11*
Nocturia, n (%)	4 (16)	2 (13.3)	0.82*
Enuresis, n (%)	12 (48)	12 (80)	0.05*
Lower urinary tract dysfunction, n (%)	7 (28)	7 (46.7)	0.23*
Constipation, n (%)	7 (28)	11 (73.3)	0.005*
Constipation score, median (IQR)	4 (1.5-6)	9 (4-11)	0.003††
Feeling of incomplete evacuation, n (%)	6 (24)	8 (53.3)	0.06*
Time in lavatory per attempt >5 minutes, n (%)	4 (16)	6 (40)	0.09*
Assistance to evacuate, n (%)	0	2 (13.3)	0.06*
Unsuccessful attempt to defecate, n (%)	6 (24)	14 (93.3)	< 0.001*
Abdominal pain, n (%)	7 (28)	7 (46.7)	0.23
Bristol Stool Scale: Types 1 and 2, n (%)	8 (32)	7 (46.7)	0.35
Use of laxatives after treatment, n (%)	6(24)	11 (73.3)	0.02

Δ = delta; IQR = interquartile range; n = number. * = Fisher's exact test; † = Student's t-test; †† = Mann Whitney test.

Figure 2. The area under the receiver operating characteristic (ROC) curve for rectal diameter as a predictor of treatment outcome in children with bladder and bowel dysfunction.

AUC: area under the curve.

dren with fecal incontinence compared to children without FC(14, 16, 23). On the other hand, there are controversies concerning the use of the Rome criteria for diagnosing FC, with differences between patients and physicians regarding what should be considered FC (24). Rectal diameter may be particularly useful in those patients meeting only one Rome criterion as this measurement could eliminate the need for digital rectal examination in these cases.

Although there are studies on rectal diameter as a tool for diagnosing FC, its prognostic value has never been investigated. Therefore, by evaluating its predictive accuracy based on the ROC curve, the present study showed that this ultrasound measurement might have prognostic value in predicting treatment outcomes in children and adolescents with BBD. This study also showed that constipated patients with enlarged rectal diameters still required laxatives after treat-

ment. This finding suggests that more aggressive management consisting of behavioral changes, electrical therapy, and laxatives is needed in children with an enlarged rectal diameter.

This study opens new perspectives to individualize patients' treatment based on rectal diameter. If the rectal diameter has a normal value, we could be less aggressive. However, a combination therapy (e.g., parasacral TENS plus laxatives) could be considered in the case of enlarged rectal diameter.

Despite laxatives being the first line for the treatment of functional constipation, behavior changes have still been used in some cases (4). We emphasize that this study is nested in a randomized clinical trial that evaluated the efficacy of the association between parasacral TENS and behavioral changes without using laxatives (13). Therefore, some patients only experienced behavioral changes because they were part of this randomized clinical trial. Some children may not tolerate the laxative's untasteful flavor and adverse effects, like abdominal pain and diarrhea. Furthermore, after intensive initial medical and behavioral treatment, about 40% of patients still were constipated at 1 year of follow-up and, 25% continue to have severe constipation during puberty (25). In this way, new therapies have been designed for the management of bowel dysfunction, such as neuromodulation.

Our results suggest that children and adolescents with less severe constipation may not require laxatives, making them useful for those with more severe constipation that doesn't respond to initial treatment. Those patients could be the ones with enlarged rectal diameters in the pre-treatment evaluation.

Moreover, we found a marginal association between maintained enuresis and increased rectal diameter. An association between enuresis and rectal diameter has already been seen by Jansson et al. (26), but the lack of larger sample size makes an underpowered analysis. Hoffman et al. (17) showed that enuresis was the only symptom associated with a poor outcome after Parasacral TENS in children with OAB, therefore, this relationship could exist making an impact on rectal diameter assessment beyond FC. In this way, the rectal di-

ameter can also be useful in the evaluation of the enuretic patient. Thus, our findings reinforce the idea that rectal diameter should be incorporated into the evaluation of children with LUTS and FC, not only as a diagnostic tool but also as a predictor of response to treatment. Regarding our study that hadn't found an association between rectal diameter and other urinary symptoms, our sample size could have influenced this result, since we had focused on children with BBD, not only in those with LUTS. Further studies should be done to elucidate the association between rectal diameter and LUTS.

As shown in Table-1, there was no association between rectal diameter and bowel symptoms associated with FC. However, children and adolescents with increased rectal diameter had a significantly higher constipation score. This finding suggests that there may not be a clear association between the diagnosis of constipation based on Rome IV and its assessment of the constipation score, since some of the signs and symptoms surveyed differ between these two instruments. This is a gap that is now being studied by other researchers in our group.

Nonetheless, there are certain limitations associated with the study that must be mentioned. The existence of two treatment groups and the size of the sample may have been confounding factors, making some analyses underpowered. However, no association was found between the type of treatment and pretreatment rectal diameter measurement or with the frequency of enlarged rectal diameter. This could be a consequence of the randomization of the initial trial. Further studies are required to confirm the hypothesis tested here that rectal diameter is a predictor of treatment outcome in children and adolescents with BBD.

Another limitation is that RD was considered enlarged when ≥ 3 cm for all patients, regardless of age. To our knowledge, there is no significant difference in this cut-off in older children and adolescents, according to Klijn et al. (21). But we think that the compliance of the rectum could change with age and consequently, change this cut-off. Further studies evaluating this question should be done to elucidate this gap in literature. As no patient in our study utilized laxatives throughout therapy, we are aware that our results

cannot be generalized to encompass alternative treatment modalities.

CONCLUSIONS

Enlarged rectal diameter (>3cm) appears to be relevant in the evaluation of children with BBD, not only as a diagnostic tool but also as a predictor of treatment outcome. However, more research should be conducted to confirm this finding, which will aid in evaluating the patient's treatment.

Abbreviations

95%CI = 95% Confidence Interval

BBD = Bladder and Bowel Dysfunction

DVSS = Dysfunctional Voiding Scoring System

FC = Functional Constipation

IQR = Interquartile Range

LUTS = Lower Urinary Tract Symptoms

OR = Odds Ratio

RD = Rectal Diameter

ROC curve = Receiver Operating Characteristic Curve

SD = Standard Deviation

TENS = Transcutaneous Electrical Nerve Stimulation

Data availability statement

The data supporting this study's findings are available on request from the corresponding author.

CONFLICT OF INTEREST

None declared.

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APPENDIX:**Supplementary File 1 - Dysfunctional Voiding Scoring System (DVSS) for children.**

Over the last month	Almost never	Less than half the time	About half the time	Almost every time	Not available
1. I have had wet clothes or wet underwear during the day.	0	1	2	3	NA
2. When I wet myself, my underwear is soaked.	0	1	2	3	NA
3. I miss having a bowel movement every day.	0	1	2	3	NA
4. I have to push for my bowel movements to come out.	0	1	2	3	NA
5. I only go to the bathroom one or two times each day.	0	1	2	3	NA
6. I can hold onto my pee by crossing my legs, squatting or doing the “pee dance”.	0	1	2	3	NA
7. When I have to pee, I cannot wait.					
8. I have to push to pee.	0	1	2	3	NA
9. When I pee it hurts.	0	1	2	3	NA
10. Parents to answer. Has your child experienced something stressful like the example below?	NO (0)			YES (3)	
TOTAL					

Supplementary File 2: Constipation Score for children.

Frequency of bowel movements 0. 1-2 times per 1-2 days 1. 2 times per week 2. Once per week 3. Less than once per week 4. Less than once per month	Minutes in the toilet to defecate 0. Less than 5 minutes 1. 5-10 minutes 2. 10-20 minutes 3. 20-30 minutes 4. More than 30 minutes
Painful evacuation effort 0. Never 1. Rarely 2. Sometimes 3. Usually 4. Always	Type of assistance 0. No assistance 1. Stimulative laxatives 2. Digital assistance or enema
Feeling incomplete evacuation 0. Never 1. Rarely 2. Sometimes 3. Usually 4. Always	Unsuccessful attempts for evacuation per 24 hours 0. Never 1. 1-3 2. 3-6 3. 6-9 4. More than 9
Abdominal pain 0. Never 1. Rarely 2. Sometimes 3. Usually 4. Always	Duration of constipation 0. Less than 1 year 1. 1-3 years 2. 3-5 years 3. 5-7 years 4. More than 7 years



Dynamic and static ultrasound features predictive of vesicoureteral reflux and renal damage in children and adolescents with neurogenic bladder

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ABSTRACT

Purpose: This study aimed to analyze the diagnostic accuracy of dynamic and static ultrasound (DSUS) in detecting vesicoureteral reflux (VUR) and renal scarring in a cohort of children with neurogenic bladder (NB).

Materials and Methods: A retrospective, longitudinal, observational study was conducted using the Reporting Diagnostic Accuracy Studies guideline. The DSUS (index test) data were compared with voiding cystourethrography (VCUG) and renal scintigraphy 99mTc-dimercaptosuccinic (reference tests). Overall performance for predicting VUR and renal scarring was assessed using renal pelvic diameter (RPD)/distal ureteral diameter and renal parenchymal thinning on DSUS, respectively.

Results: A total of 107 patients (66 girls, median age 9.6 years) participated. Seventeen patients (15.9%) presented VUR, eight bilateral. For overall reflux grade, the AUC was 0.624 for RPD and 0.630 for distal ureteral diameter. The diagnostic performance for detecting high-grade VUR was slightly better for DSUS parameters. The AUC was 0.666 for RPD and 0.691 for distal ureteral diameter. The cut-offs of 5 mm for RPD and 6.5 mm for distal ureteral diameter presented the best diagnostic odds ratio (DOR) to identify high-grade VUR. The increase of RPD during detrusor contractions showed an accuracy of 89.2%. The thinness of renal parenchyma presented an accuracy of 88% for renal scarring.

Conclusion: DSUS predicts VUR and renal scarring in children with NB with fair to good accuracy, and all measurements exhibited a high negative predictive value (NPV). The increase in RPD during voiding or detrusor contractions proved to be the most accurate parameter for indicating the presence of VUR in this study.

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INTRODUCTION

The most common cause of neurogenic bladder (NB) in children is neurospinal dysraphism (1-3). NB is present in up to 98% of children with myelomeningocele (4). About 25% of the most severe symptoms in pediatric urology are associated with neurogenic bladder (5), and 40% of children with NB develop chronic kidney disease (6). Patients with NB may present with various patterns of detrusor-sphincter dyssynergia and increased intravesical pressure, which can lead to urinary and/or fecal incontinence, urinary tract infections (UTIs), vesicoureteral reflux (VUR) and renal impairment (1, 3, 7). The diagnosis and follow-up of patients with NB involves a multidisciplinary approach, including serial clinical, laboratory, and imaging tests. The goals of managing bladder dysfunction in children are maintaining a low-pressure, high-compliance bladder, and preventing

upper urinary tract deterioration (8).

VUR, an important risk factor for pyelonephritis and renal scarring (1, 7, 9, 10), is present in up to one-third of children with NB (8), making its diagnosis and approach essential (3, 8). VCUG and renal scintigraphy are the gold standard tests for diagnosing VUR and renal scarring (9, 11, 12). The role of renal and bladder ultrasound as a screening tool for VUR and kidney damage in children with NB has been debated (13). However, in this sense, the lack of US accuracy for VUR or renal scarring may hinder its use in NB, given the need to prevent irreversible renal damage (3, 9). However, the development of the dynamic and static ultrasound (DSUS) technique made it possible to obtain essential data for the diagnosis and follow-up of patients with NB (14). We hypothesize that the magnitude of specific DSUS measurements could predict the presence of VUR and renal scars. Therefore, this study aims to analyze the diagnos-

tic accuracy of DSUS in detecting VUR and kidney damage in our cohort of children and adolescents with NB.

MATERIALS AND METHODS

Ethical approval

The study was approved by Institutional Review Committee (IRB) under protocol CAAE 37450820000005149, position statement number 4.487.114. Legal guardians and participants aged 10 and 17 signed the Informed Consent Term and the Assent Term, respectively. The medical records were selected through an active search in the Medical Service and Archive after the institution's consent and signature of the Data Use Commitment Term.

Study design and patients

This retrospective cohort study included 127 consecutive patients enrolled in the Multidisciplinary Outpatient Clinic for Children and Adolescents with NB. We designed our study and reported our findings following the STAndards for the Reporting of Diagnostic accuracy studies (STARD) presented in Supplement 1 (15). Eligibility criteria were all patients with NB enrolled in the service between 1997 to 2022 who underwent DSUS, VCUG and renal scintigraphy (99mTc-DMSA) according to the care protocol. Twenty patients were excluded from the analysis: 15 due to lack of information in the medical records, and five refused to participate in the study.

Study protocol

A systematic clinical protocol was applied to all NB patients enrolled in the multidisciplinary outpatient clinic (1-3). On admission, we performed a clinical laboratory and imaging investigation (DSUS, urodynamic study, VCUG to assess VUR, and renal scintigraphy (99mTc-DMSA) to diagnose NB status and assess renal scarring. Our follow-up protocol included clinical examination, laboratory analysis at semi-annual intervals, and DSUS, annually or as clinically necessary.

Index test

DSUS was considered the index test (test being evaluated) and was performed by the same trained examiner using a standard method (14). The exams were performed, on annual basis, using a Toshiba/Canon® Prima SLC Ultrasound Device, model Aplio 300 or 400 supplied with multifrequency convex (3.7 to 7.6 MHz), linear (8.0 to 12.0 MHz), high frequency electronic linear (13.0 to 18.0 MHz) transducers.

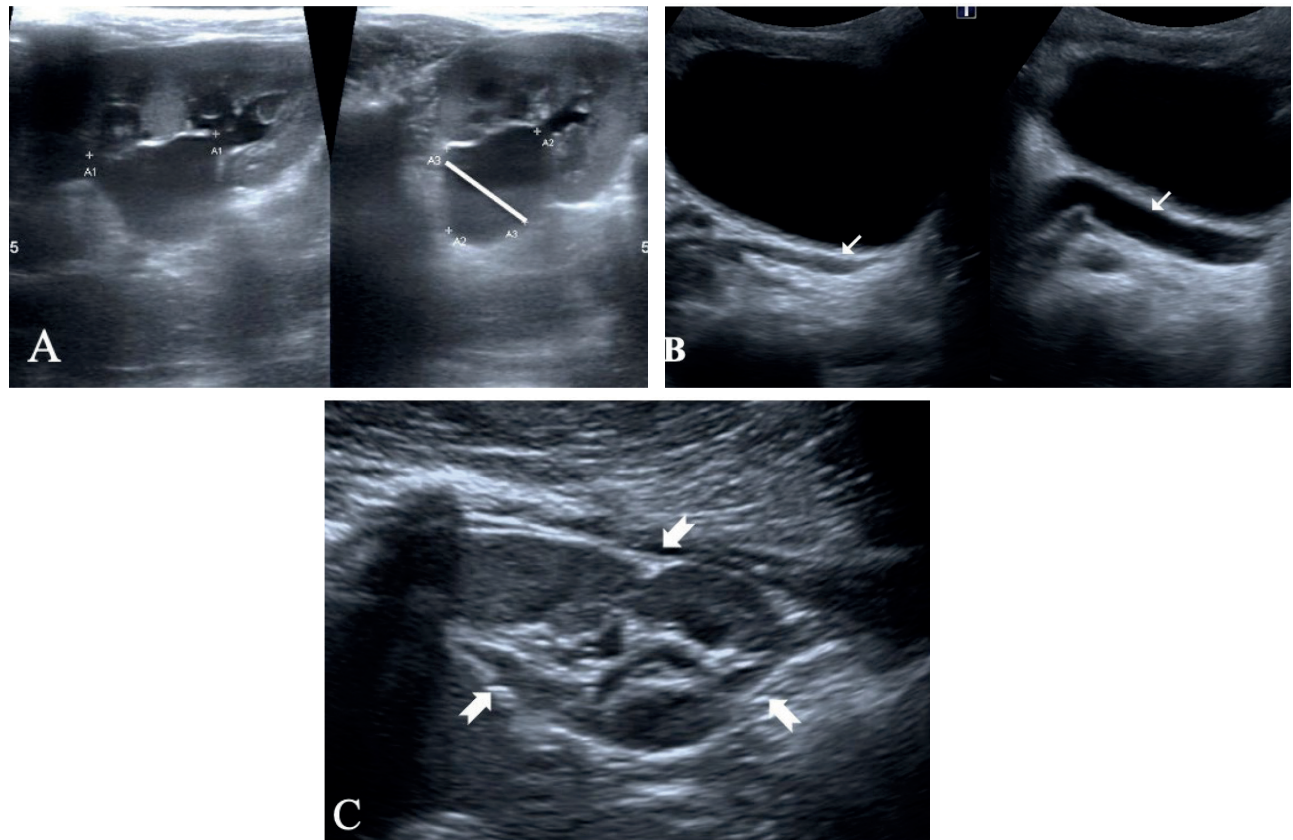
The assessed index tests were based on the first ultrasound after enrollment in the outpatient clinic. For patients with bilateral urinary tract alteration, index tests were generated for each renal unit. The following sonography indexes were determined as proposed by Dinkel et al. (16): Renal pelvic diameter (RPD) was determined by the greatest anteroposterior diameter of the renal pelvis acquired in a transverse plane on ultrasound dorsal images; Distal ureter diameter; Renal parenchyma thickness (RPT) was measured at the transverse view for each kidney; Bladder wall thickening; Bladder capacity; Presence of bladder residual urine (absent, mild, severe); Bladder trabeculation; Renal scarring. Renal scarring on DSUS was assessed using the following criteria: proximity of sinus echoes to the cortical surface, loss of pyramids, irregular outline, and loss of definition of capsular echo (17). In addition, in DSUS, we evaluated RPD increase during voiding or detrusor contractions as an indirect indicator of the presence of VUR (14) (Figure-1).

Reference tests

Examiners who were unaware of the other tests' results performed the index and standard reference tests.

The VCUG was considered the reference standard for VUR. The VCUG was requested at the beginning of the follow-up with a maximum interval of six months concerning the DSUS. We used the classification of VUR proposed by the Reflux Study Committee (18). In addition, according to reflux grade, we classified reflux as low-grade (I), mild to moderate-grade (II to III), and high-grade (IV-V) (19).

Figure 1 - Sonography indexes. (A- renal pelvic diameter, B- distal ureteral diameter, C-renal scarring).



The reference test for renal scarring was renal scintigraphy (^{99m}Tc -DMSA), performed on admission (after the fourth month of life for infants) and later according to a clinical decision (episodes of recurrent UTIs/pyelonephritis) (1-3, 7).

Statistical Analysis

Continuous data were recorded as median and 25th to 75th interquartile range (IQ). The nonparametric Mann-Whitney test was used to compare these variables. Dichotomous variables were compared using the 2-sided chi-square test.

The diagnostic accuracy of the indexes tests was assessed by sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios (LR). Receiver-operating characteristic (ROC) curves

were analyzed for the overall diagnostic accuracy of continuous indexes (RPD and distal ureteral diameter) in discriminating infants who will present the events of interest (VUR and renal scarring). The area under the curve (AUC) was interpreted as the probability that a randomly selected patient with the event of interest had a larger maximum diameter than a randomly selected patient without the event of the interest.

We also analyzed the combined results of the continuous indexes (RPD and distal ureteral diameter) (20). Therefore, two possibilities were analyzed, using the “OR” rule, i.e., considering a positive diagnosis if either test was positive and a negative diagnosis if both tests were negative, and the “AND” rule, i.e., considering a positive diagnosis only if both tests were positive and a negative diagnosis if either test was negative.

RESULTS

A total of 107 patients (66 females) were included in the analysis. The main baseline clinical characteristics of patients are summarized in Table-1. Seventeen patients (15.9%) presented VUR, eight bilateral, giving a total of 25 refluxing units (11 mild to moderate grade (II-III) and 14 high-grade (IV-V) reflux).

Vesicoureteral reflux

The diagnostic accuracy of DSUS in predicting reflux was evaluated using the maximum RPD and the maximum distal ureteral diameter. For overall reflux grade, the AUC was 0.624 (95% CI, = 0.553 - 0.692) for RPD and 0.630 (95% CI, 0.556 - 0.700) for distal ureteral diameter (Figures 1A-B). The diagnostic performance for detecting high-grade VUR (Grade IV-V) was slightly better

Table 1 - Patient clinical and demographics characteristics.

N = 107	
Gender	
Male	41 (38.3)
Female	66 (61.7)
Neural tube defect	
Spina bifida	92 (86.0)
Others	15 (14.0)
Age (years)	
Median	9.6
Interquartile range	6.1 – 17.0
Mean	11.6
Standard deviation	6.5
Vesicoureteral reflux	
Absent	90 (84.1)
Unilateral	9 (8.4)
Bilateral	8 (7.5)
Vesicoureteral reflux (units. grade)	
Absent	189 (88.3)
Mild Moderate (II III)	11 (5.1)
Severe (IV V)	14 (6.5)
Renal damage (99mTc-DMSA)	
Absent	72 (80.2)
Unilateral	
Bilateral	18 (19.6)
	2 (2.2)

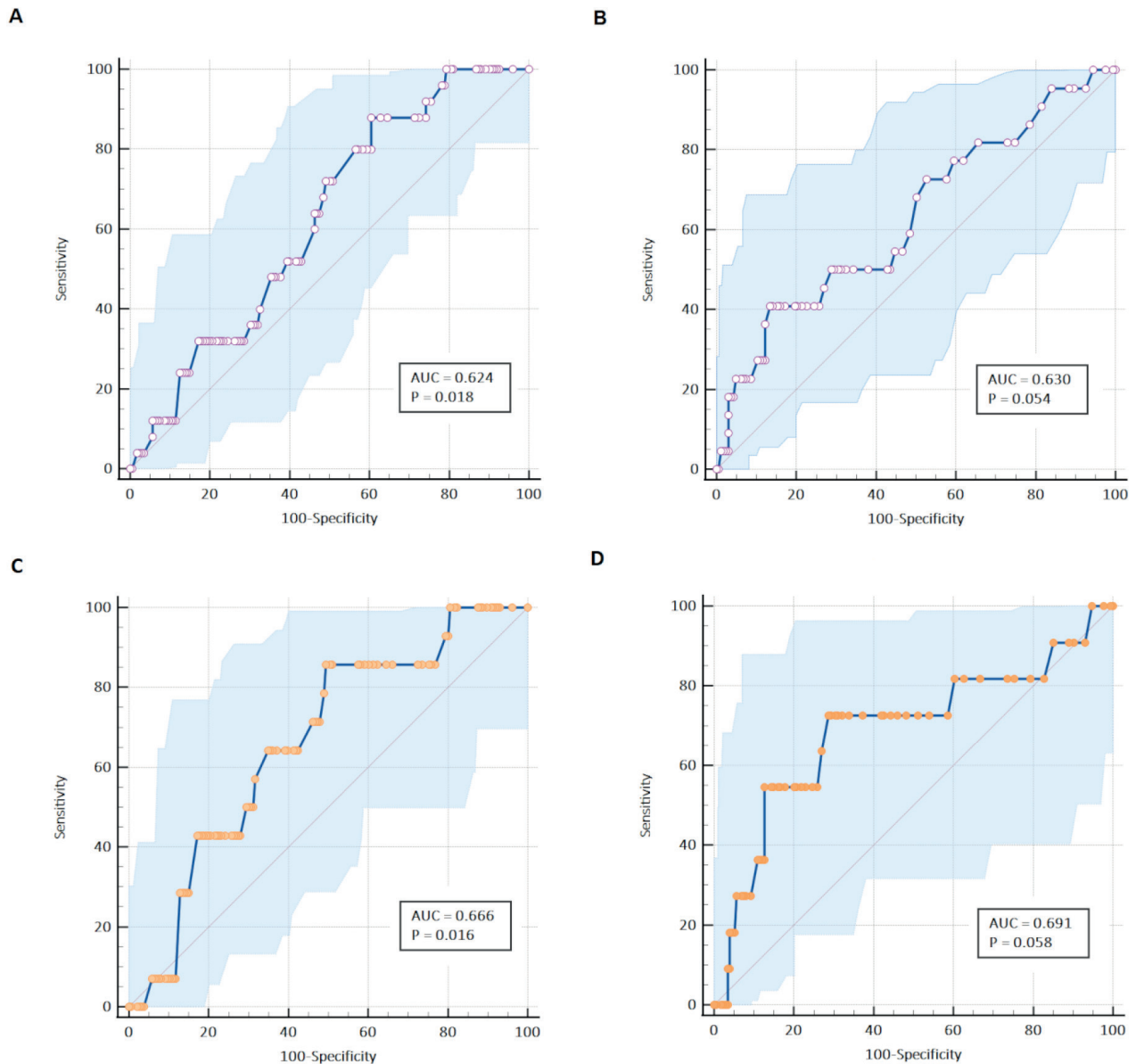
99mTc-DMSA renal scintigraphy 99mTc-dimercaptosuccinic

for both US parameters. The AUC was 0.666 (95% CI, 0.596 - 0.731) for RPD and 0.691 (95% CI, 0.619 - 0.757) for distal ureteral diameter (Figure-2).

Table-2 shows the diagnostic performance of various RPD and distal ureteral diameter thresholds indicating VUR (Grade II-V). The cut-offs of 5 mm for RPD and 6.5 mm for distal ureteral diameter presented the best diagnostic odds ratio (DOR) to identify children with high-

grade VUR. The combined results of both pelvic and ureter diameters are also shown in Table-2. Regarding both tests in parallel and using the “OR rule,” i.e., the sensitivity increased to 80% (95% CI, 59.3-93.2), and the negative predictive value (NPV) to 94.8% (95% CI, 89.8-97.6). However, considering the low prevalence of reflux, the positive predictive value (PPV) was only 17.4% (95% CI, 7.8-16.9). By contrast, using the “AND rule”,

Figure 2 - ROC curves comparing ultrasonographic measurements of RPD and the presence of general vesicoureteral reflux. (A- RPD, B- distal ureteral diameter) and high-grade vesicoureteral reflux (C- RPD, D- distal ureteral diameter).



ROC = Receiver Operating Characteristic; AUC = Area under the ROC curve; RPD = renal pelvic diameter

Table 2 - Diagnostic accuracy of sonography measurements for vesicoureteral reflux (grade II- V)

	Sensitivity% (95%CI)	Specificity% (95%CI)	PPV	NPV	DOR
RPD cut-offs					
> 5.0 mm	72.0 (50.6 - 87.9)	49.4 (41.5 - 56.8)	16.8 (13.2 - 21.2)	92.5 (86.6 - 95.9)	2.5
> 7.5 mm	36.0 (18.0 - 57.5)	68.0 (60.5 - 74.8)	13.8 (8.4 - 22.1)	88.1 (84.5 - 91.0)	1.2
> 10.0 mm	32.0 (14.9 - 53.5)	79.4 (72.7 - 85.2)	18.2 (10.5 - 29.7)	89.1 (86.1 - 91.5)	1.8
> 12.5 mm	24.0 (9.4 - 45.1)	86.3 (80.3 - 91.0)	20.0 (10.3 - 35.3)	88.8 (86.4 - 90.9)	2.0
Ureter cut-offs					
> 4.5 mm	50.0 (28.2 - 71.8)	68.7 (61.0 - 75.7)	17.7 (11.8 - 25.8)	91.1 (86.9 - 94.0)	2.2
> 5.5 mm	40.9 (20.7 - 63.6)	77.3 (70.1 - 83.5)	19.6 (12.0 - 30.2)	90.6 (87.1 - 93.3)	2.4
> 6.5 mm	40.9 (20.7 - 63.6)	86.5 (80.3 - 91.3)	29.0 (17.8 - 43.6)	91.6 (88.4 - 93.9)	4.5
> 7.5 mm	27.3 (10.7 - 50.2)	89.0 (83.1 - 93.3)	25.0 (12.9 - 42.8)	90.1 (87.5 - 92.2)	3.0
Combined indexes (OR rule)					
RPD > 5.0 mm	80.0	49.2	17.4	94.8	3.9
Ureter > 6.5 mm	(59.3- 93.2)	(41.8 - 56.6)	(7.8 – 16.9)	(89.8 – 97.6)	
Combined indexes (AND rule)					
RPD > 5.0 mm	32.0	88.7	27.6	90.7	3.7
Ureter > 6.5 mm	(14.9- 53.5)	(83.3 – 92.9)	(15.9 - 43.4)	(88.1 - 92.8)	

95% CI = Confidence Interval 95%; PPV = positive predictive value; NPV = negative predictive value; DOR = diagnostic odds ratio

the specificity increased to 88.7% (95% CI, 83.3-92.9). However, again the PPV was only 27.6% (95% CI, 15.9-43.4), but the NPV was 90.7% (95% CI, 88.1-92.8).

Table-3 shows a similar analysis for high-grade VUR (Grade IV-V). Of note, the same cutoff points of 5 mm for RPD and 6.5 mm for distal ureteral diameter had the best DOR to identify children with high-grade reflux. Regarding the two tests in parallel, using the “OR rule”, the sensitivity increased to 92.9% (CI 95%, 66.1-99.8) and the NPV to 94.8% (CI 95%, 93.5-99.8), the specificity increased to 89.5% (95% CI, 81.8-91.9). It still shows the diagnostic performance of categorical variables indicating high-grade VUR (Grade IV-V). Overall performance was relatively poor for all measurements, except for the observation, in the dynamic phase of the test, of an increase in RPD during urination, a finding that had a specificity

of 92.5% (95% CI, 87.9-95.7), NPV of 95.9% (95% CI, 93.6-97.3) and an accuracy of 89.2% (95% CI, 84.3-93.0) for reflux high-grade.

Renal damage

A total of 92 patients (86%) had information regarding renal scintigraphy (99mTc-DMSA). Twenty children, out of the 92, had renal damage (two bilateral), giving a total of 22 kidney units. The presence of renal damage was associated with high-grade reflux. Twelve units had high-grade reflux, 4 (33.3%) had renal damage, whereas, in 172 units with mild-moderate or absence of reflux, 18 (10.5%) had an abnormality on renal scintigraphy ($P = 0.04$). The presence of thinning of the renal parenchyma in DSUS predicted damage to renal scintigraphy. This finding presented a sensitivity of 40.9% (95% CI, 20.7 - 63.6), specificity of 94.4% (95% CI, 89.7 - 97.4), a PPV of

Table 3 - Diagnostic accuracy of sonography measurements for high-grade vesicoureteral reflux (grade IV- V).

	Sensitivity% (95%CI)	Specificity% (95%CI)	PPV (95%CI)	NPV (95%CI)	DOR
RPD cut-offs					
> 5.0 mm	85.7 (57.2 - 98.2)	48.9	11.2	97.8	5.8
> 7.5 mm	50.0 (23.0 - 77.0)				2.2
> 10.0 mm	42.9 (17.7 - 71.1)				2.9
> 12.5 mm	28.6 (8.4 - 58.1)				2.5
Ureter cut-offs					
> 4.5 mm	72.7(39.0 - 94.0)	68.9 (61.5 - 75.7)	12.9 (8.8 - 18.5)	97.6 (93.8 - 99.1)	5.8
> 5.5 mm	54.5 (23.4 - 83.3)	77.0(70.0 - 83.0)	13.0 (7.6 - 21.5)	96.4 (93.3 - 98.1)	4.0
> 6.5 mm	54.5 (23.4 - 83.3)	85.6 (79.5 - 90.5)	19.4 (11.1 - 31.5)	96.8 (94.0 - 98.3)	7.2
> 7.5 mm	36.4 (10.9 - 69.2)	88.5 (82.8 - 92.8)	16.7 (7.6 - 32.6)	95.7 (93.3 - 97.2)	4.4
Combined indexes (OR rule)					
RPD > 5.0 mm	92.9	48.5	11.3	98.9	12.3
Ureter > 6.5 mm	(66.1 - 99.8)	(41.3 -55.7)	(9.5 - 13.4)	(93.5 - 99.8)	
Combined indexes (AND rule)					
RPD > 5.0 mm	42.8	89.5	20.7	95.3	5.2
Ureter > 6.5 mm	(17.6 - 71.1)	(81.8 - 91.9)	(11.3 - 34.8)	(92.7 - 96.9)	
Thickness bladder wall	30.0 (6.7 - 65.2)	72.2 (62.2 - 80.8)	10.0 (3.9 - 23.2)	90.9 (86.7 - 93.8)	1.1
Trabeculated bladder wall	33.3 (7.5 -70.0)	71.2 (61.0 - 80.1)	10.0 (4.0 - 22.8)	91.8 (87.4 - 94.7)	1.2
Post-void residual urine	50.0 (18.7 - 81.3)	45.4 (35.2 - 55.8)	8.6 (4.7 - 15.2)	89.8 (82.0 - 94.4)	0.7
Large post-void residual urine	30.0 (6.7 - 65.2)	61.8 (51.4 - 71.5)	7.5 (2.9 -17.7)	89.6 (84.7 -92.9)	2.9
Bladder capacity increased	22.2 (2.8 - 60.0)	78.7 (69.0 - 86.5)	9.0 (2.7 - 26.5)	91.3 (88.0 - 93.8)	1.0
Bladder capacity diminished	44.4 (13.7 - 78.8)	69.1 (58.8 -78.3)	12.1 (5.9 - 23.3)	92.8 (87.7 - 95.9)	1.8
Bladder capacity abnormal	66.7 (29.9 - 92.5)	47.9 (37.5 - 58.4)	10.9 (6.9 - 16.8)	93.7 (85.3 - 97.5)	1.8
Bladder diverticulum	10.0 (2.5 - 44.5)	84.5 (75.8 - 91.0)	6.2 (1.9 - 31.2)	90.1 (87.9 - 91.9)	0.6
RPD increased during voiding or detrusor contraction	42.6 (17.7 - 71.1)	92.5 (87.9 - 95.7)	28.6 (15.5 - 46.5)	95.9 (93.6 - 97.3)	9.2

95% CI = Confidence Interval 95%; PPV = positive predictive value; NPV = negative predictive value; DOR = diagnostic odds ratio; RPD = Renal pelvic diameter

50% (95% CI, 30.8 - 69.2), an NPV of 92.2% (95% CI, 89.2 - 94.3), a DOR of 11.8, and an accuracy of 88% (95% CI, 82.5 - 92.3) for renal scarring.

DISCUSSION

In this retrospective cohort study, we evaluated DSUS measurements as predictors for VUR and renal scarring in a cohort of children and adolescents with NB. Our findings showed that sonography kidney measurements predict with fair to good accuracy the presence of VUR and renal scarring, which are crucial to managing children with NB. Overall, the PPV was low due to the relatively low prevalence of VUR, but the NPV was high for all renal measurements.

Clinical studies have reported that secondary VUR is prevalent in children and adolescents with NB (8). For instance, Bortolini et al. (21) described results like ours (15.9%) and demonstrated 19% of VUR in patients with NB. Sidi et al. (22) showed a higher prevalence of 52% (46.7% high grade). We evaluated the performance of two continuous measurements, RPD and distal ureter diameter, in predicting VUR. As previously mentioned, the magnitude of both measurements could indicate the presence of VUR. However, we described relatively low accuracy in identifying all grades of VUR, which did not improve for high-grade reflux. The literature is limited to specific ultrasound findings' contribution to predicting VUR in children with NB (13). Our findings agree with the study by Naseri et al. (19), who described that hydronephrosis (RPD $\geq$ 5mm) has low accuracy (0.65) for general VUR and does not improve for high-grade VUR (0.66) in patients without NB with UTI (1-18 years). On the other hand, a study demonstrated hydronephrosis in 28.8% of patients (1-144 months) with a first episode of febrile UTI and 18.5% with high-grade VUR (DOR 18.8) (23). Swanton et al. (24) showed the distal diameter of the ureter as a measure to predict VUR. In our analysis, the distal ureteral diameter (>6.5 mm) had relatively low accuracy (DOR 4.5) for general-grade VUR and slightly better accuracy (DOR 7.5) for high-grade VUR. This finding agrees with a recent study that shows the presence of hydroureteronephrosis evidenced low accuracy (0.67)

for general VUR but became moderate (0.82) for high-grade VUR (19). Lee et al. (23) reported that the presence of a hydroureter $\geq$ 7 mm in children without NB with a first UTI had a DOR of 20.4 for high-grade VUR. Recent studies suggest that measurement of the distal ureteral diameter is objective and reliable and is more predictive of the clinical outcome, regardless of the grade of VUR (24, 25). Our findings showed a considerable improvement in overall performance when we combined the two measurements (RPD and distal ureter diameter), with a sensitivity of 92.9% and an NPV of 94.8% for high-grade VUR.

Regarding the categorical measurements, we emphasize that the overall performance was low for all measures, except for the increase in RPD in the dynamic phase of the test. One of the peculiarities of DSUS is the assessment of RPD during urination or detrusor contractions as an indirect sign of VUR (14). In our analysis, this finding demonstrated a good accuracy (89%) in predicting VUR.

DSUS has been used in our clinic since developing the technique in 2003 (14), including for diagnosing patients with non-neurogenic dysfunction (26). Filgueiras et al. (14) demonstrated that DSUS is a sensitive method and correlates well with urodynamic findings. In this sense, Bortolini et al. (21) showed excellent accuracy (90% accuracy, kappa coefficient of 0.8, $p < 0.001$) of DSUS in identifying detrusor overactivity in patients with NB due to myelomeningocele when compared to urodynamic testing. The DSUS, a noninvasive test, has guided us in the follow-up of children with NB, as it can anticipate clinical worsening and help us in decision-making.

One of the main goals in monitoring children with NB is to identify early changes in the upper urinary tract and thus prevent long-term kidney damage (2, 7). Renal scintigraphy (99mTc-DMSA) is the gold standard test for detecting renal scarring, present in 25% of children with spina bifida with some degree of VUR (27). Scar detection was observed in adults with spinal dysraphism in 10% by ultrasonography and 46% by renal scintigraphy (99mTc-DMSA). Renal injury has been associated with high-grade VUR (28). Finkelstein et al. (12) demonstrated low accuracy

in detecting renal scars by ultrasonography. Our findings showed the presence of renal scarring in 19.2% of patients submitted to renal scintigraphy (99mTc-DMSA). DSUS showed that renal parenchymal thinning predicts renal scarring on renal scintigraphy with moderate accuracy (88%). In a previous study in our clinic, renal scarring was detected in 31.7% of patients, with bladder wall thickness in DSUS being a marginal risk factor of renal scarring (29).

Our study has limitations. First, it is a retrospective study with inherent issues concerning this design, such as missing data. In this regard, we had to exclude some patients from the analysis due to the incomplete registry of the index tests. In addition, we tried to minimize the DSUS and VCUG findings of interpretation variability with a highly trained team using the same methodology. Also, we tried to mitigate the risk of verification bias by selecting the indexes and reference tests at the closest intervals with blinded radiologists. Thus, even though it is a retrospective study, when we present the results of a non-invasive test, such as the DSUS, with the possibility of predicting VUR in children with NB, we believe that it can be of great value in managing these patients. Thus, this finding could help minimize harm to these children and adolescents with such a severe and complex condition, including risks of urinary tract infection, exposure to ionizing radiation, discomfort and anxiety during an invasive test such as the VCUG.

CONCLUSIONS

Dynamic and static ultrasound predict vesicoureteral reflux and renal scarring in children with neurogenic bladder with fair to good accuracy, and all ultrasound measurements exhibited a high negative predictive value, meaning that the absence of these findings indicates the absence of vesicoureteral reflux clinically significant. The increase in renal pelvic diameter during urination or detrusor contractions proved to be the most accurate parameter to indicate the presence of vesicoureteral reflux in this study. The thickness of the renal parenchyma showed good accuracy for renal scarring. Thus, our findings suggest that dynamic

and static ultrasound and voiding cystourethrography should be considered complementary in the initial approach for children and adolescents with neurogenic bladder.

ABBREVIATIONS

NB = Neurogenic bladder
 VUR = Vesicoureteral reflux
 VCUG = Voiding cystourethrography.
 DSUS = Dynamic and static ultrasound
 RPD = Renal pelvic diameter
 RPT = Renal parenchyma thickness
 ROC = Receiver operating characteristic curve
 AUC = Area under the ROC curve
 IQ = Interquartile range
 LR = Likelihood ratio
 DOR = Diagnostic odds ratio
 NPV = Negative predictive value
 PPV = Positive predictive value
 US = Ultrasound
 99mTc-DMSA = 99-Technetium dimercaptosuccinic acid

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ETHICAL APPROVAL

The institution's Ethics Committee approved the study under protocol CAAE 37450820000005149 (position statement 4487114). Legal guardians and participants over 10 years of age signed the Free and Informed Consent Term and the Assent Term, respectively.

CONFLICT OF INTEREST

None declared.

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APPENDIX

Supplement 1 - STARD (STAndards for the Reporting of Diagnostic accuracy studies) Checklist (15).

Section & Topic	No	Item	Reported on page
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	1
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	2
	4	Study objectives and hypotheses	2
METHODS			
<i>Study design</i>	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	3
<i>Participants</i>	6	Eligibility criteria	3
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	3
	8	Where and when potentially eligible participants were identified (setting, location and dates)	3
	9	Whether participants formed a consecutive, random or convenience series	3
<i>Test methods</i>	10a	Index test, in sufficient detail to allow replication	3-4
	10b	Reference standard, in sufficient detail to allow replication	4-5
	11	Rationale for choosing the reference standard (if alternatives exist)	4-5
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	4-5
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	4-5
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	4-5
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	4-5

<i>Analysis</i>	14	Methods for estimating or comparing measures of diagnostic accuracy	5
	15	How indeterminate index test or reference standard results were handled	5
	16	How missing data on the index test and reference standard were handled	5
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	5
	18	Intended sample size and how it was determined	5
RESULTS			
<i>Participants</i>	19	Flow of participants, using a diagram	N/A
	20	Baseline demographic and clinical characteristics of participants	5-6 (Table 1)
	21a	Distribution of severity of disease in those with the target condition	6-7
	21b	Distribution of alternative diagnoses in those without the target condition	6-7
	22	Time interval and any clinical interventions between index test and reference standard	6-7
<i>Test results</i>	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	6-7
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	6-7
	25	Any adverse events from performing the index test or the reference standard	6-7
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	7-10
	27	Implications for practice, including the intended use and clinical role of the index test	7-10
OTHER INFORMATION			
	28	Registration number and name of registry	N/A
	29	Where the full study protocol can be accessed	Supplementary information
	30	Sources of funding and other support; role of funders	FAPEMIG

N/A-not applicable

STARD 2015

AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition**. This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test**. A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on <http://www.equator-network.org/reporting-guidelines/stard>.

Supplement 2 - Propaedeutic Protocol for Neurogenic Bladder in Pediatrics (1-3).**Propaedeutics to confirm the diagnosis and establish the status of the neurogenic bladder.**

Apply a structured questionnaire, including questions about bladder emptying, urination, urinary leakage, use of catheterization and bladder drainage (daily filling of the bladder), and bowel function.

Perform a complete physical examination with an evaluation of the external genitalia, lumbosacral region, and neurological reflexes.

Laboratory tests: blood gas analysis, serum creatinine, urea, electrolytes, urinalysis, and urine culture

Dynamic and static ultrasound (DSUS).

Urodynamic study and voiding cystourethrography (VCUG) will be performed six weeks after surgery to correct spinal dysraphism due to spinal shock phase evaluation. If the correction of dysraphism is intrauterine, it will not be necessary to wait six weeks.

Renal scintigraphy (99mTc-DMSA).

Propaedeutics to follow-up

Clinical examination, including clean bladder catheterization technique evaluation by nursing staff every six months.

Laboratory tests: blood gas analysis, serum creatinine, urea, electrolytes, urinalysis, and urine culture every six months.

Six-monthly DSUS through age two years and after that, annually or as clinically necessary and as soon as possible in the case of patients who have abandoned treatment and follow-up.

Urodynamic study annually and as soon as possible in the case of patients who have abandoned treatment and follow-up.

VCUG depends on the clinical evolution and will be repeated annually in the patient with high-grade VUR before urological surgery and as soon as possible in the case of patients who have abandoned treatment and follow-up.

Renal scintigraphy (99mTc-DMSA) depends on the clinical and ultrasonographic evolution.

Patients with worsening the neurological, orthopedic, or urological status, a neurosurgical evaluation should be performed (risk of symptomatic chord, syringomyelia, increased intracranial pressure caused by valve system dysfunction).

Follow-up propaedeutics for bladder augmentation surgery using small bowel, colon, or gastric segments



Head-to-head comparisons of enhanced CT, ^{68}Ga -PSMA-11 PET/CT and ^{18}F -FDG PET/CT in identifying adverse pathology of clear-cell renal cell carcinoma: a prospective study

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ABSTRACT

Objectives: Accurate preoperative prediction of adverse pathology is crucial for treatment planning of renal cell carcinoma (RCC). Previous studies have emphasized the potential of prostate-specific membrane antigen positron emission tomography / computed tomography (PSMA PET/CT) in differentiating between benign and malignant localized renal tumors. However, there is a scarcity of case reports elucidating the identification of aggressive pathological features using PET/CT. Our study was designed to prospectively compare the diagnostic value of enhanced CT, ^{68}Ga -PSMA-11 and ^{18}F -fluorodeoxyglucose (^{18}F -FDG) PET/CT in clear-cell renal cell carcinoma (ccRCC) with necrosis or sarcomatoid or rhabdoid differentiation.

Materials and Methods: A prospective case series of patients with a newly diagnosed renal mass who underwent enhanced CT, ^{68}Ga -PSMA-11 and ^{18}F -FDG PET/CT within 30 days prior to nephrectomy was included. Complete preoperative and postoperative clinicopathological data were recorded. Patients who received neoadjuvant targeted therapy, declined enhanced CT or PET/CT scanning, refused surgical treatment or had non-ccRCC pathological indications were excluded. Radiological parameters were compared within subgroups of pathological characteristics. Bonferroni corrections were used to adjust for multiple testing and statistical significance was set at a p-value less than 0.017.

Results: Seventy-two patients were available for the final analysis. Enhanced CT demonstrated poor performance in identifying necrosis, sarcomatoid or rhabdoid differentiation and adverse pathology (all $P > 0.05$). The maximum standardized uptake value (SUVmax) of ^{68}Ga -PSMA-11 PET/CT was more effective than ^{18}F -FDG PET/CT in identifying tumor necrosis and adverse pathology, with an area under the curve (AUC) of 0.85 (cutoff value=25.26, $p < 0.001$; Delong test $z = 2.709$, $p = 0.007$) for tumor necrosis and AUC of 0.90 (cutoff value=25.26, $p < 0.001$; Delong test $z = 3.433$, $p < 0.001$) for adverse pathology. However, no significant statistical difference was found between ^{68}Ga -PSMA-11 and ^{18}F -FDG PET/CT in predicting sarcomatoid or rhabdoid feature (AUC of 0.91 vs. 0.75, Delong test $z = 1.998$, $p = 0.046$). Subgroup analyses based on age, sex, tumor location, maximal diameter, stage and WHO/ISUP grade demonstrated that ^{68}Ga -PSMA-11 PET/CT SUVmax had a significant predictive value for adverse pathology. Enhanced CT value and SUVmax demonstrated strong reliability [intraclass correlation coefficient (ICC) > 0.80], indicating a robust correlation.

Conclusions: ^{68}Ga -PSMA-11 PET/CT demonstrates distinct advantages in identifying aggressive pathological features of primary ccRCC when compared to enhanced CT and ^{18}F -FDG PET/CT. Further research and assessment are warranted to fully establish the clinical utility of ^{68}Ga -PSMA-11 PET/CT in ccRCC.

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INTRODUCTION

In recent years, the incidence rate of renal cell carcinoma (RCC) has been increasing, ranking as the 9th most frequently diagnosed cancer in women and the 6th in men (1). Clear-cell RCC (ccRCC) is the main histologic subtype, accounting for 78.6% of all RCC tumors (2). Tumor necro-

sis (3), sarcomatoid (4) or rhabdoid differentiation (5) are well recognized as unfavorable outcomes, which are frequently observed in ccRCC. Immune checkpoint therapy (ICT) has exhibited encouraging outcomes in these subtypes (6), emphasizing the significance of precise preoperative prediction of aggressive pathological features to optimize treatment planning and enhance long-term

survival. Although percutaneous biopsy can accurately diagnose pathological types, it carries risks of invasiveness and potential non-diagnostic results. Moreover, the intratumoral heterogeneity in ccRCC increases the likelihood of false negatives for the detection of adverse pathology due to spatial sampling bias (7).

The detection efficiency of ccRCC has been greatly enhanced owing to the extensive application of various imaging modalities (8). However, conventional imaging studies, such as enhanced computed tomography (CT), have only moderate accuracy in predicting histology (9). Molecular imaging with positron emission tomography (PET) potentially offers a more sensitive and specific alternative (10). ¹⁸F-fluoro-2-deoxy-2-d-glucose (FDG) PET/CT, a critical molecular imaging modality, has been used to evaluate RCC since the 1990s (11). However, its usefulness in characterizing renal masses has shown heterogeneity and limited benefits over CT (12), leading to its exclusion from routine practice guidelines for initial RCC diagnosis.

Prostate-specific membrane antigen (PSMA) PET/CT has been validated as a method to determine the benignity/malignancy of localized renal tumors and the WHO/ISUP grade of ccRCC (13, 14). Subsequently, Spatz et.al confirmed the prognostic value of PSMA in ccRCC at the protein level. However, case reports elucidating the identification of aggressive pathological features using PET/CT remain scarce (15). In this prospective study, we aim to compare the diagnostic value of enhanced CT, ⁶⁸Ga-PSMA-11 and ¹⁸F-FDG PET/CT in ccRCC patients with adverse pathology and investigate the associations between radiological and pathological characteristics in these patients.

MATERIALS AND METHODS

Study design and patients

This prospective case series study was approved by the Ethics Committee of the Medical University. The study protocol was registered in the Chinese Clinical Trial Registry (www.chictr.org.cn; registration number: ChiCTR2100044927). Written informed consents were obtained from all

included patients. Pathological tumor characteristics and radiographic tumor features were collected. The inclusion criteria were as follows: (1) enhanced CT, ⁶⁸Ga-PSMA-11 and ¹⁸F-FDG PET/CT performed within 30 days before surgery; (2) complete preoperative and postoperative clinicopathological data; (3) underwent partial, radical, or cytoreductive nephrectomy. The exclusion criteria were as follows: (1) radiotherapy, targeted therapy, immunotherapy, or other neoadjuvant treatment before operation; (2) refusal of enhanced CT or PET/CT imaging; (3) refusal of surgical treatment; (4) pathological results suggesting urothelial carcinoma, benign tumor or other renal malignancies.

Enhanced CT examination

All CT imaging was performed using Aquilion ONE 320-detector row helical scanners (Canon Medical Systems™). Patients were scanned in a supine position and asked to hold their breath during the imaging procedure. Enhanced CT examination was performed by injecting iohexol through the elbow vein via a high-pressure syringe at a flow rate of 3.0 mL/s. Corticomedullary phase (CMP) was acquired 30s after contrast injection, nephrographic phase (NP) at 80s and excretory phase (EP) at 180s after injection.

⁶⁸Ga-PSMA-11 PET/CT exam

All patients received an intravenous injection of ⁶⁸Ga-PSMA-11 (⁶⁸Ga-HBED-CC-11-PSMA) tracer. PET/CT imaging was performed using a PET/CT scanner (Biograph mCT64, Siemens Healthcare™). Approximately 40-60 minutes after injecting ⁶⁸Ga-PSMA-11 (1.85 MBq/kg), a non-contrast-agent CT scan was acquired from the top of the skull to the level of the middle leg (120 keV, 80 mAs, slice thickness 3.0 mm). Static emission scanned PET images were acquired in three dimensions (matrix 200×200) from the apex to the proximal leg, with corrections applied for dead time, scattering and attenuation. A total of 6-8 bed positions (each for two minutes) were acquired. Images were reconstructed iteratively (2 iterations and 21 subsets) using an ordered subset expectation maximization (OSEM) algorithm with

CT-based attenuation correction. PET/CT images were co-registered and displayed by dedicated software (TrueD software, Siemens™).

¹⁸F-FDG PET/CT examination

Patients were required to fast for at least 6 hours prior to examination. ¹⁸F-FDG PET/CT imaging was performed using a PET/CT scanner (Biograph mCT64, Siemens Healthcare™). Approximately 40–60 minutes after intravenous injection of ¹⁸F-FDG at a dose of 3.7 MBq/kg, low-dose CT was acquired for attenuation correction and accurate anatomical positioning (tube voltage, 120 kV; tube current, automatic mA). Patients were instructed to maintain shallow breathing during the scan and three-dimensional imaging was obtained from the top of the skull to the middle leg level, with a duration of 2 minutes per bed position. The PET images were reconstructed iteratively with attenuation correction.

PET/CT imaging analyses

All PET/CT images were independently reviewed and analyzed by two nuclear physicians, including a double-trained board-certified physician. Any discrepancies between the readers were resolved through consensus reading. The following features were assessed: (a) lesion count; (b) lesion localization; (c) presence of focal radiotracer uptake. PET/CT fusion images were constructed, and regions of interest (ROIs) were drawn around the contours of the primary tumors on continuous axial fusion images. To minimize the influence of normal kidney tissues, ROIs were drawn in distal parts of the tumor. Additionally, a normal background ROI with a diameter of 3 cm was drawn in non-tumor normal liver tissue of the right lobe of the liver. The maximum standardized uptake value (SUV_{max}), mean SUV (SUV_{mean}) and peak SUV (SUV_{peak}) of each primary tumor and normal background liver were measured, and the tumor-to-liver SUV ratio (TLR) was calculated.

CT scanning evaluation

The CT images were independently scrutinized by two experienced radiologists who were blinded to the clinicopathological data. Any disagreements were resolved through consensus reading. To standardize the evaluation of tumor

enhancement, ROIs were selected to observe the changes in CT values during different scan phases. Since the tumor enhancement could be better visualized on the corticomedullary phase (CMP) images and the various heterogenous components of the tumor could be observed at this stage, all enhanced CT values in this study were measured based on the CMP images.

Histopathology analysis

After nephrectomy, renal tumor specimens were fixed in formalin, embedded in paraffin, step-sectioned at 3–4 μm intervals, and mounted on treated glass slides. At least 10 blocks were selected for each case. For large tumors, at least one block was selected every one centimeter of the tumor. The percentage of necrosis, sarcomatoid or rhabdoid differentiation was recorded. Hematoxylin and eosin (H&E) staining was routinely performed and assessed microscopically. The pathological features of the tumor were evaluated. T1 and T2 ccRCC were defined as localized ccRCC, while T3 and T4 ccRCC were defined as locally advanced ccRCC (16). The presence of tumor necrosis (3) and sarcomatoid (4) and rhabdoid (5) features was defined as adverse pathology.

Statistical Analyses

SPSS 26.0 (IBM Corp, Armonk, NY, USA) and MedCalc version 15.2 (Ostend, Belgium) were used for statistical analyses. Normally distributed data were expressed as mean ± standard deviation (SD) and analyzed using Student's t-test, while non-normally distributed data were expressed as median and interquartile range (IQR) and analyzed using the Mann-Whitney U test. Receiver operating characteristics (ROC) curves were constructed to identify optimal cutoff values and evaluate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) based on the maximal Youden index. The area under the ROC curve (AUC) and its 95% confidence intervals (CIs) were calculated. DeLong' test was used to compare the AUCs of different variables (17). Interobserver agreement for PET/CT and CT image evaluations were assessed using intraclass correlation coefficients (ICCs), categorized as poor (less than 0.20),

fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80) or almost perfect agreement (0.81-1.00) (18). Bonferroni corrections were applied to adjust for multiple testing and a two-sided p-value <0.017 was considered statistically significant.

RESULTS

Demographics and Clinical Data of ccRCC

A total of 348 patients were initially included in the database between March 30th, 2021, and December 15th, 2022. Ten patients were excluded due to neoadjuvant targeted therapy, two hundred and thirteen were excluded because they refused enhanced CT or PET/CT scanning, four were excluded because of the refusal of surgical treatment

and others because their pathological results were non-ccRCC (two cases of urothelial carcinoma, nine of benign tumor and twenty-eight of other renal malignancies (Figure-1). Seventy-two patients were available for the final analysis, and their demographics and clinical data are shown in Table 1. The median age was 57 years (IQR 51-66). Tumor necrosis was present in 13 patients (18.1%), sarcomatoid or rhabdoid feature in 6 (8.3%), adverse pathology in 17 (23.6%) and vascular cancer embolus in 8 (11.1%). Among the malignant lesions, 39 (54.2%) were categorized as localized ccRCC and 33 (45.8%) as locally advanced ccRCC. The distribution of WHO/ISUP grades was as follows: grade 1, 11 (15.3%); grade 2, 33 (45.8%); grade 3, 15 (20.8%); and grade 4, 13 (18.1%).

Figure 1 - Flow chart of patient recruitment and study procedures.

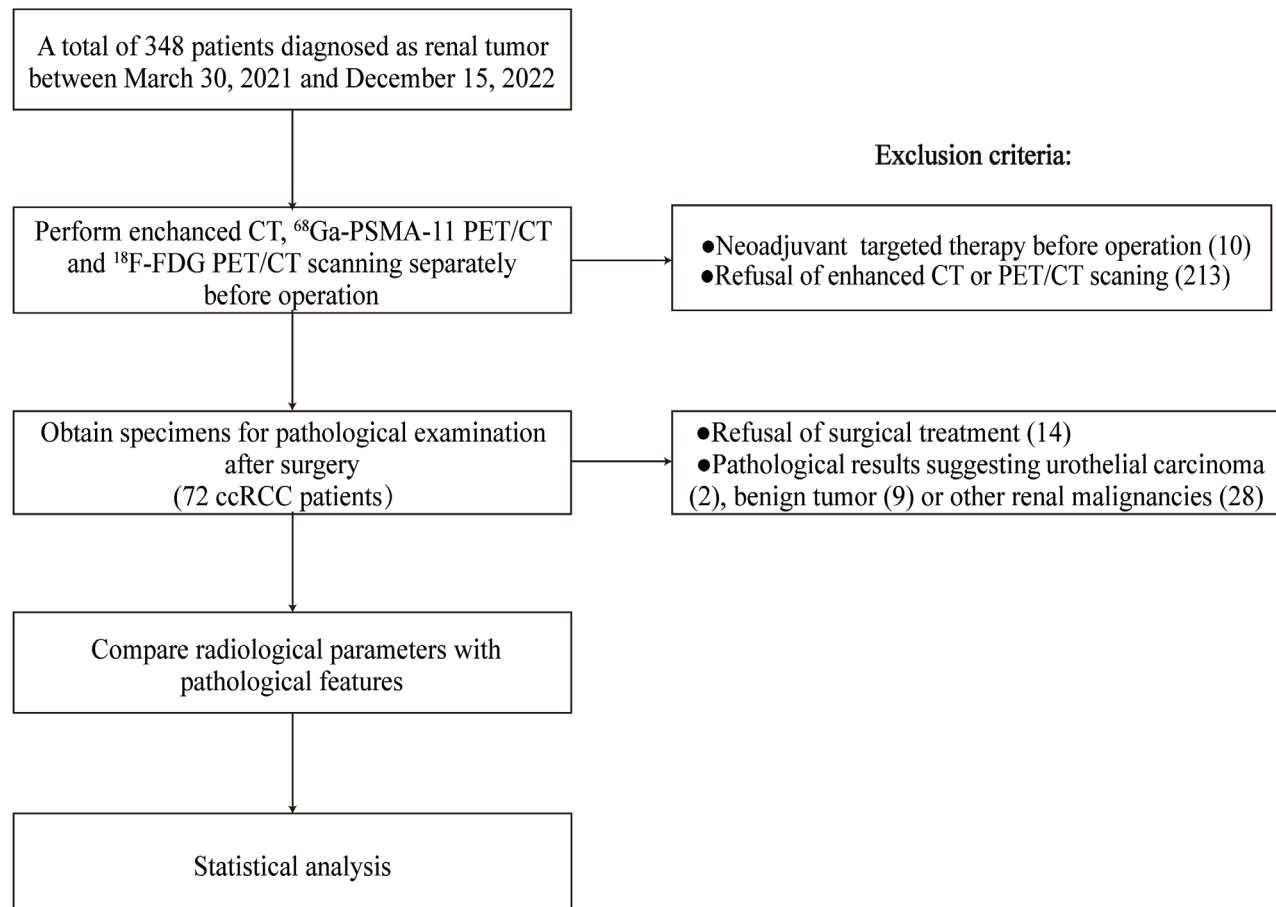


Table 1- Demographics and Clinical Characteristics of the 72 Patients with ccRCC

Parameter	Value
Age (y)	57(51-66)
Tumor maximal diameter (cm)	6.7(4.1-10.2)
Sex, (%)	
Male	38(52.7)
Female	34(47.3)
Tumor location, (%)	
Left	33(45.8)
Right	39(54.2)
Vascular cancer embolus, (%)	
Positive	8(11.1)
Negative	64(88.9)
Tumor necrosis, (%)	
Positive	13(18.1)
Negative	59(81.9)
Sarcomatoid or rhabdoid feature, (%)	
Positive	6(8.3)
Negative	66(91.7)
Adverse pathology, (%)*	
Positive	17(23.6)
Negative	55(76.4)
pT stage, (%)	
T1	26(36.1)
T2	13(18.1)
T3	22(30.6)
T4	11(15.2)
WHO/ISUP grade, (%)	
1	11(15.3)
2	33(45.8)
3	15(20.8)
4	13(18.1)

*Adverse pathology: tumor presenting with necrosis or a sarcomatoid or rhabdoid feature. Two of the tumor has both tumor necrosis and sarcomatoid feature.
ccRCC = clear-cell renal cell carcinoma; WHO/ISUP = World Health Organization / International Society of Urological Pathology
Data are median (interquartile range) for age and tumor maximal diameter.

Relationships of Enhanced CT and PET/CT Imaging Features for Identification of Pathological Characteristics in ccRCC

To explore the diagnostic performance of enhanced CT and PET/CT imaging for discriminating pathological characteristics of ccRCC, we derived radiological parameters including CT value from enhanced CT scanning and SUV from PET/CT images. Representative radio-pathological matching cases are shown in Figure-2. Several radiological parameters were compared by subgroups of pathological characteristics (Table-2 and Supplementary Table-1). The ICCs between the two inter-observers were 0.935 [95% CI (0.959-0.975)] for enhanced CT value, 0.972 [95% CI (0.955-0.983)] for ⁶⁸Ga-PSMA-11 PET/CT and 0.911 [95% CI (0.862-0.943)] for ¹⁸F-FDG PET/CT for all cases. In all three subgroups of pathological characteristics, the ICCs were 0.8 or greater, indicating an almost perfect correlation (Table-2).

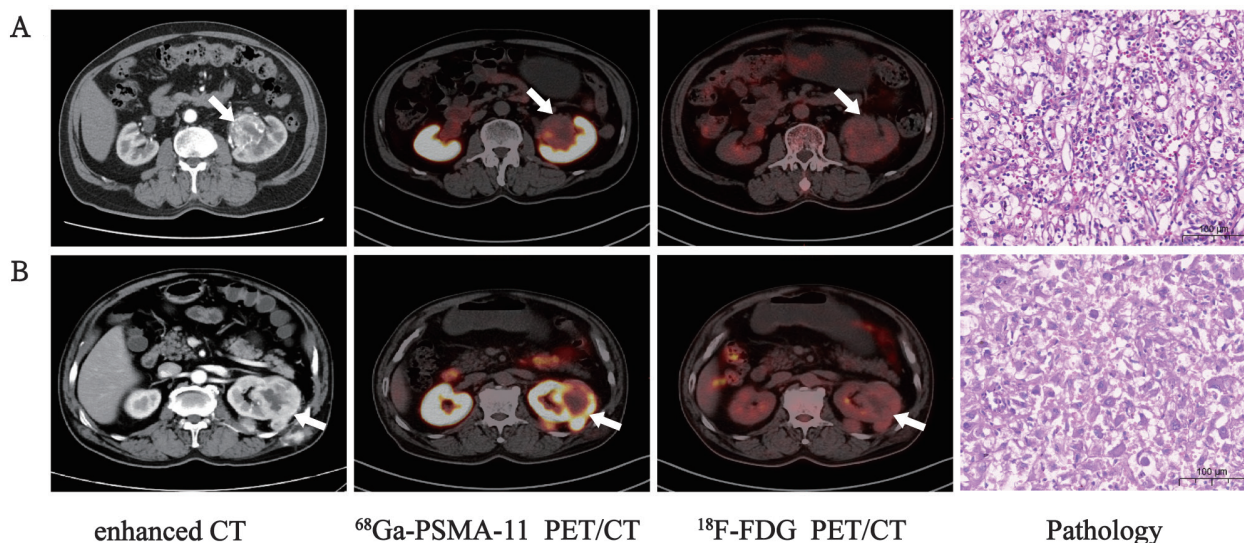
As can be seen in Table-2, Figure-2 and Figure-3, enhanced CT values demonstrated poor

performance in identifying tumor necrosis, sarcomatoid or rhabdoid feature and adverse pathology (all $P > 0.05$) (Figure-2, Figures 3A, 3B and 3C). In contrast, ⁶⁸Ga-PSMA-11 PET/CT SUVmax significantly differed by subgroups of tumor necrosis, sarcomatoid or rhabdoid feature and adverse pathology (all $P < 0.01$) (Figure-2, Figures 3D, 3E and 3F). Among the four SUV parameters, SUVmax demonstrated more significant differences in most pathological characteristics compared to SUVmean, SUVpeak and TLR (Supplementary Table-1). As for ¹⁸F-FDG PET/CT, SUVmax did not significantly differ by subgroups of tumor necrosis ($P = 0.119$), sarcomatoid or rhabdoid feature ($P = 0.038$) and adverse pathology ($P = 0.049$) (Table-2) (Figure-2, Figures 3G, 3H and 3I).

Effectiveness of Radiological Parameters for Identifying Adverse Pathology of ccRCC

ROC analysis was used to evaluate the effectiveness of radiological parameters in identifying aggressive pathological features of ccRCC,

Figure 2 - Representative images depicting radio-pathological matched cases, exemplifying variations in radiotracer uptake in ccRCC with different degrees of differentiation.



A) In a 65-year-old man with a renal tumor on the left kidney, pathological results suggested ccRCC without necrosis or sarcomatoid or rhabdoid differentiation, WHO/ISUP grade 1, and pT1, and imaging revealed a maximal tumor diameter of 5.8 cm, enhanced CT value of 131 Hu, ⁶⁸Ga-PSMA-11 PET/CT SUVmax of 17.81, and ¹⁸F-FDG PET/CT SUVmax of 2.90. B) In a 71-year-old man with a renal tumor on the left kidney, pathological results suggested ccRCC with sarcomatoid differentiation, WHO/ISUP grade 4, and pT3, and imaging revealed a maximal tumor diameter of 4.5 cm, enhanced CT value of 147 Hu, ⁶⁸Ga-PSMA-11 PET/CT SUVmax of 34.15, and ¹⁸F-FDG PET/CT SUVmax of 5.89. Tumor lesion is indicated with a white arrow. PET/CT, positron emission tomography/computed tomography; ccRCC, clear-cell renal cell carcinoma; WHO/ISUP, World Health Organization/International Society of Urological Pathology; SUVmax, maximum standardized uptake value.

including tumor necrosis (Figure-4A), sarcomatoid or rhabdoid feature (Figure-4B) and adverse pathology (Figure-4C). Enhanced CT value showed poor performance in identifying necrosis, sarcomatoid or rhabdoid feature and adverse pathology, with AUC values of 0.57, 0.62, and 0.57, respectively (all $P > 0.05$) (Table-3 and Figure-4). ^{68}Ga -PSMA-11 PET/CT SUVmax performed better

than ^{18}F -FDG PET/CT SUVmax in identifying tumor necrosis with a PPV of 46%, NPV of 100% and the AUC values of 0.85 (95% CI, 0.76-0.94, $P < 0.001$; Delong test $z=2.709$, $p<0.01$) (Figure-4A). When the SUVmax cutoff value from the ROC curve for ccRCC with tumor necrosis was stratified by 25.26, the corresponding sensitivity and specificity were 100% and 75%, respectively

Table 2- Relevance of Enhanced CT, ^{68}Ga -PSMA-11 PET/CT and ^{18}F -FDG PET/CT Parameters for Identification of Pathological Characteristics in ccRCC.

Pathological features	Radiological parameters								
	Enhanced CT			^{68}Ga -PSMA-11 PET/CT			^{18}F -FDG PET/CT		
	CT value	ICC ^a	P ^b value	SUV _{max}	ICC ^a	P ^c value	SUV _{max}	ICC ^a	P ^c value
Tumor necrosis			0.221			<0.001			0.119
Negative	128.97± 31.86	0.936 [0.895-0.961]		17.39 (7.58-25.20)	0.969 [0.949-0.982]		3.97 (2.98-6.40)	0.906 [0.848-0.943]	
Positive	141.08± 32.87	0.929 [0.787-0.961]		30.51 (26.18-32.54)	0.898 [0.679-0.968]		5.92 (3.32-6.81)	0.922 [0.767-0.975]	
Sarcomatoid or rhabdoid feature			0.262			<0.001			0.038
Negative	129.86 32.66	0.937 [0.899-0.961]		18.76 (8.91-26.93)	0.971 [0.952-0.982]		4.02 (3.03-6.79)	0.907 [0.852-0.942]	
Positive	145.33± 23.48	0.895 [0.477-0.984]		33.93 (32.54-35.33)	0.837 [0.195-0.976]		6.79 (5.45-8.04)	0.914 [0.537-0.987]	
Adverse pathology*			0.179			<0.001			0.049
Negative	128.31± 32.63	0.937 [0.894-0.962]		14.94 (7.36-23.32)	0.967 [0.944-0.981]		3.69 (2.94-6.40)	0.915 [0.859-0.949]	
Positive	140.35± 29.63	0.927 [0.811-0.973]		31.55 (27.87-34.39)	0.869 [0.683-0.950]		5.59 (4.52-6.81)	0.900 [0.745-0.963]	

*Adverse pathology is defined as tumor presenting with necrosis or a sarcomatoid or rhabdoid feature

^aICC: Data in the brackets are 95% confidence intervals

^bP values were calculated with Student's t test

^cP values were calculated with Mann-Whitney U test

ccRCC = clear-cell renal cell carcinoma; CT = computed tomography; ICC = Intraclass correlation coefficient; SUV_{max} = maximum standardized uptake value
Data are mean ± standard deviation for CT value, median (interquartile range) for SUV_{max}

(Table-3). When used to identify adverse pathology, the SUVmax of ^{68}Ga -PSMA-11 PET/CT performed better than ^{18}F -FDG PET/CT, with a PPV of 61% vs. 40%, NPV of 100% vs. 92% and the AUC value of 0.90 (95% CI, 0.83-0.97) vs. 0.66(95% CI, 0.52-0.79) (Delong test, $z=3.433$, $p<0.001$) (Figure-4C). With the specific cutoff value of 25.26, ^{68}Ga -PSMA-11 PET/CT SUVmax showed sensitivity 100% and specificity 80% for adverse pathology (positive vs. negative). Moreover, there was no significant statistical difference between ^{68}Ga -

PSMA-11 and ^{18}F -FDG PET/CT in predicting sarcomatoid or rhabdoid feature, with a specificity of 83% vs. 56%, PPV of 35% vs.17% and the AUC value of 0.91 (95% CI, 0.84-0.98) vs. 0.75(95% CI, 0.61-0.90) (Delong test, $z=1.998$, $p=0.046$) (Figure-4B). Subgroup analyses based on age, sex, tumor location, tumor maximal diameter, tumor stage and WHO/ISUP grade consistently showed that ^{68}Ga -PSMA-11 PET/CT SUVmax had a significant predictive value for adverse pathology (Supplementary Table-2).

Figure 3 - Box plot illustrating the distribution of enhanced CT value (A-C), ^{68}Ga -PSMA-11 (D-F) and ^{18}F -FDG PET/CT SUV_{max} (G-I) according to the pathological features of ccRCC. The pathological characteristics include tumor necrosis (A, D, G), sarcomatoid or rhabdoid differentiation (B, E, H) and adverse pathology (C, F, I). Adverse pathology is defined as a tumor presenting with necrosis or a sarcomatoid or rhabdoid feature; SUV_{max}, maximum standardized uptake value; CT, computed tomography; ccRCC, clear-cell renal cell carcinoma.

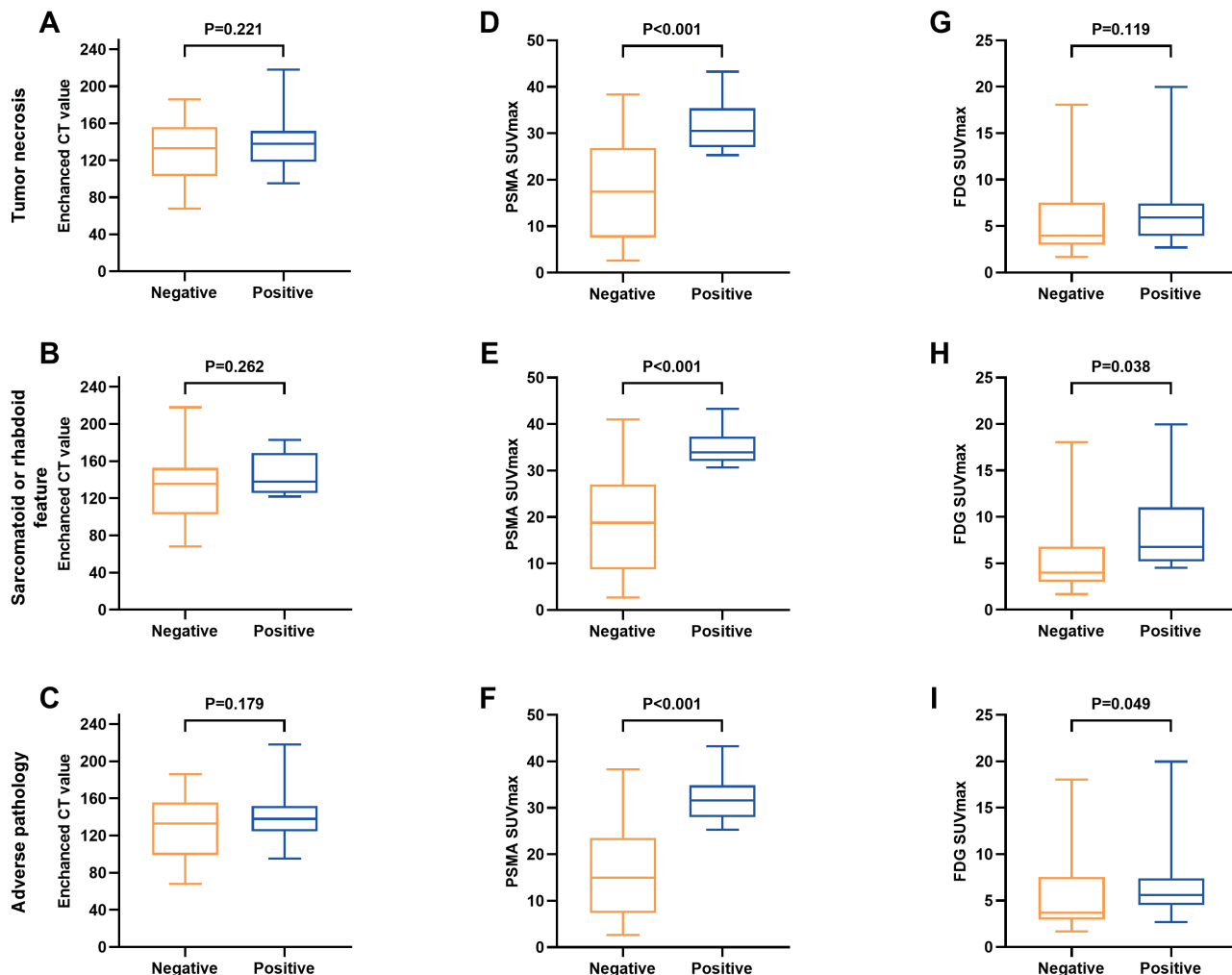


Figure 4 - ROC curves comparing the effectiveness of radiological parameters in predicting the pathological characteristics of ccRCC. Radiological parameters: enhanced CT value, ⁶⁸Ga-PSMA-11 and ¹⁸F-FDG PET/CT SUV_{max}; pathological characteristics: tumor necrosis, sarcomatoid or rhabdoid differentiation and adverse pathology. Adverse pathology is defined as a tumor presenting with necrosis or a sarcomatoid or rhabdoid feature; ROC, Receiver operating characteristics; AUC, area under the curve; SUV_{max}, maximum standardized uptake value; CT, computed tomography; ccRCC, clear-cell renal cell carcinoma.

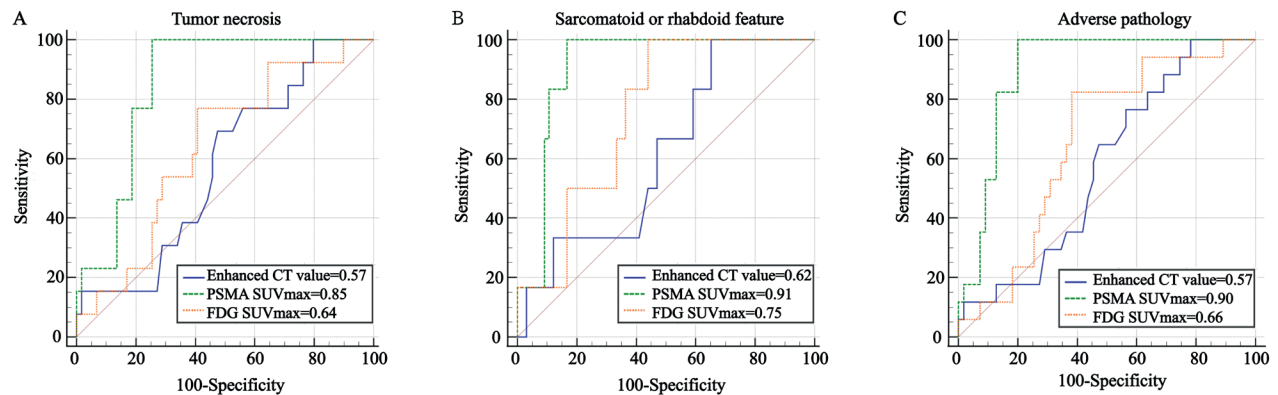


Table 3 - Effectiveness of Enhanced CT, ⁶⁸Ga-PSMA-11 and ¹⁸F-FDG PET/CT Parameters for Identifying the Pathological Features of ccRCC Patients by ROC Curve Analysis.

Pathological features (positive vs. negative)	Radiological parameters	AUC (95%CI)	Cutoff value	Sensitivity	Specificity	PPV	NPV	P value
Tumor necrosis	CT value	0.57(0.42-0.73)	94.00	1.00	0.20	0.22	1.00	0.221
	SUV _{max} (⁶⁸ Ga-PSMA-11 PET/CT)	0.85(0.76-0.94)	25.26	1.00	0.75	0.46	1.00	<0.001
	SUV _{max} (¹⁸ F-FDG PET/CT)	0.64(0.48-0.79)	4.54	0.77	0.59	0.29	0.92	0.119
Sarcomatoid or rhabdoid feature	CT value	0.62(0.42-0.82)	118.00	1.00	0.35	0.12	1.00	0.262
	SUV _{max} (⁶⁸ Ga-PSMA-11 PET/CT) ^a	0.91(0.84-0.98)	30.58	1.00	0.83	0.35	1.00	<0.001
	SUV _{max} (¹⁸ F-FDG PET/CT) ^a	0.75(0.61-0.90)	4.52	1.00	0.56	0.17	1.00	0.038
Adverse pathology [*]	CT value	0.57(0.43-0.72)	94.00	1.00	0.22	0.28	1.00	0.179
	SUV _{max} (⁶⁸ Ga-PSMA-11 PET/CT) ^b	0.90(0.83-0.97)	25.26	1.00	0.80	0.61	1.00	<0.001
	SUV _{max} (¹⁸ F-FDG PET/CT) ^b	0.66(0.52-0.79)	4.52	0.82	0.62	0.40	0.92	0.049

^aSUV_{max} (⁶⁸Ga-PSMA-11 PET/CT) vs. SUV_{max} (¹⁸F-FDG PET/CT) in distinguishing sarcomatoid or rhabdoid feature (Delong test, z=1.998, p=0.046)

^bSUV_{max} (⁶⁸Ga-PSMA-11 PET/CT) vs. SUV_{max} (¹⁸F-FDG PET/CT) in distinguishing adverse pathology (Delong test, z=3.433, p<0.001)

^{*}Adverse pathology is defined as tumor presenting with necrosis or a sarcomatoid or rhabdoid feature

Units: CT value, Hu

ccRCC = clear-cell renal cell carcinoma; CT = computed tomography; SUV_{max} = maximum standardized uptake value; AUC = area under the ROC curve; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value

DISCUSSION

As an immunologically and histologically heterogeneous tumor, ccRCC exhibits diverse prognoses and responses to systemic therapy. In previous studies, necrosis (3) and differentiation (including sarcomatoid (4) or rhabdoid (5) feature) within the tumor specimen have been reported as adverse prognostic factors in patients with RCC, independently associated with worse survival. The utility and timing of cytoreductive nephrectomy were questioned by results from the CARMENA and SURTIME trials, respectively (19, 20). Early stage localized small RCC responds well to partial nephrectomy, but for those with aggressive pathological features, radical nephrectomy or post-operative combination immunotherapy is often required. Therefore, exploring approaches to the accurate preoperative prediction of these aggressive pathological features will be helpful in therapeutic decision-making and clinical management. Deutsch et al. (21) recently reported a mutiparametric method, including tumor necrosis, for predicting outcomes to anti-PD-1 therapy in ccRCC. Currently, there is great debate with inconsistent data demonstrating the efficacy of adjuvant immunotherapy in resected high-risk ccRCC. However, it is clear that immunotherapy treatments are more effective in sarcomatoid disease (reasonable extrapolation from data in the metastatic setting) - hence the critical need to have predictive biomarkers in this setting (6).

Currently, contrast-agent-enhanced CT and MRI are the most commonly used diagnostic imaging methods for ccRCC. However, some studies have shown that these two imaging diagnostic methods have limitations in the early diagnosis of ccRCC (22-24). The retrospective study of Oh et al. (22) found no significant correlation between CT findings of ccRCC and Fuhrman grade. Zhu et al. (23) found enhanced CT had no statistically significant difference in identifying sarcomatoid ccRCC, with a P-value of 0.09. For MRI, Tsili et al. (24) found that diffusion-weighted imaging (DWI), which can be used to predict RCC histologic grade, had limitations in the effectiveness of qualitative analysis of renal parenchymal masses due to significant overlapping of apparent diffu-

sion coefficient (ADC) values among different histologic subtypes, further limiting its use in clinical activity in the early diagnosis of ccRCC. In this context, PET/CT imaging, with its higher sensitivity and specificity, becomes an appealing option.

Namura et al. (25) considered that ^{18}F -FDG-PET/CT had potency as an "imaging biomarker" for providing valuable information for clinical decision-making. In addition, as products of its folate hydrolase activity are associated with angiogenesis, the highly vascularized nature of ccRCC makes it a potential PSMA-avid tumor (26). There is also preliminary evidence suggesting that PSMA PET/CT may be valuable in staging, restaging and response assessment in ccRCC (13, 14). Unfortunately, the molecular imaging phenotype of ccRCC with aggressive pathological features is less well established, with only limited case reports and retrospective studies describing intense ^{18}F -FDG uptake within rapidly progressive sarcomatoid sites on ^{18}F -FDG PET/CT. Liang et al. (27) reported that sarcomatoid ccRCC with high SUVmax showed more aggressive biological behavior through case reports. Zhu et al. (23) found that it was helpful to indicate the sarcomatoid differentiation of ccRCC when FDG PET/CT SUVmax, SUVmean and SUVpeak cutoff values of 5.4, 4.2 and 5.0 respectively, which were consistent with our statistical analysis results. In the current study, ^{18}F -FDG PET/CT exhibited limited ability to distinguish tumor necrosis in ccRCC, whereas ^{68}Ga -PSMA-11 PET/CT demonstrated superior discriminatory capabilities.

To our knowledge, this is the first prospective study comparing the diagnostic value of enhanced CT, ^{68}Ga -PSMA-11 and ^{18}F -FDG PET/CT parameters in ccRCC with necrosis or sarcomatoid or rhabdoid differentiation. Our results indicate that enhanced CT had limited performance in identifying necrosis, sarcomatoid or rhabdoid feature and adverse pathology in ccRCC. Moreover, ^{68}Ga -PSMA-11 PET/CT SUVmax demonstrated a sensitivity of 100% and specificity of 75% for discriminating tumor necrosis, and a sensitivity of 100% and specificity of 80% for adverse pathology, suggesting that ^{68}Ga -PSMA-11 PET/CT performs better than enhanced CT and ^{18}F -FDG PET/

CT in identifying tumor necrosis and adverse pathology. These findings align with previous case reports and retrospective cohort studies (15, 28), emphasizing the advantage of receptor ligand-targeted molecular imaging with its higher specificity compared to metabolic uptake represented by FDG.

Although there are only a few studies of PSMA PET/CT in renal tumors, an increasing number of scholars are recognizing its growing role (29). In a retrospective study involving 36 ccRCC patients, Gao et al. (14) concluded that ^{68}Ga -PSMA-11 PET/CT SUVmax could effectively identify adverse pathology with an AUC of 0.92 (cutoff value=18.5, $P<0.001$). Nadebaum et al. (15) demonstrated intense ^{68}Ga -PSMA uptake within the site of renal tumor with sarcomatoid feature through quantitative analysis of clinical images (SUVmax=16.1). These research findings are consistent with our preliminary conclusions. Additionally, we observed that ^{68}Ga -PSMA-11 PET/CT SUVmax values were also increased in ccRCC with necrosis (30.51 vs.17.39, $P<0.001$). Consequently, in clinical practice, patients who undergo preoperative ^{68}Ga -PSMA-11 PET/CT scanning and exhibit intense SUVmax values should be highly alert to contain aggressive pathological features. Such patients ought to receive more comprehensive and radical treatment, along with increased caution when dealing with advanced diseases.

There are several limitations in our study. First, the sample size was relatively small. Further research with a larger sample size and involving multiple centers is necessary to validate our findings. Second, imaging PSMA in the kidney remains challenging due to its high uptake in that organ. Third, the drawing of ROIs was subjective as it depended on the observer's evaluation and could introduce variability. Fourth, a considerable number of patients were excluded because of the refusal of enhanced CT or PET/CT scanning, which could potentially introduce selection bias and affect the generalizability of the results. Finally, the lack of a reference standard diagnostic method might impact the diagnostic value of ^{68}Ga -PSMA-11 and ^{18}F -FDG PET/CT.

CONCLUSIONS

^{68}Ga -PSMA-11 PET/CT offers distinct advantages over enhanced CT and ^{18}F -FDG PET/CT in identifying adverse pathology in primary ccRCC. This non-invasive imaging modality shows potential for aiding in early decision-making, evaluating treatment efficacy and predicting the risk of adverse outcomes in ccRCC patients. The findings support the potential clinical application of ^{68}Ga -PSMA-11 PET/CT in ccRCC patients' management. Further research with larger patient cohorts is warranted to validate these findings and explore its full clinical utility.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the institutional review board of the Ethics Committee of the First Affiliated Hospital of Fujian Medical University. The protocol was registered in the Chinese Clinical Trial Registry (www.chictr.org.cn; registration number: ChiCTR2100044927).

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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CONFLICT OF INTEREST

None declared.

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APPENDIX:

Supplementary Table 1 - Association between PET parameters and pathological characteristics of ccRCC.

68Ga-PSMA-11 PET/CT										18F-FDG PET/CT						
	SUV _{max}	P ^a value	SUV _{mean}	P ^a value	SUV _{peak}	P ^a value	TLR	P ^a value	SUV _{max}	P ^a value	SUV _{mean}	P ^a value	SUV _{peak}	P ^a value	TLR	P ^a value
Tumor necrosis		<0.001		0.016		0.026		0.017		0.119		0.057		0.107		0.241
Negative	17.39 (7.58-25.20)		9.01 (4.04-13.68)		10.72 (5.39-18.44)		2.17 (1.32-3.93)		3.97 (2.98-6.40)		2.51 (1.82-3.48)		2.95 (2.33-4.95)		1.26 (1.04-1.96)	
Positive	30.51 (26.18-32.54)		15.39 (12.58-19.25)		20.79(16.91- 23.47)		4.15 (3.29-4.81)		5.92 (3.32-6.81)		3.79 (2.57-4.49)		4.15 (2.88-5.61)		1.96 (1.16-2.06)	
Sarcomatoid or rhabdoid feature		<0.001		0.001		0.003		0.001		0.038		0.148		0.126		0.089
Negative	18.76 (8.91-26.93)		10.23 (5.06-13.21)		13.91 (6.85-19.35)		2.64 (1.50-4.03)		4.02 (3.03-6.79)		2.69 (1.83-4.05)		3.44 (2.34-5.38)		1.26 (1.04-2.06)	
Positive	33.93 (32.54-35.33)		15.67 (15.39-18.53)		20.80(19.74- 22.74)		4.82 (4.39-4.87)		6.79 (5.45-8.04)		3.55 (2.56-6.31)		4.71 (3.57-7.11)		1.82 (1.61-2.50)	
Adverse pathology*		<0.001		0.001		0.001		0.001		0.049		0.055		0.079		0.150
Negative	14.94 (7.36-23.32)		8.39 (4.02-12.65)		9.89 (5.22-23.52)		2.10 (1.20-3.39)		3.69 (2.94-6.40)		2.35 (1.77-3.48)		2.76 (2.32-4.95)		1.23 (1.04-2.17)	
Positive	31.55 (27.87-34.39)		15.48 (10.21-15.86)		20.79 (18.02-22.74)		4.30 (3.51-4.82)		5.59 (4.52-6.81)		2.99 (2.56-4.49)		4.44 (2.95-5.61)		1.68 (1.33-2.01)	

*Adverse pathology is defined as tumor presenting with necrosis or a sarcomatoid or rhabdoid feature

*P values were calculated with Mann-Whitney U test

ccRCC = clear-cell renal cell carcinoma; SUV_{max} = maximal standard uptake value; SUV_{mean} = mean standard uptake value; SUV_{peak} = peak standard uptake value; TLR = tumor-to-liver standard uptake value ratio
Data are median (interquartile range) for SUV_{max}, SUV_{mean}, SUV_{peak} and TLR

Supplementary Table 2 - Subgroup analyses of ⁶⁸Ga-PSMA-11 PET/CT SUVmax in patients with or without adverse pathology.

Factors	Variable	⁶⁸ Ga-PSMA-11 PET/CT SUV _{max}		P ^a value
		Without adverse pathology*	With adverse pathology	
Age (y)	≤ 57	14.57(8.25-26.89)	32.03(28.19-34.39)	<0.001
	> 57	14.39(6.43-19.24)	29.98(27.87-32.54)	<0.001
Sex	Male	13.83(6.26-19.12)	31.55(28.19-33.47)	<0.001
	Female	17.01(8.91-26.81)	31.00(26.18-34.39)	0.008
Tumor location	Left	13.99(6.43-19.55)	32.54(29.45-35.33)	<0.001
	Right	14.94(8.25-23.32)	29.19(25.78-32.03)	0.002
Tumor maximal diameter (cm)	≤ 6.7	11.49(6.71-14.99)	30.51(26.18-32.03)	<0.001
	> 6.7	20.44(7.58-26.93)	33.47(29.45-35.33)	0.001
Tumor stage	T1-T2	10.39(6.26-17.39)	26.18(25.31-28.19)	<0.001
	T3-T4	23.52(14.94-34.97)	33.00(30.64-35.33)	0.003
WHO/ISUP grade	1-2	10.39(6.26-14.99)	27.03(25.31-29.45)	0.001
	3-4	26.93(23.52-32.98)	33.47(31.55-35.33)	0.015

*Adverse pathology is defined as tumor presenting with necrosis or a sarcomatoid or rhabdoid feature

^aP values were calculated with Mann-Whitney U testSUV_{max} = maximum standardized uptake value; WHO/ISUP = World Health Organization / International Society of Urological PathologyData are median (interquartile range) for SUV_{max}



"Single-Surgeon" versus "Dual-Surgeon" Robot-Assisted Radical Prostatectomy and Pelvic Lymph-nodes Dissection: Comparative Analysis of Perioperative Outcomes

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ABSTRACT

Purpose: To compare the perioperative outcomes of robot-assisted radical prostatectomy (RARP) with pelvic lymph-nodes dissection (PLND) when the same surgeon performs RARP and PLND versus one surgeon performs RARP and another surgeon performs PLND.

Materials and Methods: From January 2022 to March 2023, data of consecutive patients who underwent RARP with PLND were prospectively collected. The surgeries were performed by two "young" surgeons with detailed profile. Specifically for the study purpose, one surgeon performed RARP, and the other surgeon performed PLND. A set of surgeries performed according to the standard setup (i.e., the same surgeon performing both RARP and PLND) was retrieved from the institutional database and used as comparator arm. To test the study hypothesis, patients were divided into two groups: "dual-surgeon" versus "single-surgeon".

Results: Fifty patients underwent RARP and PLND performed according to dual-surgeon setup and were compared to the last 50 procedures performed according to the standard single-surgeon setup. Patients in the groups had comparable baseline characteristics. Dual-surgeon interventions had significantly shorter median total operative (194 [IQR 178–215] versus 174 [IQR 146–195] minutes, $p < 0.001$) and console time (173 [IQR 158–194] versus 154 [IQR 129–170] minutes, $p < 0.001$). No significant differences were found in terms of blood loss, intraoperative complications, postoperative outcomes, and final pathology results.

Conclusions: The present analysis found that when RARP and PLND are split onto two surgeons, the operative time is shorter by 20 minutes compared to when a single surgeon performs RARP and PLND. This is an interesting finding that could sponsor further studies.

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INTRODUCTION

Robot-assisted radical prostatectomy (RARP) is nowadays an established minimally invasive option for the treatment of prostate cancer (1). Patients who underwent RARP do benefit from the inherent advantages of laparoscopic surgery paired to superior functional and oncological outcomes (2).

During RARP, the surgeon stays focused on the console, looking at the three-dimensional surgical field. The possibility of adjusting the console to the surgeon's individual preferences may increase the comfort of her / his workstation. On the other hand, working for hours at a monitor-based workstation has been reported to be exhausting (3-7)

Despite the understanding of this phenomenon, there is scarce literature evaluating the surgical outcomes of either prolonged or consecutive surgical procedures.

In daily practice our surgeons noticed the potential for showing a different performance during RARP, if RARP is performed with or without pelvic lymph-nodes dissection (PLND).

To test such hypothesis, we started with splitting the two steps of the procedure (RARP and PLND) among two surgeons. The aim of the study was to compare the perioperative outcomes of RARP with PLND when the same surgeon performs both RARP and PLND versus one surgeon performs RARP and another surgeon performs PLND.

MATERIALS AND METHODS

Patients

From January 2022 to March 2023, perioperative data of consecutive patients who underwent both RARP and PLND were prospectively collected into an institutional dedicated database (IRB 845/CE Lazio 1). PLND was planned based upon the individual patient's risk of harbouring positive lymph-nodes, as estimated by the validated Gandaglia's nomogram (8).

The surgeries were performed by two surgeons with detailed profile (< 40 years-old, > 1000 robotic surgeries assisted at bedside, > 200 robotic

surgical interventions performed as console surgeon of which > 150 RARP interventions).

For the purpose of the study, within the "experimental" arm, one surgeon performed RARP and the other one performed PLND (and vice versa for each consecutive case).

A set of surgeries performed according to the standard setup at our institution (i.e., the same surgeon performs both RARP and PLND) was retrieved from the institutional database and used as comparator arm. The patients were divided into two groups: Group "dual-surgeon" versus Group "single-surgeon".

Surgical technique

All patients underwent Da Vinci Xi extended PLND and RARP with transperitoneal approach. Briefly, extended PLND was performed as previously described, as including the removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery (9).

For RARP, an incision of the parietal peritoneum (without transecting the urachus) was made to access the retropubic space. The prostate was identified and dissected free from the periprostatic fat. The endopelvic fascia was incised on both sides, while preserving the pubo-prostatic ligaments. The bladder neck was dissected according to a "bladder neck sparing" technique, whenever feasible. To gain access to the retro-trigonal space, the muscular fibres that anchor the bladder to the base of the prostate were dissected while leaving a lingula of muscular tissue attached to the posterior aspect of the bladder neck (the so-called "retro-trigonal fascia"). The anterior layer of the Denonvilliers' fascia was incised, then the seminal vesicles were identified and dissected. The posterior layer of the Denonvilliers' fascia was incised in an "inverse U-shape" in the proximity of the prostate gland, to gain access to the perirectal space that was developed as much as possible towards the posterior prostate apex.

The visceral layer of the endopelvic fascia and the underlying apron still covering the an-

terior surface of the prostate were then incised while sparing the pubo-prostatic ligaments. The prostate apex was managed via a combination of blunt and sharp dissection, until the urethra was incised. The deep venous complex was selectively closed by 3/0 “barbed” suture. The posterior reconstruction was performed in a double layer by using a 3/0 “barbed” suture. To create the first layer, the needle was passed into the median raphe and the cranial portion of the previously divided retro-trigonal fascia. The second layer involved the bladder neck and the posterior aspect of the urethra. The urethro-vesical anastomosis was performed by using two 3/0 “barbed” hemi-running sutures, according to a modified Van Velthoven’s single-knot technique (10).

Outcome measurements

Demographic characteristics as well as intra- and post-operative data of patients in both groups were compared. Preoperative patient’s and disease’s information included age, body mass index, Charlson’s comorbidity index, and the International Society of Urological Pathology (ISUP) prognostic grade groups at prostate biopsy (11).

Perioperative outcomes included operative time, estimated blood loss, intraoperative complications, length of hospital stay, catheterization time, and complications, as classified according to the Clavien-Dindo classification (12).

Surgical specimens underwent final pathology examination to have grading, staging (both for prostate and retrieved lymph-nodes), surgical margin status, and prostate size reported.

Statistical Analysis

Descriptive statistics for the Single-surgeon and the Dual-surgeon groups were summarized by median and interquartile range (IQR) for continuous variables. Frequencies and proportions were used for categorical variables, as appropriate.

Continuous variables were analysed with the Wilcoxon’s test. Differences between categorical variables were assessed by using the chi-square and Fisher’s exact tests, as appropriate. Multivariate analysis was performed to ac-

count for independent factors impacting on the observed differences between the groups.

The minimal required sample size was 48 versus 48 patients, calculated by hypothesizing an expected difference of 20 minutes between the arms at the time of study design ($\alpha = 0.05$, $\beta = 0.2$, power = 0.8).

Statistical analyses were performed by using SPSS software v.24.0 (IBM Corp, Armonk, NY, USA). All tests were two sided, with significance set at p -value < 0.05.

RESULTS

Fifty patients underwent RARP and PLND performed according to a dual-surgeon setup and were compared to the last 50 procedures retrieved from the institutional dataset, performed according to the standard single-surgeon setup.

The patients in the groups had comparable demographic and disease characteristics (Table-1).

Interventions performed according to the dual-surgeon setup had significantly shorter median total operative (194 [IQR 178 – 215] versus 174 [IQR 146 – 195] minutes, $p < 0.001$) and console time (173 [IQR 158 – 194] versus 154 [IQR 129 – 170] minutes, $p < 0.001$).

No significant differences were found in terms of estimated blood loss and occurrence of intraoperative complications. No significant differences were found in terms of postoperative outcomes of interest, including final pathology results (Table-2). Multivariate analysis did not find any independent factors impacting on the observed differences between the groups in operative and console time.

DISCUSSION

The fact that the surgeon has to stay focused on a monitor-based workstation (i.e. the robotic console) during RARP has reported to be exhausting [2-6]. Martinschek et al. assessed human concentration via a computer-assisted attention test at the time that surgeons were performing RARP. They found an association between prolonged console time and decreased concentration. Furthermore, when consecutive surgeries

Table 1 - Distribution of baseline characteristics.

	Single-Surgeon (n = 50)	Dual-Surgeon (n = 50)	p-value
Age, median (IQR), years	67 (62 – 72)	67 (59 – 71)	0.9
PSA, median, (IQR), ng/mL	8.5 (5.9 – 12.7)	8.6 (6.5 – 12.0)	0.7
BMI, median (IQR), kg/m ²	25.3 (24.2 – 28.1)	25.4 (23.4 – 28.4)	0.9
Charlson comorbidity index, no. (%)			0.8
0-1	19 (38)	17 (34)	
2-3	29 (58)	30 (60)	
≥ 4	2 (4)	3 (6)	
Biopsy ISUP grade group, no. (%)			0.9
Grade group 1	2 (4)	2 (4)	
Grade group 2	14 (28)	13 (26)	
Grade group 3	19 (38)	18 (36)	
Grade group 4	12 (24)	14 (28)	
Grade group 5	3 (6)	3 (6)	

were performed, they reported an increase in the total number of errors (13). In contrast, Bukavina et al. recently analysed a multi-institutional retrospective cohort aimed to determine whether the outcomes of RARP differed when two RARP interventions were performed one after another by the same team. In their hands, case sequence was found not associated with operative time, positive margins, and lymph-nodes yield (14). Similarly, Bagrodia et al. reported that performance of several consecutive complex urological procedures (including RARP) was not associated with the worsening of outcomes (15).

Despite some understanding, literature lacks in evaluating the outcomes of “prolonged” robotic surgeries. In this setting, we felt our research of interest. The most “pathos” step of surgery for prostate cancer is PLND, which is typically performed as first act. At the end of such a “procedure in the procedure”, the surgeon can experience a sort of “fall” in the adrenergic tone. We hypothesized that this could be able to impact on the performance of the RARP performed just after.

The present analysis of our institutional data found that when RARP and PLND are split onto two surgeons, the operative time is shorter by 20 minutes if compared to when a single surgeon performs both RARP and PLND.

The reader could argue whether such a reduction in operative time was relevant. It has been demonstrated that having an experienced team able to anticipate the surgeon’s actions can reduce the operative time: this does increase the efficiency in the operative room dedicated to robotic surgery (16). However, it is challenging to evaluate the reduction in the absolute costs of RARP relative to such an increased “efficiency”.

Lone et al. tried to mitigate the financial burden of RARP and prospectively implemented a cost reduction plan that included a lower number of robotic instruments used per surgery. The authors investigated whether these changes did impact on the costs of RARP as well as the perioperative outcomes. Interestingly, the authors found that their cost reduction plan corresponded to a significant decrease in the console time and calculated \$200 savings per case (95% [CI] \$150-\$250,

Table 2 - Distribution of Perioperative Outcomes and Pathology Outcomes.

	Single-Surgeon (n = 50)	Dual-Surgeon (n = 50)	p-value
Perioperative Outcomes			
Total operative time, median (IQR), min	194 (178-215)	174 (146-195)	< 0.001
Console time, median (IQR), min	173 (158-194)	154 (129-170)	< 0.001
Estimated blood loss, median (IQR), mL	150 (100-200)	150 (100-250)	0.2
Nerve Sparing (at least unilateral), no. (%)	8 (16)	9 (18)	0.8
Intraoperative complications, no. (%)	2 (4)	1 (2)	0.6
Catheterization time, median (IQR), days	5 (4-6)	5 (4-6)	--
Grade ≥ 2 postoperative complications, no (%)	4 (8)	3 (6)	0.7
Postoperative readmissions, no (%)	1 (2)	1 (2)	--
Pathology Outcomes			
Prostate weight, median (IQR), g	56 (40 – 62)	53 (43 – 67)	0.5
Pathological ISUP grade group, no. (%)			0.6
Grade group 1	--	--	
Grade group 2	14 (28)	11 (22)	
Grade group 3	19 (38)	19 (38)	
Grade group 4	9 (18)	10 (20)	
Grade group 5	8 (16)	10 (20)	
Pathological T stage, no. (%)			0.8
pT2	21 (42)	20 (40)	
$\geq$ pT3	29 (58)	30 (60)	
Pathological N stage, no. (%)			0.8
pN0	41 (82)	42 (84)	
pN+	9 (18)	8 (16)	
No. lymph-nodes removed, median (IQR)	14 (11 – 20)	14 (12 – 19)	0.8
Positive surgical margins, no (%)			0.8
Total	12 (24)	11 (22)	
pT2 cases	5	5	
pT3 cases	7	6	

$p < 0.0001$) per each 15-minute reductions in surgery time (17).

In addition to the interest in saving “out-of-pocket” costs, the shorter surgical times (particularly if the reader adds up the time saved after 2–3 procedures/day) could translate into the potential for performing an additional procedure within the same 12-hour day shift. This, in turn, could translate into a higher volume of surgeries with a 1-year time horizon and increase the amortization of the robotic platform costs from the perspective of the healthcare system (18). Moreover, we are unable to value the invaluable fact that, with the configuration suggested herein, the exposure to robotic surgery is doubled up for each surgeon.

Finally, longer operative time during RARP is reported to be associated with longer hospitalization, longer catheterization, and higher likelihood of adverse events. This is why we believe that anything that can be done for reducing the operating time should be welcome (19).

One issue that could detract from the value of our results could be the experience of the surgeons involved. Specifically, the reader could argue that the latter set of procedures was performed by surgeons with wider experience (they had 50 more surgeries on their shoulders). We prove that this is not the case. A recent systematic review from the United Kingdom focused on the learning curves of major laparoscopic and robotic procedures in urology reported a considerable variation in the definitions of outcome measures and performance thresholds of RARP. Specifically, the learning curve for operative time was identified as ranging from 10 to 250 cases for RARP (20). Ambinder et al. performed a retrospective analysis of RARP procedures performed by a new attending surgeon and observed a 25-case learning curve for a fellowship-trained urologist to achieve stable operative performance in RARP. Procedural components demonstrated variable learning curves including the urethro-vesical anastomosis that required upward of 50 cases (21).

A panel of experts developed and validated a modular training and assessment pathway via Healthcare Failure Mode and Effect Analysis for trainees undertaking RARP and evaluated learning curves for procedural steps. The authors

demonstrated plateaus for many steps of RARP, including anterior and posterior bladder neck dissection (16 and 18 cases, respectively), posterior dissection (9 cases), dissection of prostatic pedicles and seminal vesicles (15 cases), and anastomosis (17 cases) (22). If one does not like to base upon such arbitrary cut-offs of the total cases, Tamhanekar et al. analysed a large dataset of RARP interventions and demonstrated that it takes about 300 cases and nearly 4 years to standardise operative and console times, with a requirement of around 80 cases per year for a single surgical team to optimise the outcomes of RARP (23).

Finally, it has been reported that the quality of PLND during RARP seems to be not related to the number of procedures performed, allowing for the removal of a number of lymph-nodes by a less experienced surgeon that is clinically comparable to that of a high-volume surgeon (24).

In summary, the experience matured by the Centre and the surgeons involved within the setting of the present study was by far enough to meaningfully discuss the observed difference in operative time.

We acknowledge the limitations of the study. First, although the data of the experimental cohort were prospectively collected, our analysis was retrospective and partly based on a historical cohort, with inherent bias. Moreover, the study considered subjective inclusion criteria. We might have missed the full establishment of causal inference, due to potential confounders that remained not observed. These, alone, could have contributed to the observed difference in operative time. Second, we did not control for the bedside assistant experience, although all the bedside assistants involved had comparable background. On the other hand, we underline that our results could be not fully generalized, given the surgical profile of the involved console surgeons. As reported above, they had assisted > 1000 robotic procedures before the study start. To note, it has been demonstrated that serving as a bedside surgeon before performing RARP improves the outcomes of the surgeon once at the console (25).

Third, being the analysis focused on early outcomes of RARP, biochemical recurrence was not reported with only surgical margins status

provided as a proxy. Interestingly, within a multicentric experience, Bravi et al. investigated the relationship between biochemical recurrence after RARP and surgeon's experience. As opposed to open and laparoscopic radical prostatectomy series, the authors found that "novice" surgeons performing RARP achieved adequate cancer control since the early phase of their career. In this setting, we believe that further research should explore why the learning curve for RARP differs from prior findings about open and laparoscopic surgery. It has been hypothesized that surgical education (including simulation) and the adoption of performance metrics are contributing at flattening the learning curve of the new generations of surgeons (26).

Finally, although of paramount importance in the quality assessment of RARP, continence and potency outcomes were not reported being beyond the scopes of our study (27).

Notwithstanding the aforementioned limitations, our analysis suggests an interesting impact from splitting RARP and PLND onto two surgeons, showing a certain shortening in the operative time which we feel worth of further investigation.

CONCLUSIONS

The present analysis found that when RARP and PLND are split onto two surgeons, the operative time is shorter by 20 minutes compared to when a single surgeon performs RARP and PLND. This is an interesting finding that could sponsor further studies.

CONFLICT OF INTEREST

None declared.

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A new treatment of concealed penis: symmetrical pterygoid flap surgery

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ABSTRACT

Purpose: Considerable controversy exists regarding the surgery for concealed penis. We describe a new technique for repairing concealed penis by symmetrical pterygoid flap surgery.

Methods: From January 2016 to July 2022, we evaluated 181 cases of concealed penis that were surgically treated using the symmetrical pterygoid flap surgery. We measured the penile size preoperative and 2, 4, 12 weeks, and 1 year postoperative to confirm the improvement. A questionnaire was administered to the patients and parents to assess satisfaction regarding penile size, morphology, and hygiene.

Result: The perpendicular penile length was 1.59 ± 0.32 cm preoperative and 3.82 ± 1.02 cm after the procedure ($p < 0.05$), and 4.21 ± 1.91 cm after one year of postoperative ($p < 0.05$). The overall satisfaction of patients was 97.89%, while the overall satisfaction of older children patients (age > 7) was 75.24%. Parents focus more on the penile exposure size, while patients focus more on the penile morphology. Almost every patient had postoperative penile foreskin edema. However, this symptom had spontaneously resolved by 4–6 weeks. The complications such as skin necrosis, tissue contracture, or wound infection were 4.42%.

Conclusion: The symmetrical pterygoid flap surgery is an effective surgical technique for the management of concealed penis in children producing predictable results and excellent satisfaction of the parents and patients.

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INTRODUCTION

Concealed penis refers to a poorly developed penis which is hidden in the subcutaneous tissue (1). The anomaly is specifically associated with a lack of adequate outer penile skin and inadequate subcutaneous attachment to Buck's fascia, due to which the penis seems to be fused with the scrotum (2). When the penis is not erected, it is often shaped like a beak, and its normal shape disappears (Figure-1). Concealed penis can cause phimosis, balanitis, and in severe cases may cause difficulty in urinating (3). If the penis is concealed until adolescence or adulthood, it is a significant cause of psychological trauma and sexual dysfunction in adolescents and adults (4, 5). Therefore, surgical treatment is necessary for patients with concealed penis, and it has been extensively promoted by urologists. It was reported that there are numerous surgical techniques for surgical

treatment; however, the postoperative results obtained by different surgical methods are significantly different, which leads to no single surgical method being widely adopted (2, 5, 6). One of the numerous surgical techniques for concealed penis, named symmetrical pterygoid flap surgery, is rarely reported. In our centre, some children with concealed penis were treated in this way and have achieved stunning postoperative results. Therefore, this study aims to share our experience and hope to provide some reference to the treatment of children with concealed penis.

METHODS

Patients and study design

From January 2016 to July 2022, we evaluated 181 cases of concealed penis that were surgically treated using the symmetrical pterygoid flap surgery. The clinical manifestation of all cases was

Figure 1 - Picture of Concealed Penis before surgery.



as follows: the appearance of the penis looks like a “bird’s beak”, the penis appears to fuse with the scrotum and the penile shaft is entrapped within the subcutaneous tissue, and the normal penile shaft could be palpated while applying pressure on the opposite side of the shaft base (5-7). All patients were scheduled for regular follow-up visits at 2, 4, 12 weeks, and 1 years postoperative. Data were collected and analyzed on the patient’s preoperative penile length, postoperative penile length, penile circumference, and postoperative complications. At last, patients’ and their parents’ expectations and satisfaction about the surgery were also collected and analyzed.

Surgical Technique

All surgical procedures were carried out by a single urologist. The procedures were conducted under general anesthesia with patients in the supine position. The critical surgical steps

were as follows. First, a longitudinal skin incision was performed at the mid-ventral aspect of the prepuce, from the penile scrotal junction section to the proximal to the coronary sulcus, releasing of the stenotic ring and exposure of the glans (Figure-2a). Then, the penis is given control and pulled. At a distance of about 0.5 cm from the coronary sulcus, a circumcision at the inner prepuce was performed, and circumferential dissection along Buck’s fascia freed the penis from its deep tethering to the penile base. Removal of the dysplastic and shrunk frenulum through an inverted V-shaped incision, and dissecting the inner prepuce around of foreskin frenum, lengthened the foreskin frenum by anastomosis (Figure-2b). Penoscrotal angles were reconstructed using 4-0 silk thread sewed between the tunica albuginea corporis sponge and dermis at the penile base, placed in the 10 and 2 o’clock positions (Figure-2c). The dorsal foreskin was longitudinally and symmetrically cut, forming two pedicled skin

flaps. The subcutaneous fascia and vessels should be preserved, and the deep branches of the superficial vascular should be kept (Figure-2d). We then transferred the two pedicled skin flaps to the penile ventral area and inosculated the original foreskin. The two pedicled skin flaps were respectively

connect with the ventral foreskin (Figure-2e). The superfluous inner plate of the penis was resected, and the foreskin was reconstructed with midline symmetric anastomosis on the ventral side of the penis (Figure-2f). The postoperative appearance of the penis was satisfactory (Figure-3).

Figure 2 - Diagram of surgical steps and Intraoperative picture.

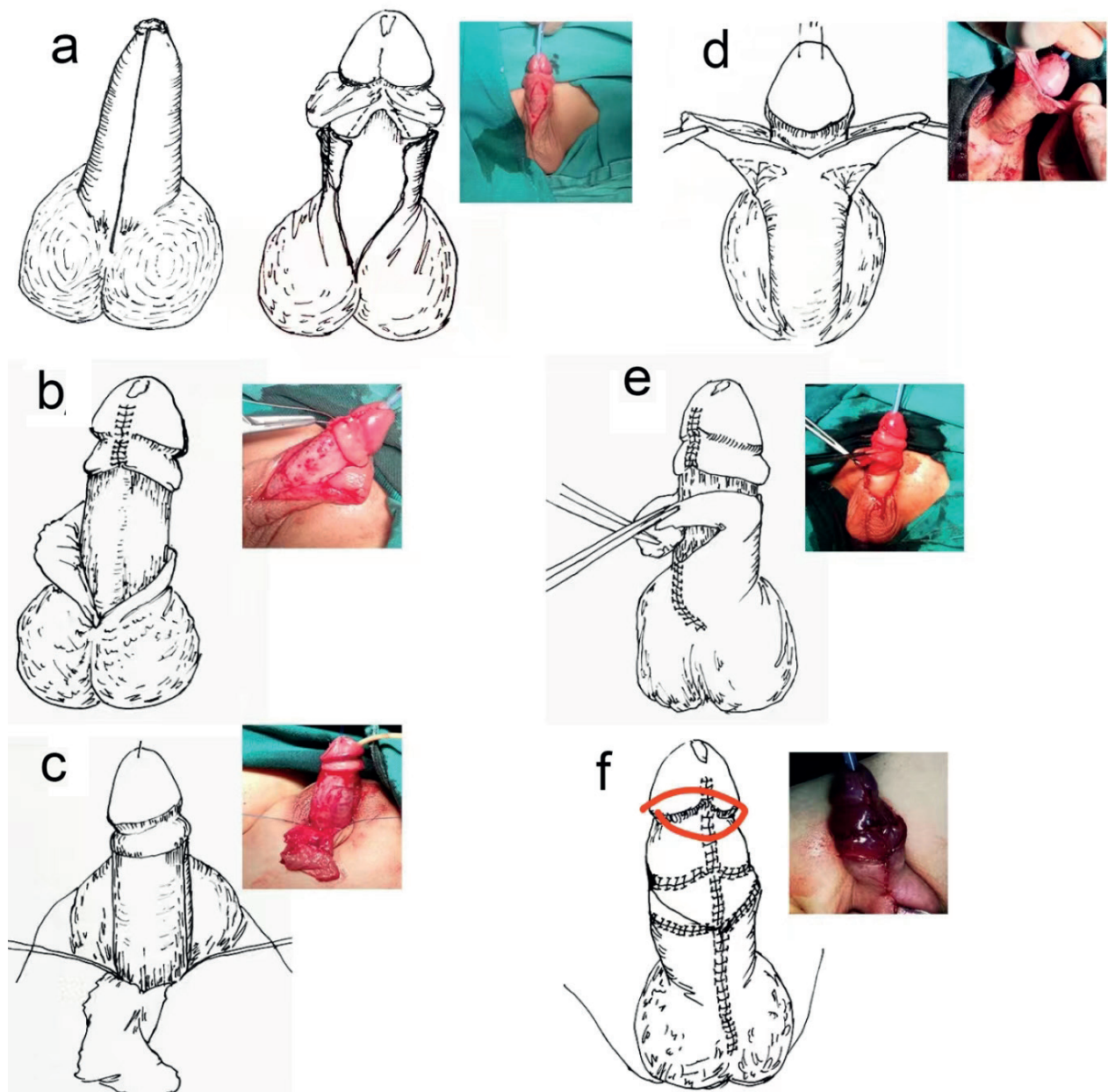


Figure 3 - Postoperative picture of Concealed Penis.



Statistical Analysis

All statistical analyses were performed using SPSS, version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). All data were presented as mean $\pm$ standard deviation. Postoperative data were compared with preoperative values using the t-test. P-values lower than 0.05 were considered statistically significant.

Ethical statement

Ethical approval was obtained from the Ethics Committee of Affiliated Hospital of North Sichuan Medical College (2022112412). The clinical operations involved in this article were evident to the children's parents. The children's parents signed the informed consent and agreed to disclose all the data.

RESULTS

A total of 181 patients underwent the symmetrical pterygoid flap surgery for the concealed penis during the study period. The mean age of the patients in this study was 8.48 ± 2.57 years, and the mean follow-up period was 35.67 ± 17.73 months. The average operation time was 46.12 ± 5.6 minutes. There was a statistically significant increase in penile length, from 1.59 ± 0.32 cm to 3.82 ± 1.02 cm after the procedure ($p < 0.05$), and to 4.21 ± 1.91 cm after one year of postoperative ($p < 0.05$). But the circumference of the penis was increased from 4.78 ± 0.65 cm to 5.88 ± 1.11 cm ($p > 0.05$), and the width of the glans was increased from 1.27 ± 1.12 cm to 1.46 ± 0.19 cm after one year of postoperative ($p > 0.05$), and the results were not statistically significant (Table-1a).

All patients had postoperative penile foreskin edema, which resolved within four weeks. There were no complications, such as voiding difficulty or erectile dysfunction. Complications were noted in 8 patients and consisted of infection and dehiscence of skin on the ventral side of the penis (5 patients), penile skin flap necrosis (2 patients), scar hyperplasia of the penis (1 patient).

The postoperative satisfaction scale was used to investigate the satisfaction degree of the parents and the older children patients (Supplementary materials). The parents were more concerned about the exposed penile size ($p < 0.05$). Besides, they were also concerned about the penile morphology. When the size and the appearance couldn't be satisfied simultaneously, the parents chose the size rather than morphology ($p < 0.05$), but the older children patients chose the morphology rather than the size ($p < 0.05$) (Table-1b).

DISCUSSION

Parents complain that their child's penis is small during the physical examination; however, a penis of normal size can be palpated in most of these boys [6].

Table 1 - Penile size changes and satisfaction of postoperative.

Table-1a					
	Preoperative	Postoperative			
		2nd week	4 months	12 months	1 year
Penis length	1.59 ± 0.32	3.82 ± 1.02	3.80 ± 0.99	3.93 ± 0.99	4.21 ± 1.91
Glans width	1.27 ± 1.12	1.27 ± 1.12	1.31 ± 1.12	1.34 ± 0.14	1.46 ± 0.19
Penis circumference	4.78 ± 0.65	5.88 ± 1.11	5.60 ± 0.95	5.67 ± 0.95	5.91 ± 1.02

Table-1b			
		Parents (n=181)	Patients (n=164)
Focus point of postoperative	Size	43.75%	17.40%
	morphology	15.62%	52.17%
	Both	40.63%	30.43%
	Recovery process	97.89%	75.24%
	Overall satisfaction	97.89%	75.24%

The small size of the penis is only on appearance, but the penis is of normal size. The small appearance of the penis is named concealed penis. Concealed penis refers to a poorly developed penis, which is hidden in the subcutaneous tissue (1). According to the different causes, the concealed penis is divided into five subgroups: buried penis, trapped penis, hidden penis, inconspicuous penis and concealed penis (8, 9). Some concealed penis moderately retracted after release, and the phimosis and small penis should be excluded (10). The diverse causes of the concealed penis have been explored, including scarce outer penile skin, dysgenetic dartos fascia, poor skin fixation at the penile base, excessive suprapubic fat and inelastic fibrous bands (11-13). In addition to the poor display of the penis, we found the ventral foreskin was fused with the penile scrotum. All cases with severe concealed penis in this study presented with penile-scrotal fusion. In this study, we chose children with severely concealed penis. These children showed no significant pre-pubic fat accumulation, more than 1/2 of the penis body

is hidden under the skin, the penis body is not exposed, and the appearance of the penis in an erect state is short conical, with penile-scrotum fusion.

Various surgical techniques have been described for the correction of the concealed penis. The key points of these procedures are removing excess pubic fat, releasing the dartos strip by peeling off the penis skin, anchoring the suprapubic skin to determine the penopubic angle, and repairing the shaft skin using various skin covering methods to correct the sparse skin shaft (1, 5, 6, 13-16). Many surgical methods reported so far can effectively expose the penis. And the major difference in methods is which skin flap is used for the penile skin defect. This surgery has some limitations, like a poor release of the dartos fascia, lack of fixation at the penile base and poor esthetic results. The various surgical methods reported can increase the amount of penis exposure to a certain extent. However, for a severely concealed penis, the existing surgical methods can't fully satisfy the consideration of penis exposure and the aesthetic appearance of the penis.

We used a symmetrical pterygoid flap for covering the ventral skin defect after penile degloving during the surgical correction of the concealed penis. After observing a large number of normal children's penis, we have found a clear fusion line in the ventral centre of the normal foreskin, which is consistent with the left-right symmetry of the human body. If there is a deviation of the ventral midline of the foreskin, it is often combined with penile torsion in the clinic. The anatomical feature of the foreskin is that its superficial artery gives off a primary branch at the proximal and middle third of the penis. Therefore, the vascular branches are fan-shaped on the skin and foreskin of the penis. The branch of the superficial dorsal artery and the perforator of the dorsal artery come from a rich vascular network in the penis, distal skin and foreskin (17). The scrotal skin has many hair follicles, and the wear resistance is worse than that of the foreskin. We made the following changes to our surgical procedure. First of all, we sewed between the tunica albuginea and dermis in the 10 and 2 o'clock positions at the penile base, reconstructing the penoscrotal angles and preventing retraction of the corpus penis. Second, to make the reconstructed appearance closer to a normal foreskin, we performed two pedicled skin flaps that were respectively connected with the ventral foreskin and reconstructed with midline symmetric anastomosis on the ventral side of the penis. Finally, we re-covered the corpus penis with a pedicled skin flap, which significantly reduced the tension after the foreskin anastomosis. The foreskin can be maximized to cover the penis that has been completely exposed and this reduces the risk of skin flap ischemia and postoperative scar formation.

Considering the voiding problems, poor hygiene, urinary tract infection, the pessimistic thoughts of patients with the concealed penis, and the parents' anxiety, more researchers suggest that surgery should be completed before puberty (9, 18). We also tend to complete surgery before puberty, but it is not a fatal disease. Therefore, the operation's success depends on the satisfaction of the patients and their parents, and their satisfaction is based on the functional and cosmetic appearance. But there was a significant difference in satisfaction between

parents and patients. The overall satisfaction of parents was 97.89%, while it was 75.24% for patients of older children. A possible reason for the lower satisfaction of patients may be the pain and the activity restriction they suffered and their concern for the penile morphology. There also exists a significant difference in their concerns between the penile exposure size and the penile morphology. Parents focus more on the penile exposure size, while patients focus more on the penile morphology. After follow-up, the results showed that the parents were satisfied with the size, morphology, voiding status and hygiene, but the patient's mental health and the damage of surgical treatment have not to be taken seriously. We also found that the patients and their parents not only need a perfected size of the penis, but also a perfected morphology of the penis. The symmetrical pterygoid flap surgery has a significant correction effect for patients with the concealed penis, and the patient's penis is closer to the appearance of the normal foreskin.

There are some disadvantages to our surgical method. First, the surgical method involves a skin transposition flap, and there is a risk of flap infection, flap ischemia and flap necrosis. The complication rate in our case series was 4.42% only; among the cases reported in this group, 7 cases had related complications. Second, this technique is suitable for concealed penis with severe poor exposure; and it has high requirements for surgical techniques. Lastly, the mean follow-up period was months. There is no follow-up regarding sexual intercourse. However, there was no obvious discomfort for postoperative penile erection, and restoration of sexual self-confidence may be useful.

CONCLUSIONS

The symmetrical pterygoid flap surgery is an effective surgical technique for the management of concealed penis in children producing predictable results and excellent parent and patients' satisfaction. The low rate of complications and good cosmetic outcomes support its use in clinical practice. The postoperative appearance of the penis recovered well. We believe that this surgical method is more effective than the traditional method for selected patients with a concealed penis.

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CONFLICT OF INTEREST

None declared.

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APPENDIX:**Supplementary materials - Follow-up Table of Concealed Penis.****Hidden penis postoperative return visit**

Name: _____, Age: _____ Year, Postoperative time: _____ Week;

Peripheral body circumference: _____ cm; glans width: _____ cm return appearance:

Penis length: dorsal side: _____ cm; ventral side: _____ cm

Scar condition: dorsal side: _____ ventral side: _____

Evaluation of children and their families**1. Satisfied with the appearance of the postoperative:**

(1) Very satisfied () ; (2) Satisfied () ; (3) Satisfactory () ; (4) Unsatisfactory ()

problem: _____

1.Recovery time satisfaction:

(1) Very satisfied () ; (2) Satisfied () ; (3) Satisfactory () ; (4) Unsatisfactory ()

problem: _____

2.Recovery process satisfaction:

(1) Very satisfied () ; (2) Satisfied () ; (3) Satisfactory () ; (4) Unsatisfactory ()

problem: _____

3.The improvement of the appearance of the penis is more focused on:

(1) It is required to reach the maximum length, and the shape is almost indifferent ()

(2) as long as it can be revealed ()

(3) can be good for appearance, do not care less dew point ()

(4) the largest length and look good ()

4.Is it possible to recommend a child with the same problem in relatives and friends after the recovery of his child's surgery?

6.Satisfaction with the overall effect of the surgery: (0-10 points)



Abdominal testicular vessel distribution in human fetuses – basis for Fowler–Stephens surgery

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ABSTRACT

Purpose: To analyze the histology and distribution of abdominal testicular vessels in human fetuses

Patients and Methods: We studied 19 fetuses (34 testes) ranging in age from 12 to 19 weeks post-conception. The fetuses were evaluated regarding crown-rump length (CRL), total length (TL) and body weight immediately before dissection. Each testis was dissected and embedded in paraffin, from which 5 µm thick sections were obtained and stained with Masson's trichrome and Anti-CD31 antibody to quantify the vessels. The stereological analysis was carried out with the Image Pro and Image J programs, using a grid to determine volumetric densities (Vv). Means were statistically compared using the unpaired T-test ($p < 0.05$).

Results: The fetuses presented mean weight of 222.5g, mean CRL of 15.3 cm and mean TL of 23.2 cm. All testes were in the abdominal position. The mean percentage of vessels (Vv) in the upper portion of the testis was 7.6% (4.6 to 15%) and in the lower portion the mean was 5.11% (2.3 to 9.8%), with a significant difference ($p = 0.0001$). In the analysis between the upper portion of the right and left testes ($p = 0.99$) and in the analysis of the lower portion of the right and left testes ($p = 0.83$), we did not observe significant differences.

Conclusion: The upper portion of the abdominal testis in human fetuses had a higher concentration of vessels than the lower portion. These results suggest that manipulation of the lower end of the testis during Fowler–Stephens surgery should be avoided in order to preserve the collateral circulation.

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INTRODUCTION

The testes can be located in the abdomen, inguinal canal, or external inguinal ring (pre-pubic) in patients with cryptorchidism (1). The purpose of surgical treatment of undescended testes is to decrease the risk of testicular cancer or fertility issues and the placement of the testes in the scrotum without atrophy or recurrence. Surgical complications are more common in cases of testicular anomalies, such as small or short vessel testicles (2).

In cases where the testicles are not palpable, laparoscopic or open surgical exploration is necessary to identify the morphology and anatomical locations of the testes, vas deferens and testicular vessels and thus select the most appropriate surgical technique (3). Most orchidopexies can be performed through inguinal or even scrotal access. Laparoscopy is often used to diagnose non-palpable testes, by assessing testicular position if the testes are atrophic or absent (4, 5). Laparoscopy allows simultaneous performance of orchidopexy with high success rates (6, 7).

Two-stage Fowler-Stephens surgery is one of the surgical options to treat high abdominal undescended testis (8). The knowledge of testicular vascular anatomy is a key point in this procedure (9-11). We hypothesized that there are no differences in vessel distribution between the superior and inferior testicular portions. The objective of this study was to analyze the histology and distribution of testicular vessels during the human fetal period.

MATERIAL AND METHODS

The study was approved according to the ethical standards of the hospital's institutional committee on experimentation with human beings (IRB number: 30706720.8.0000.5259).

We studied 34 testes obtained from 19 human male fetuses ranging in age from 12 to 19 weeks post-conception (WPC) during the period from January 2021 to October 2022. All the fetuses were obtained from the maternity service of our hospital with parental approval. The fetuses were macroscopically well preserved, without anomalies

of the urinary and genital system, and fetuses with syndromes were excluded.

The gestational age of the fetuses was determined in WPC according to the foot-length criterion, which is currently considered the most acceptable parameter to calculate gestational age (12-15). The fetuses were also evaluated regarding crown-rump length (CRL) and body weight immediately before dissection. The same observer performed the measurements.

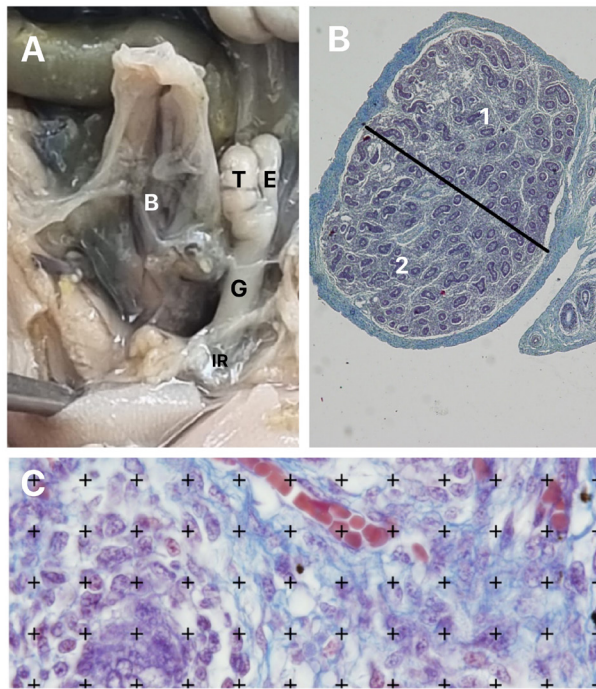
After the measurements, the fetuses were carefully dissected with the aid of a stereoscopic lens with 16/25X magnification. The abdomen and pelvis were opened to expose and identify the urogenital organs. Each testis and this respective genital mesentery were separated from the other structures and was fixed in 10% buffered formalin, and routinely processed for paraffin embedding, after which 5 µm thick sections were obtained at 15 µm intervals (Figure-1A).

The testicular vessels were studied by histochemical and immunohistochemical methods. The sections were stained with hematoxylin-eosin to assess the integrity of the tissue. We also performed the following staining: Masson's trichrome and CD-31 antibody (ABCAM- rabbit polyclonal anti- human and mouse CD31 with 1:50 dilution) to quantify and observe the testicular vessels (16).

Five sections were stained, and five fields of each section were selected. All selected fields were photographed with a digital camera (Olympus DP70, Tokyo, Japan) under the same conditions at a resolution of 2040 x 1536 pixels, directly coupled to the microscope (Olympus BX51, Tokyo, Japan). and stored in a TIFF file. A line was drawn approximately in the middle part of the cut, dividing the testicle into upper and lower half. The area density of blood vessels was calculated in each of the upper and lower parts (Figure-1B).

We used the Image J software, version 1.46r, loaded with its own plug-in to determine the vessels' volumetric density (Vv). Results for each field were obtained through the quantification assessment method, by superimposing a 100-point test grid (multipurpose test system) on the video monitor screen (Figure-1C). The arithmetic mean of the quantification in 5 fields of each section was determined (17, 18). Afterwards, we obtained

Figure 1 - A) The figure shows a fetus with 17 weeks post conception (WPC) with the testis in abdominal position. After the dissection, the bladder (B), the testis (T), the gubernaculum (g), epididymis (e) and the internal inguinal ring (IR) can be observed; **B)** The photomicrograph shows the testis of a fetus with 16 WPC. A line was drawn, approximately in the middle part of the cut, dividing the testicle into upper (1) and lower half (1). Masson's trichrome X40; and **C)** morphometric analysis of the fetal testis. The photomicrograph shows the quantification of the vessels in a fetus with 16 WPC using the Image J Test grid software (Masson's trichrome X1000).



the mean quantification value for the 5 sections studied from each testis (total of 25 test areas).

Statistical Analysis

All parameters were statistically processed and graphically described. The Student t-test was used for comparison of quantitative data between upper and lower testicular portions. The results obtained were compared using analysis of variance (ANOVA) with Tukey's multiple comparisons post-test ($p < 0.05$). Simple linear correlations were calculated for all variables (where r^2 values less than 0.4 reflect very weak correlation, r^2 between 0.4

and 0.7 reflect moderate correlation and r^2 greater than 0.7 indicate strong correlation): fetal weight, fetal age in post-conception weeks and percentage of vessel density in the upper and lower portions of the right and left testicles. The statistical analysis was performed with GraphPad Prism.

RESULTS

The fetuses ranged in age from 12 to 19 WPC, weighed between 58 g and 551 g (mean=222.5 g), had CRL between 8 cm and 25 cm (mean=15.3cm) and total length between 11 cm and 56.5 cm (mean= 23.2cm). In 19 fetuses, all the 38 testes were in abdominal position. Table-1 reports all biometric data of the 19 fetuses in our sample.

During the histologic preparation we lost 4 testes, so we only analyzed 34 of the 38 testes. The statistical analysis of vessel volumetric density in the upper and lower portion of the testes studied is also reported in Table-1. In turn, Figure-2 shows the histological aspects of the vessel distribution in the upper and lower portions of the testes. The histological analysis showed that the upper pole had more vessels during the gestational period studied.

The quantitative analysis indicated no significant differences comparing the upper portion of the right and left testes ($p=0.99$) and in the analysis of the lower portion of the right and left testes ($p=0.83$), but the mean vessel volumetric density in the upper portion of the testes was 7.6% (4.6 to 15%, $SD=0.42$) and in the lower portion the average was 5.11% (2.3 to 9.8%, $SD=0.31$), with a significant difference ($p=0.0001$).

Linear regression analysis showed in the left testis that gestational age does not correlate with vessel density in the upper portion ($y=0.2237x + 4.257$; $r^2=0.02600$; $p=0.5227$, not significant) and nor in the lower portion ($y=0.08122x + 3.902$; $r^2=0.005674$; $p=0.7739$, not significant). In the right testicles, gestational age also did not correlate with vessel density in the upper portion ($y= -0.3163x + 12.16$; $r^2=0.1233$; $p=0.1823$, not significant) and nor in the lower portion ($y=0.1720x + 2.312$; $r^2=0.04234$; $p=0.4282$, not significant) (Figure-3).

Table 1 - The table shows the biometric data of the fetus studied and the analysis of the vascular density in the 19 fetuses of our sample.

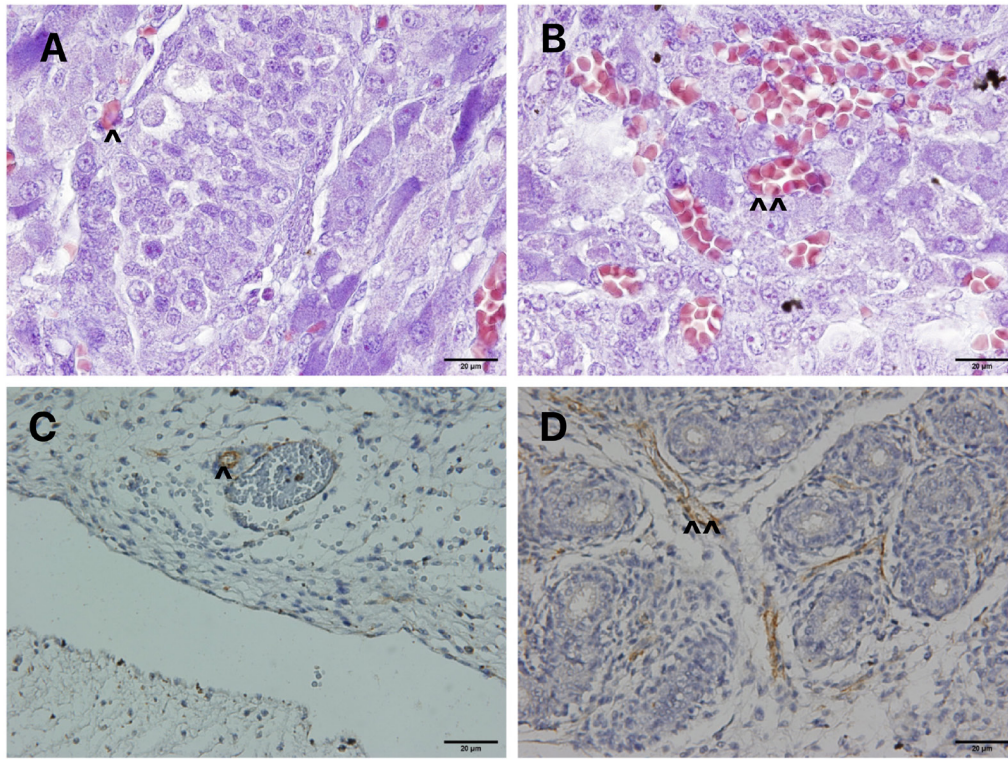
Fetus	WPC	RT UP Density (%)	RT LP Density (%)	LT UP Density (%)	LT LP Density (%)	Weight(g)	CRL (cm)	TL (cm)
1	12.9	7.3	3.6	6.0	4.0	58	8.0	11.0
2	13.1	6.6	4.4	5.7	4.7	66	15.0	21.5
3	13.1	9.8	5.0	10.0	6.3	70	11.0	14.0
4	13.8	x	x	6.4	3.8	80	14.0	17.0
5	13.9	8.6	6.8	15.0	9.8	107	17.5	21.0
6	14.7	7.8	4.8	7.0	4.5	170	15.0	18.5
7	16.0	5.5	3.8	x	x	130	15.5	22.0
8	16.0	7.2	5.4	5.3	2.3	246	18.9	24.7
9	16.0	8.0	4.3	5.5	3.5	286	18.2	24.2
10	16.1	5.6	7.4	7.0	4.3	192	8.5	18.0
11	16.3	5.0	4.8	7.5	5.5	247	13.5	18.5
12	16.3	10.0	5.0	5.8	3.3	250	17.0	23.0
13	16.5	7.0	5.4	6.3	3.3	230	17.5	25.0
14	17.0	5.8	3.3	8.2	7.6	348	14.0	56.5
15	17.4	x	X	7.6	8.6	252	18.0	24.5
16	17.6	6.5	4.0	9.0	6.0	250	16.5	24.0
17	18.1	9.2	5.0	4.6	4.4	214	11.5	20.0
18	19.1	4.8	3.3	12.0	6.2	481	17.0	25.0
19	19.4	14.2	9.8	x	x	551	25.0	32.5
Mean	15.9	7.58	5.06	7.58	5.18	222.53	15.35	23.21

WPC = weeks post conception; RT = Right testis; LT = Left testis; UP = Upper extremity of the testis; LP = Lower Extremity of the testis; CRL = crown rump length; TL = Total Length

Linear regression analysis, in the left testis, showed that fetal weight did not significantly correlate with vessel density in the upper portion ($y=0.006440x + 6.362$; $r^2=0.09690$; $p=0.2086$, not significant), nor in the lower portion ($y=0.001423x + 4.886$; $r^2=0.006150$; $p=0.7648$, not significant). In the right testis, fetal weight also did not significantly correlate with vessel density in the upper portion ($y= 0.003964x + 6.674$; $r^2=0.05365$; $p=0.3711$, not significant) nor in with vessel density in the lower portion. ($y =0.003416x + 4.282$; $r^2=0.07985$; $p=0.2718$, not significant) (Figure-3).

DISCUSSION

High abdominal undescended testis is a challenging situation in pediatric urology. Irrespective of the surgical technique, preservation of an adequate arterial supply for the testes is crucial for successful orchidopexy to ensure normal testicular size and texture (19). The anatomy of testicular arteries is very important to the success of the surgical procedures (11,20). Each testis is irrigated by three arteries: the testicular artery (internal spermatic artery), a branch of the aor-

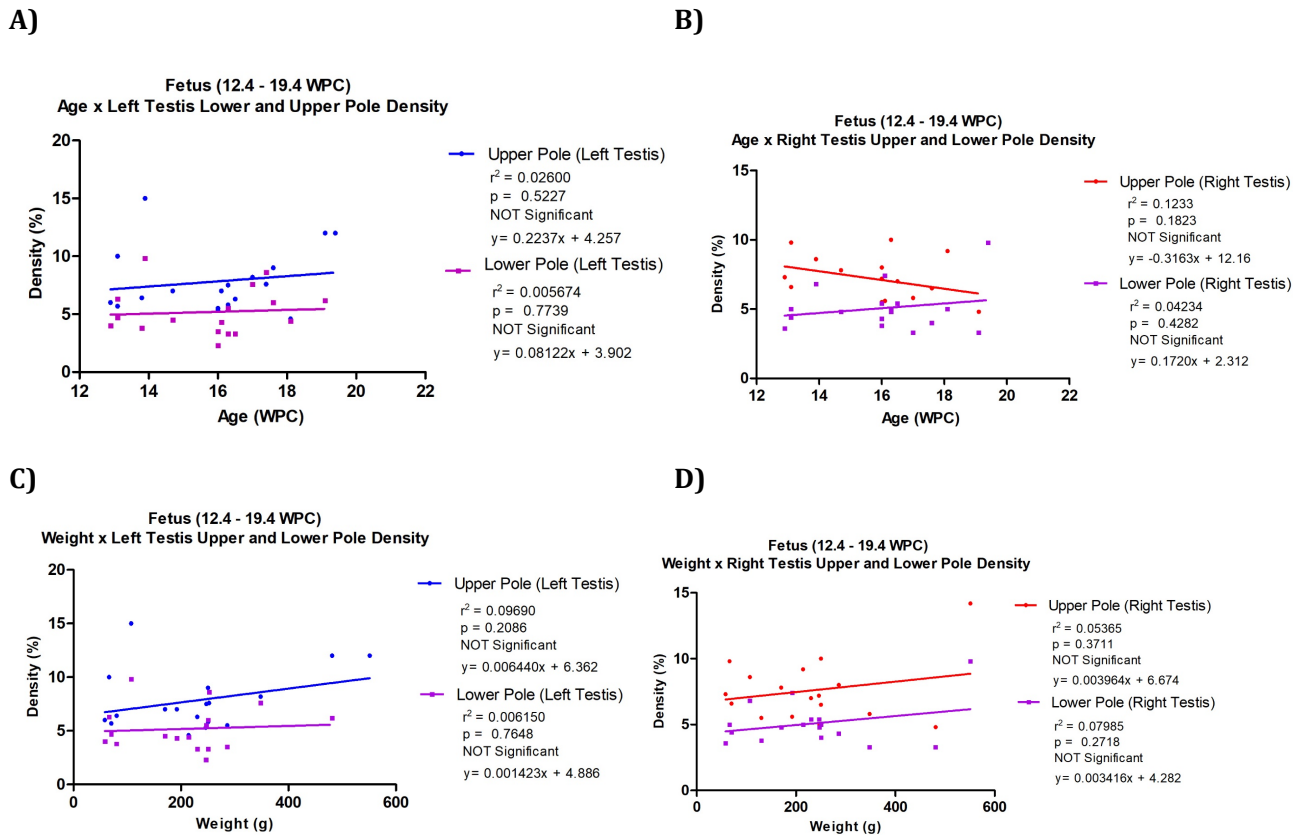
Figure 2 - Histologic analysis of the testicular vessels.

A) Photomicrograph showing the distribution of the vessels (arrowhead) in the lower portion of a fetus with 16 weeks post-conception (WPC). Masson's trichrome X1000; B) Photomicrograph showing the distribution of the vessels (arrowhead) in upper portion in a fetus with 17 WPC. Masson's trichrome X1000; C) Photomicrograph showing the distribution of the vessels (arrowhead) in lower portion in a fetus with 19 weeks post-conception (WPC). Immunohistochemical with CD-31 antibody x1000 and D) Photomicrograph showing the distribution of the vessels (arrowhead) in lower portion in a fetus with 18 weeks post-conception (WPC). Immunohistochemical with CD-31 antibody x1000.

ta; deferential artery (vasal artery), a branch of the inferior vesicle artery that originates from the anterior trunk of internal iliac artery and cremasteric artery (external spermatic artery), a branch of the inferior epigastric artery. These three arteries penetrate the organ in the mediastinal region, where they provide ample communication (11, 21).

The majority of vessels ending to the testis, regardless of their origin, enter through the testis hilum and hence the upper testis (11, 21). The anastomoses between the testicular, deferential and cremasteric arteries occur outside the testis (21,22). The cremasteric anastomoses possibly occur via the epididymal branch of the testicular artery and gubernaculum vessels what makes gubernaculum preservation important to maximise collateral flow to the testis during Fowler Stephens orchidopexy (11).

When orchidopexy is performed in patients with intra-abdominal testicles, one of four surgical techniques is applied: conventional orchidopexy, laparoscopic orchidopexy, Fowler-Stephens orchidopexy in one stage, and Fowler-Stephens orchidopexy in two stages (23). In the four types, surgery consists of locating each testis, dissecting it near the spermatic cord, acquiring free tension, and then repositioning it near the scrotum. When performed open, a medial inguinal incision is made from the anterior superior iliac spine to the external oblique fascia to allow exploration of the peritoneal cavity (24). Advantages of performing these techniques by laparoscopy include improved visualization, more extensive vascular dissection ability to vessel origin, lower morbidity, and ability to create a medial inner ring to the lower epigastric vessels and perform a straight course to the scrotum (25).

Figure 3 - Linear regression analysis. The points plotted represent the mean values obtained for each week studied.

A) The figure shows linear regression analysis comparing the vessel density of the left testis with fetal age (WPC); B) the figure shows linear regression comparing the vessel density of the right testis with fetal age (WPC); C) the figure shows linear regression comparing the vessel density of the left testis with fetal weight; and D) the figure shows linear regression comparing the vessel density of the right testis with fetal weight.

Conventional laparoscopic Fowler-Stephens orchidopexy (CLO), both in one and two stages, is adopted when the testes are located high, and the testicular vessels are too short to be fixed in the scrotum. The vessels are ligated and the blood supply to the testes is preserved via collateral circulation between testicular and deferential arteries, followed by repositioning and fixation of the testes (8, 26). In this surgery, the gubernaculum is divided, and each testis is brought down medially to the inferior epigastric vessels and a straight course to the scrotum is performed (4, 5).

CLO is an accepted technique when the spermatic vessels' length is short and to perform tension-free testicular mobilization at the scrotum. CLO atrophy rates can be as high as 33% (25). In this technique, previous testicular sur-

gery and vas abnormalities are factors associated with testicular atrophy (26-28).

Recently, an alternative of CLO with gubernaculum preservation and anatomical delivery of the testis through the internal inguinal ring was described, called gubernaculum-sparing laparoscopic orchidopexy (GLSO) (29). It improves the collateral blood supply to the testes by preserving the gubernaculum and cremasteric vessels, with less atrophy than in CLO (29).

A previous anatomical study of cadavers with undescended testes demonstrated that all testicles studied, including the undescended ones, had testicular, deferential and cremasteric arteries and good communication among the three arteries, with visible anastomotic channels between the testicular and deferential arteries (30). An interesting study in human fetuses showed that the

incidence of extra-numerical arteries in fetuses with testicles located in the abdomen is rare, and in cases of surgery by the Fowler-Stephens technique, they would be maintained by the deferential and cremasteric arteries (30).

This article is the first to evaluate the histology of testicular vessels in human fetuses with the testes positioned in the abdomen and demonstrates a significant difference between the vascular density in the upper and lower ends of the testicle, which reinforces the importance of preserving the vessels that will give rise to testicular collateral circulation in the lower extremity. Our study demonstrates that vascular density was positively correlated with the age and weight of the studied fetuses. Our results also show that the lower region of the testes has a significantly lower vascular concentration and corroborates the importance of preserving the vascularization that reaches the testes through the region of the testicular gubernaculum and the cremasteric vessels. As described for GSLO, this can be of great benefit and explain the lower atrophy rates observed with this technique (30).

Some limitations of our study should be mentioned: (a) the sample size was small (however, fetuses are rare, so observations of small samples are still relevant); and (b) the ideal sample for the present study would be children aged less than 1 year with cryptorchidism, but due to the rarity of this ideal sample, the study with human fetuses can provide important information for the treatment of cryptorchidism.

We concluded that the upper portion of the abdominal testis in human fetuses had a higher concentration of vessels than the lower portion. These results suggest that manipulation of the lower end of the testis during Fowler-Stephens surgery should be avoided in order to preserve the collateral circulation.

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CONFLICT OF INTEREST

None declared.

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Single Port Robotic Pyeloplasty: early single-center experience

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ABSTRACT

Purpose: Ureteropelvic junction obstruction (UPJO) is a prevalent cause of hydronephrosis, especially in young patients. The treatment paradigm for this condition has shifted from open to minimally invasive pyeloplasty. In the present study we describe our initial single centre experience with single port (SP) robot-assisted pyeloplasty (RAP) via periumbilical incision.

Material and methods: With the patient in a 60-degree left flank position, the SP system is docked with the Access port (Intuitive Surgical, Sunnyvale, CA, US) placed in a periumbilical 3 cm incision. Robotic instruments are deployed as follows: camera at 12 o'clock, bipolar grasper at 9 o'clock, scissors at 3 o'clock and Cadiere at 6 o'clock. After isolation and identification of the ureter and the ureteropelvic junction (UPJ), the ureter is transected at this level and then spatulated. Anastomosis is carried out by two hemi-continuous running sutures, over a JJ stent.

Results: Between 2021 and 2023, a total of 8 SP RAP have been performed at our institution, with a median (interquartile range, IQR) of 23 years (20.5-36.5). Intraoperative outcomes showed a median (IQR) OT of 210.5 minutes (190-240.5) and a median (IQR) estimated blood loss (EBL) of 50 mL (22.5-50). No postoperative complications were encountered, with a median (IQR) length of stay (LOS) of 31 hours (28.5-34).

Conclusion: In the present study we evaluated the feasibility and safety of SP RAP. The observed outcomes and potential benefits, combined with the adaptability of the SP platform, hold promising implications for the application of SP system in pyeloplasty treatment.

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INTRODUCTION

Ureteropelvic junction obstruction (UPJO) is a prevalent cause of hydronephrosis, characterized by flank pain and urinary tract infections (UTIs) as its most common clinical presentation. The widespread adoption of laparoscopic and robotic approaches has transformed the treatment paradigm for this condition, shifting from an open approach to a minimally invasive surgery, particularly in adults (1). Despite the clear advantages of laparoscopy over the open approach, including shorter hospital stays and lower rates of perioperative complications, it is associated with several drawbacks, such as a longer learning curve, advanced skill requirements, ergonomic limitations and increased operative time (OT) (2). When laparo-endoscopic single site (LESS) pyeloplasty was described, to reduce the need for analgesics while enhancing recovery time, it failed to demonstrate any advantage over conventional laparoscopy (3). On the contrary, the most important drawback of LESS pyeloplasty was represented by the ergonomics of the procedure, especially when a precise dissection and intracorporeal reconstruction is needed (4). The advent of robotic surgery, with its three-dimensional vision and tremor filtration capabilities, has simplified this procedure, overcame the limitations of conventional laparoscopy, and enabled easier dissection and suturing (5). Therefore, the number of pyeloplasty performed with a robot-assisted approach had a 10-fold increase between 2002 and 2008 (1).

With the aim of minimizing skin incision and working in smaller spaces while retaining the advantages of robotic instruments, the Da Vinci Single Port (SP) system (Intuitive Surgical, Sunnyvale, CA™) has gained popularity among surgeons trained in robotic procedures and is currently adopted for many urologic procedures. Preliminary data with this approach reveal encouraging results, demonstrating perioperative and intermediate-term outcomes comparable to standard MP robotic-assisted pyeloplasty (6, 7). Nonetheless, up to date, the available literature on SP pyeloplasty in adults is limited to retrospective studies, consisting mainly of initial clinical experiences and small case series.

In the present study we share our initial single centre experience encompassing all consecutive patients who underwent SP robot-assisted pyeloplasty (RAP) via an umbilical incision between November 2021 and July 2023.

SURGICAL TECHNIQUE

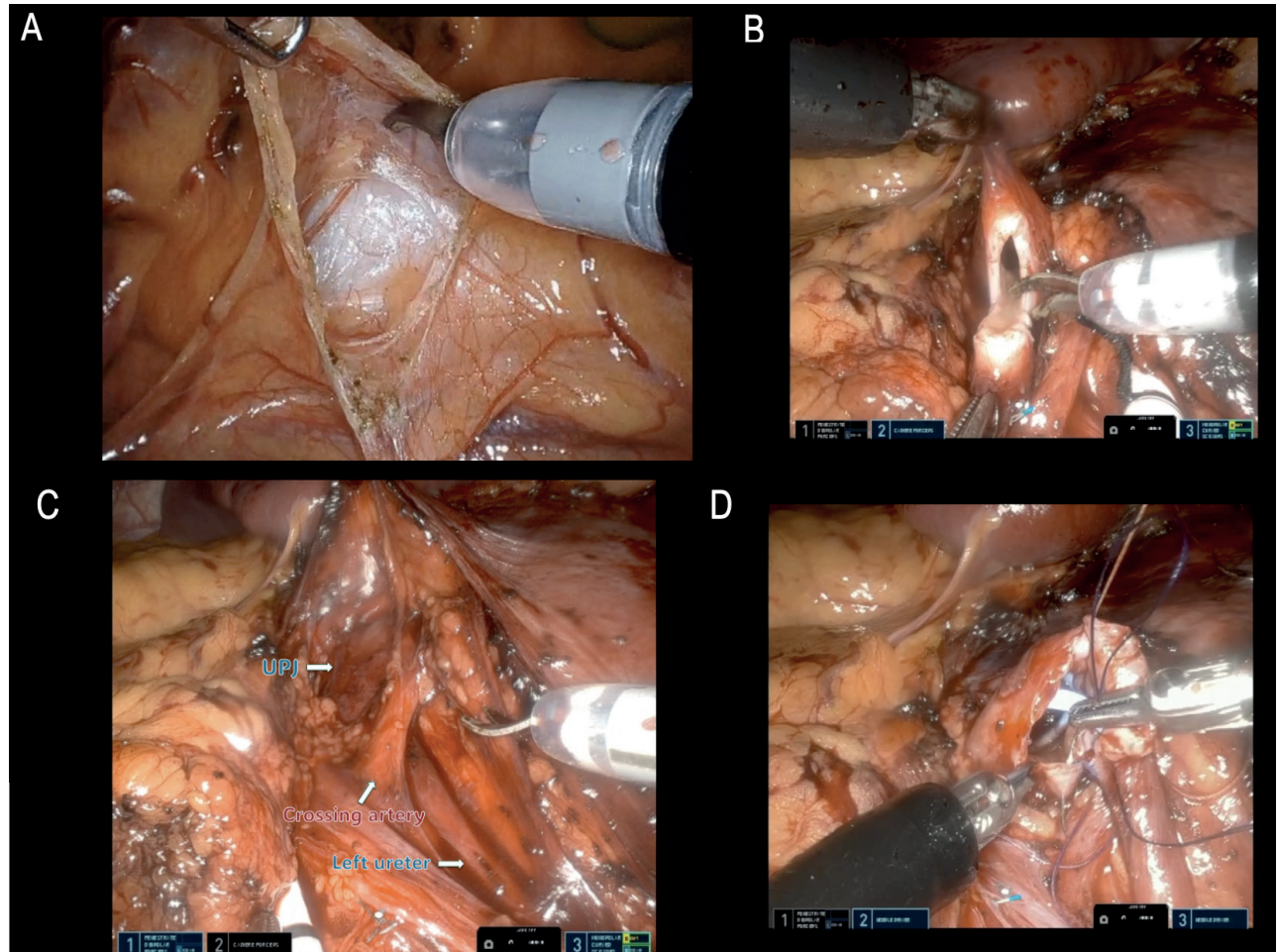
At our Rush University Medical Center, IRB criteria was met, and approval granted (protocol no. 22111003) prior to surgery and data collection.

SP RAP is performed following the Anderson-Hynes dismembered pyeloplasty technique (8).

The patient is placed in a 60-degree left flank position, under general anaesthetic. Through a periumbilical 3 cm incision, peritoneum is entered under direct vision and the Access port (Intuitive Surgical, Sunnyvale, CA, US™) introduced, with an 8mm Airseal port to allow pneumoperitoneum, set at 10-12 mmHg. The SP robot is docked with camera at 12 o'clock, bipolar grasper at 9 o'clock, scissors at 3 o'clock and Cadere at 6 o'clock. Suction is carried out using the remotely operated suction irrigation system (ROSI, Vascular Technology Inc, Nashua, NH), directly manipulated by the surgeon using robotic instruments.

After entering peritoneal cavity, the descending colon is reflected medially using cautery and scissors. Dissection is carried out until psoas muscle and ureter are identified and traced upwards. As an alternative, a transmesenteric approach may be employed for left pyeloplasty, allowing for direct access to the renal pelvis (Figure-1A). The ureter is then transected at level of the UPJ and then spatulated (Figure-1B). When encountering a transecting vessel, the UPJ is transposed and reconstructed anteriorly to it (Figure-1C). At this point, the renal pelvis can be reduced, according to its grade of dilatation. In our index case we did not perform this step, given its normal size. Anastomosis is carried out by two hemicontinuous 4-0 RB-1 Vicryl running sutures. Through the Access port and before completing the anterior part of the UPJ anastomosis, a JJ stent is introduced into the ureter over a guide, with the proximal coil placed in the renal pelvis (Figure-1D). Once the two sides of the anastomosis are completed, the sutures are tied together at its vertex. Drain was omitted

Figure 1 - Step by step surgical procedure (A: left mesenteric incision for direct access to ureteropelvic junction; B: Ureter transection at ureteropelvic junction level; C: a crossing polar renal artery clearly abutting the ureter at the level of the lower pole; D: anterior aspect of the ureteropelvic anastomosis after JJ stent placement).



in all cases. The fascia is closed with interrupted figure-of-eight, skin edges with subcuticular and Dermabond applied. Step-by-step procedure is visually displayed in the Supplementary video (Supplementary material).

Between 2021 and 2023, a total of 8 SP RAP have been performed at our institution, with a median (interquartile range, IQR) of 23 years (20.5-36.5). Most common presentations were flank pain (5, 62.5%), and only one case of previous UTI was observed. All the patients had mild to moderate hydronephrosis at preoperative imaging, with a median (IQR) preoperative serum creatinine (SCr) of 1.06 mg/dL (0.96-1.18) and a preoperative estimated glomerular filtration rate

(eGFR) of 86 mL/min/1.73 m² (78-97). Intraoperative outcomes showed a median (IQR) OT of 210.5 minutes (190-240.5) and a median (IQR) estimated blood loss (EBL) of 50 mL (22.5-50). No postoperative complications were encountered, with a median (IQR) length of stay (LOS) of 31 hours (28.5-34). Median (IQR) DVPRS (Defense and Veterans Pain Rating Scale) score at discharge was 4 (2.5-6). Postoperative opioids consumption has been quantified in morphine milligram equivalent (MME). Median (IQR) daily MME amounted to 20 mg (range: 10-30), whereas the total postoperative MME was 55 mg (17.5-87.5). The median (IQR) time to stent removal was 42 days (30-46.5). At early follow-

-up, postoperative renal function resulted in a SCr of 1.07 mg/dL (0.89-1.11), with an eGFR of 93 mL/min/1.73 m² (80.5-113.5) (Table-1).

Table 1 - Patients baseline features and perioperative outcomes.

SP RAP (n=8)	
Preoperative features	Median (IQR)
Age (years)	23 (20.5-36.5)
Presentation	
Flank pain (n, %)	5/8 (62.5%)
UTI (n, %)	2/8 (20%)
Hydronephrosis (n, %)	8/8 (100%)
Preop SCr (mg/dL)	1.06 (0.96-1.18)
Preop eGFR (mL/min/1.73 m ²)	86 (78-97)
Perioperative outcomes	
	Median (IQR)
OT (min)	210.5 (190-240.5)
EBL (mL)	50 (22.5-50)
LOS (hours)	31 (28.5-34)
DVPRS score	4 (2.5-6)
Complications (n, %)	0/8 (0%)
Time to stent removal (days)	42 (30-46.5)
Postop SCr (mg/dL)	1.07 (0.89-1.11)
Postop eGFR (mL/min/1.73 m ²)	93 (80.5-113.5)

Abbreviations: SP RAP (single port robot-assisted pyeloplasty); UTI (Urinary tract infection); SCr (serum creatinine); eGFR (estimated glomerular filtration rate); OT (operative time); EBL (estimated blood loss); LOS (length of stay); DVPRS (Defense and Veterans Pain Rating Scale).

COMMENTS

In our initial experience SP RAP demonstrated its safety and feasibility for the treatment of UPJO in adults, as already suggested by evidence available in the current literature.

For what concerns intraoperative outcomes, Bekcsac et al. reported an OT of 159 min, with 22.27 mL of EBL, with no significant difference compared to multi-port (MP) approach (7). Interestingly, in a larger series recently published by Harrison et al. the OT was significantly longer for SP RAP, compared to MP RAP (128 min vs 88 min, p=.04), with no difference in terms of EBL (6).

In our initial experience, we observed a longer OT (233 minutes), possibly attributable to the learning curve that surgeons involved in the procedure are experiencing. Although a specific learning curve is required when approaching the SP system, it is considerably shorter for surgeons who already have experience in robotic surgery. Consequently, outcomes obtained with the SP approach are readily comparable to those obtained with the MP approach. An extremely low EBL was observed in this series, as it was in previous studies (6, 7, 9), confirming the safety of this procedure. Moreover, no postoperative complications were registered, and all the patients were discharged on postoperative day one, following an internal protocol, with a median LOS of 31 hours and a median DVPRS score of 4. A recent systematic review and meta-analysis by Gu et al. reported no major complications following SP RAP, with no significant difference between SP-RP and MP-RP in terms of complications rate, thus corroborating our results (9). An additional potential benefit associated with SP approach may be related to the shorter LOS. Indeed, Beksac et al. provided evidence of significantly reduced LOS in patients undergoing SP RAP (12.18 hours), compared to MP RAP (42.66 hours, p<.001) (7). This finding was further confirmed by Gu et al. in their meta-analysis, which confirmed the advantage of the SP platform in terms of significantly shorter LOS for patients undergoing pyeloplasty (9). Thus, SP technique is highly appealing in the context of inpatient care, potentially leading to cost advantages for both patients and the healthcare system.

Several features of the SP platform make it well-suited for pyeloplasty, such as the need of a small working area and the possible application in bilateral UPJO. The added value of SP platform lies in its pliability, showed by its capability to perform various types of accesses and docking, enabling surgeons to adapt their approach to specific patient anatomy and procedural requirements. Therefore, in addition to a transperitoneal approach, the same procedure could be carried out in a retroperitoneal fashion, with patient placed in flank or supine position, while retaining the advantages reported in the present study. The feasibility of a supine approach for renal surgery

has been demonstrated by Pellegrino et al. in a pilot study, wherein they applied a retroperitoneal approach for upper urinary tract pathologies with the patient in supine position using the da Vinci SP robot (10). The adoption of this approach for SP RAP could extend to this procedure the benefits associated with retroperitoneal surgery, including enhanced control of hilar structures, reduced operative times and hospital stays, and decreased post-operative discomfort and pain. A reduction in postoperative pain may lead to a decrease in opioid usage, which constitutes the most employed analgesic for postoperative pain in the United States. Similarly, opioid dependence and their excessive utilization following urologic surgery pose a significant public health concern, particularly among younger patients with extended hospital stays (7). The adoption of a SP approach led to an opioid use of 20 mg of MME/daily, and 55 mg of MME in the whole postoperative course.

Among other factors, the potential for improved postoperative cosmesis is highly regarded, considering that young or paediatric patients are frequently involved in this procedure. Various incision sites for SP RAP have been documented in the literature, all yielding satisfactory outcomes. We believe the umbilical incision can achieve a favourable cosmesis results, as the scar remains completely concealed within the umbilicus after healing, and this can be an added benefit in the young adult population. Beckas et al. proposed a mini-Pfennestel incision with the aim of improving cosmesis and reducing postoperative pain (7). While this may not appear to be the primary determinant when selecting one approach over another, this aspect gains particular significance when considering the relatively young age of patients with UPJO that makes cosmesis potentially of high importance for this specific subgroup of patients.

Our study is not devoid of limitations, in particular the small sample size and the single-center experience which may hamper the validity and generalizability of our results. Furthermore, our study lacks long-term follow-up data, thus no conclusion about long-term functional results can be drawn. Nevertheless, we documented the feasibility and safety of SP RAP,

confirming the emerging evidence on this novel approach, and further supporting the use of SP RAP for the treatment of UPJO as an appealing alternative to MP RAP.

CONCLUSIONS

The present study adds to the expanding field of SP RAP for UPJO in young adults. The observed outcomes and potential benefits, combined with the adaptability of the SP platform, hold promising implications for the application of SP system in pyeloplasty treatment. Further investigations in larger patient cohorts and longitudinal studies are needed to further support the role of SP RAP and confirm its non-inferiority compared to MP RAP, considering its potential advantages in terms of cosmesis, opioid use, and postoperative pain.

DECLARATIONS

Data Availability. The data sets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

None declared.

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Technology description, initial experience and first impression of HUGO™ RAS robot platform in urologic procedures in Brazil

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COMMENT

Robotic surgery is a reality in the practice of urologists in developed and in several undeveloped countries. The first clinical procedures were performed in 2000 and since then was observed a fast spread in surgical practice, especially in Urology (1).

The Intuitive company remained exclusive in the market of production of robotic platforms in the past two decades. With the end of patent, different companies are developing new robotic platforms. The market will select which equipment will add real clinical benefits to be incorporated into daily practice (2).

To be able to evaluate a new technology, is necessary to remember the main issues related to the standard robotic platform with impact on the improvement of quality and surgical technique. Among them, it is important to mention (3, 4):

- Surgeon's ergonomic;
- Surgeon autonomy in controlling the camera and others instruments.
- Three dimensions vision;
- Tremor elimination;
- Instruments that allow a wide movement similar to surgeon hands;
- Safety devices.

Is also important quote the issues and limitations of the first platforms that still hinder or preclude them from being implemented in many centers. Among them can be mentioned: high cost, availability for training and qualification.

Thus, for a new technology to be interesting, it must offers the same benefits and supply some needs and limitations not met by other platforms.

The company that is entering in the competition and in this technological race is Medtronic. One of the largest medical device companies in the world produced its first robotic surgery platform called Hugo™ RAS (HR) - Medtronic, Minneapolis, MN, USA.

This platform emerged with the aim of offering a safe tool that allows the surgeons to operate with the same quality as they perform with the “standard” platform.

As a challenge, this technology comes with the proposal of having more accessible cost, allo-

wing access to a greater number of patients and the training of more surgeons.

The “open” console brings the concept that people in training can follow the surgery with the same view of the surgeon, improving the learning curve. Other possible benefit is to be multi-modular with the objective of being more versatile and able to favor “docking” using only the necessary number of arms.

To talk about incorporating a new technology, is necessary remember that there are two sorts of surgeon’s profiles. Those who have no experience with robotic surgery and those who are already used to the Da Vinci (DV) platform and in this moment must adapt to a new one.

The aim of this article is to report the results that are already in the literature and our initial experience as well as future perspectives important to highlight.

LITERATURE REVIEW

The literature about Hugo™ RAS system (Medtronic, Minneapolis, MN, USA) and Urology is still scarce due to the fact that the first surgeries with this platform started in 2021.

The initial studies proposed to prove the safety and functionality of this platform in performing oncological and non-oncological urological surgeries.

Among the uro-oncologic surgeries, the radical prostatectomy is the urologic surgery most performed worldwide. In this direction, it is also the most discussed topic at articles. The use of HR to treat prostate cancer appears to be a safe technique, without losing agility and maintaining satisfactory perioperative results (5-8).

The same feasibility was identified when performing adrenalectomies and nephrectomies. Despite these studies being observational and with few patients included, the initial results described generate an inference that the using the HR the oncologic results are satisfactory and maintains the perioperative results obtained with the standard platform (9-11).

The application of the new robot system is not restricted to the cases already mentioned, studies have also shown a role in non-oncological

surgeries such as simple prostatectomy, sacropepy and others (12-14).

Description and characteristics of the new platform

For the adoption and adaptation with a new platform, it is of fundamental importance for the surgeon to have detailed knowledge of the platform and its resources, as well as its limitations.

It is important to highlight that before the start of the transition to the new platform, our team already had the experience of more than 2,000 procedures with the “Da Vinci” platform and, therefore, it is natural to compare different parts of each equipment with the other.

The HR robot consists of a surgeon console, modular Arms carts and a main tower (Figure-1).

Console 3D screen

In the DV robot, the surgeon is “immersed” in the console and the surgeon needs to remove the head from the console to have visual contact with the operating room.

In HR, the surgeon looks at a “television screen” with 3D glasses and, with that, it is possible to follow the team’s movement.

It is important to highlight that the surgeon’s glasses have a sensor that, if the surgeon looks to the sides, the arms are locked for safety. This feature of the HR has the advantage of allowing other people to follow the surgery with the same view of the surgeon and allows the surgeon to keep informed about everything that is happening around, however, the great disadvantage is that external factors can disturb the concentration of surgeon.

Our impression is that this console allows a better ergonomic position because is possible to sit more comfortably. In DV the surgeon has to lean a little forward to have a great view of the screen (Figure-2).

For some surgeons the open console was strange and more challenging because the frequency of movements in the room distracts the surgeon attention. However, in our case to avoid this, we placed the monitor facing the wall and request that as few people as possible circulate in the operating room during the procedure. The

Figure 1 - Complete system with surgeon console, main tower, and modular Arms carts (from the right to left).



Figure 2 - A) Fellows and students watching the surgery with the same 3D view of the surgeon; B) HUGO™ RAS console, pay attention to the surgeon's ergonomics; C) Sensor on top of the screen that, when the surgeon removes his face, the arms stop working; D: DV Console, pay attention to the surgeon's ergonomics.



image quality is excellent, the major difference is that we do not have the feeling of being immersed and the image is a little further away, in our view this does not affect the performance of surgeries.

Pedal

The Pedal is similar to the DV containing additional pedals for future harmonic instruments implementation. In contrast with DV, the HR pedals have some safety mechanisms for activation energy and changing the arm in movement (Figure-3).

For both monopolar and bipolar power activation, it is necessary to initially press the pedal for 1.5 seconds, release it and then activate it again. If the energy pedals remain for more than 30 seconds without being used, a new activation will be necessary. In the same way is the instruments swap pedal; in the DV one click is enough and the arm in use changes, in the HR it is necessary to keep it pressed for 1.5 seconds for the change occurs.

Initially these issues did not please us, as it delayed the procedure since we often did not activate it. However, with the passing of the procedures, activation became something natural.

We believe that, for surgeons at the beginning of the learning curve, this is an important safety mechanism, as we often experience surgeons in training inadvertently activating the energy pedals, however, we believe that it may be an option that could be activated according to the surgeon preference and necessity.

Manual control

HR hand control has a different format than DV. In HUGO™, we hold it as if it were a “revolver handle”, we work with the index fingers and the first finger, and the third finger is used for the “Clutch” (Figure-4 and Figure 5).

The “trigger” button has two functions. A superficial grip locks the arm, and a deep grip performs the “clutch”, that is, the surgeon moves his hands to have poor ergonomics without the tweezers moving inside the patient. This double function is one of the functions that we least like about this console, because often we

Figure 3 - A) Pedal of Da Vinci; B) Pedal of Hugo™ RAS.



just touch it superficially and the arm locks, and the idea was to make a clutch. But we also observed that with more cases performed these events became more infrequent.

Modular arms

The HR has modular arms carts. In this perspective, the surgeon can decide how many arms are needed for each type of procedure. The arms have a wide range of motion and can be placed in a very versatile way.

Initially, we believed that, as it is multi-modular, it would occupy less space in the operating room, however the arms are still large with a robust base and takes up more space than DV (Figure-6).

The arms of the HR have 85 cm, bigger than those of the DV that have 53 cm (Figure-7). These longer arms make it a little more difficult for the assistant to manipulate and are more susceptible to collisions during the procedure.

This is an important point of attention because the assistant always works in a more uncomfortable way in relation to the DV and he needs to be attentive to robot arm does not collide with his body.

Figure 4 - A) Manual control of Hugo™ RAS (right hand); B) Manual control of HUGO™ RAS (left hand); C) manual control of Da Vinci.

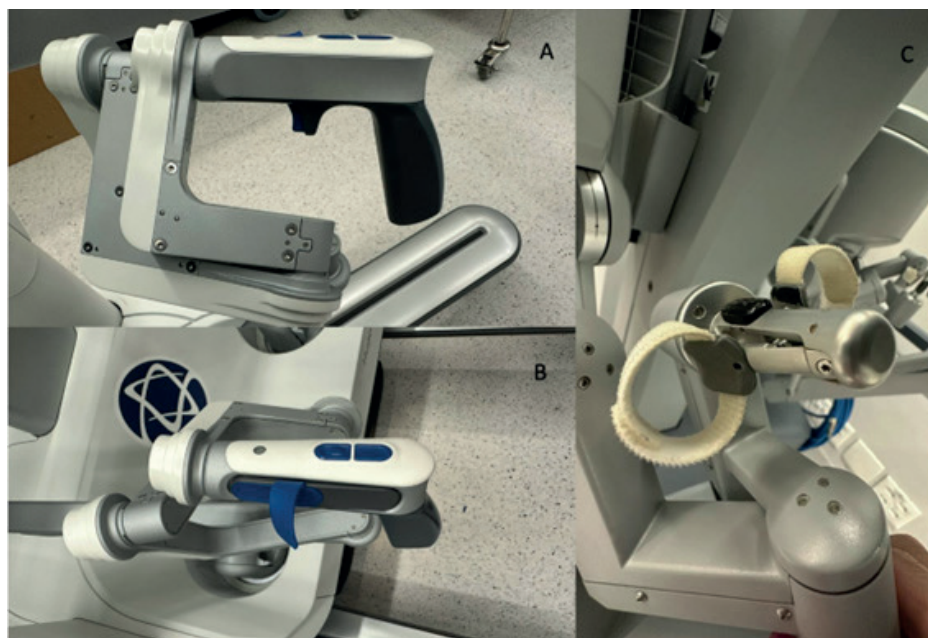


Figure 5 - A) manual control of Da Vinci; B) Manual control of Hugo™ RAS.

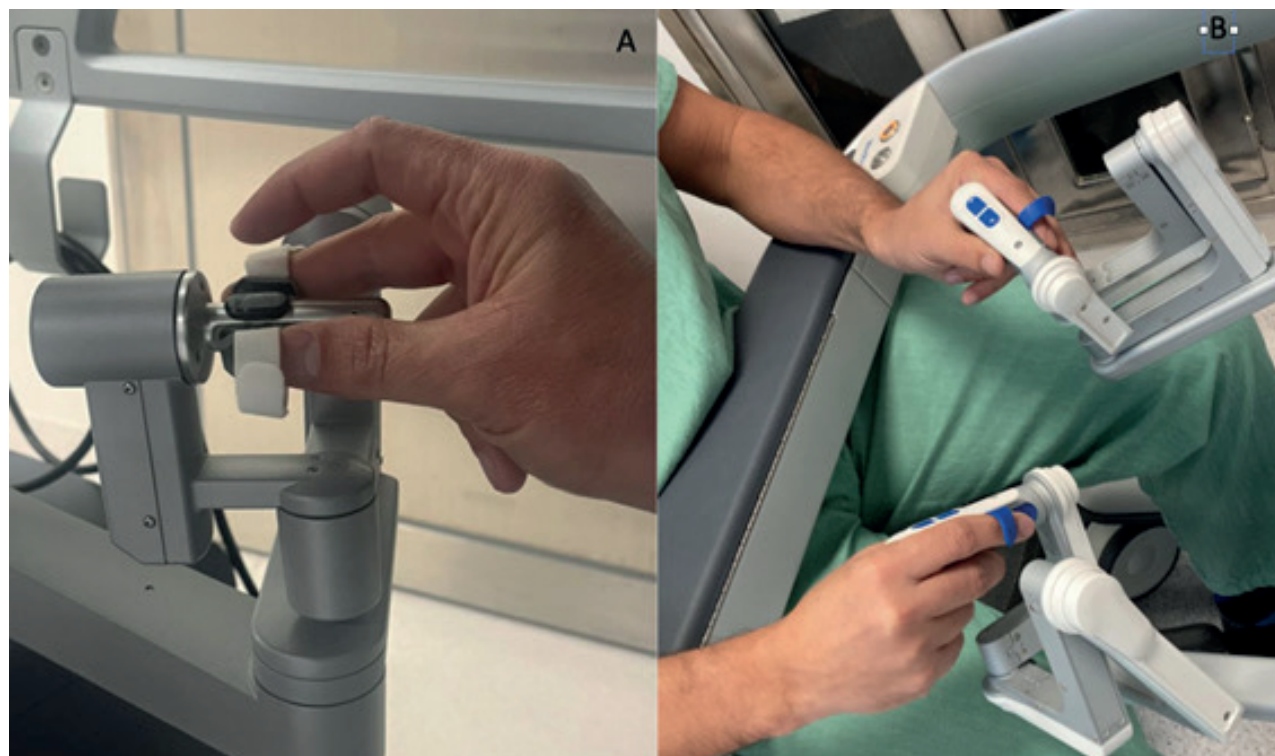


Figure 6 - A) Da Vinci Xi arms; B) Hugo™ RAS Modular arms.

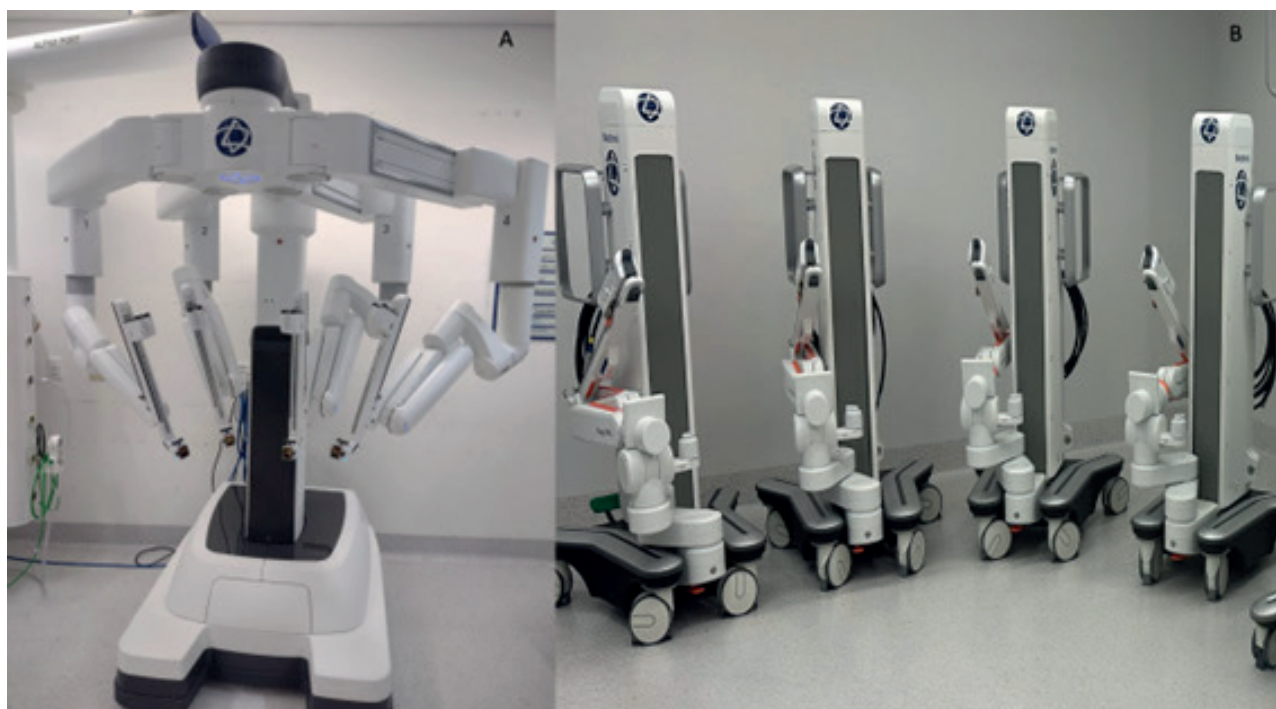
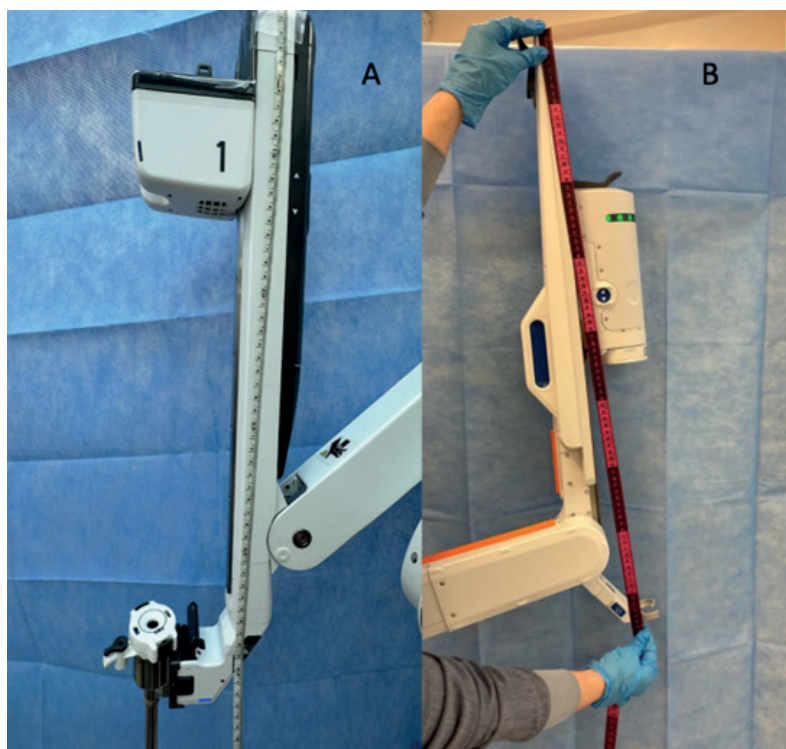


Figure 7 - A) Da Vinci Xi arm length; B) Hugo™ RAS Modular arm length.



Instruments

The HR instruments are shorter than DV instruments (Figure-8).

HR Maryland forceps has 53 cm and HR large needle driver has 52 cm. The longest HR instrument commonly used in urology is the double fenestrated with 54.3 cm total length. DV Maryland forceps and large needle driver has, respectively, 62 cm total and 61 cm total size. The longest DV instrument used in urology is prograsper with 63 cm (Figure-9).

The instruments disposable in Hugo™ RAS are: scissors, fenestrated bipolar, Maryland bipolar, large needle driver, extra-large needle driver, Cadere forceps, Cadere secure, double fenestrated and toothed claw.

The needle driver has an excellent gripping force, and the system has a possibility to set a “2 times” rotation. This was a very interesting characteristic that facilitated the performance of the vesicourethral anastomosis. There are two kinds of needle driver: the large and the extra-large.

Scissors are more delicate and sharper, however, at the moment they are still single-use and every 40-50 minutes you have to change a new one. At first, we found it odd and worried about the cost. But the company does not charge extra for this.

The great advantage is that we operate all the time with excellent quality scissors. When we close the scissors, they give a little bounce. At first it seemed strange but during the procedure it did not impact safety and quality. But it is certainly a relevant point for the company to improve.

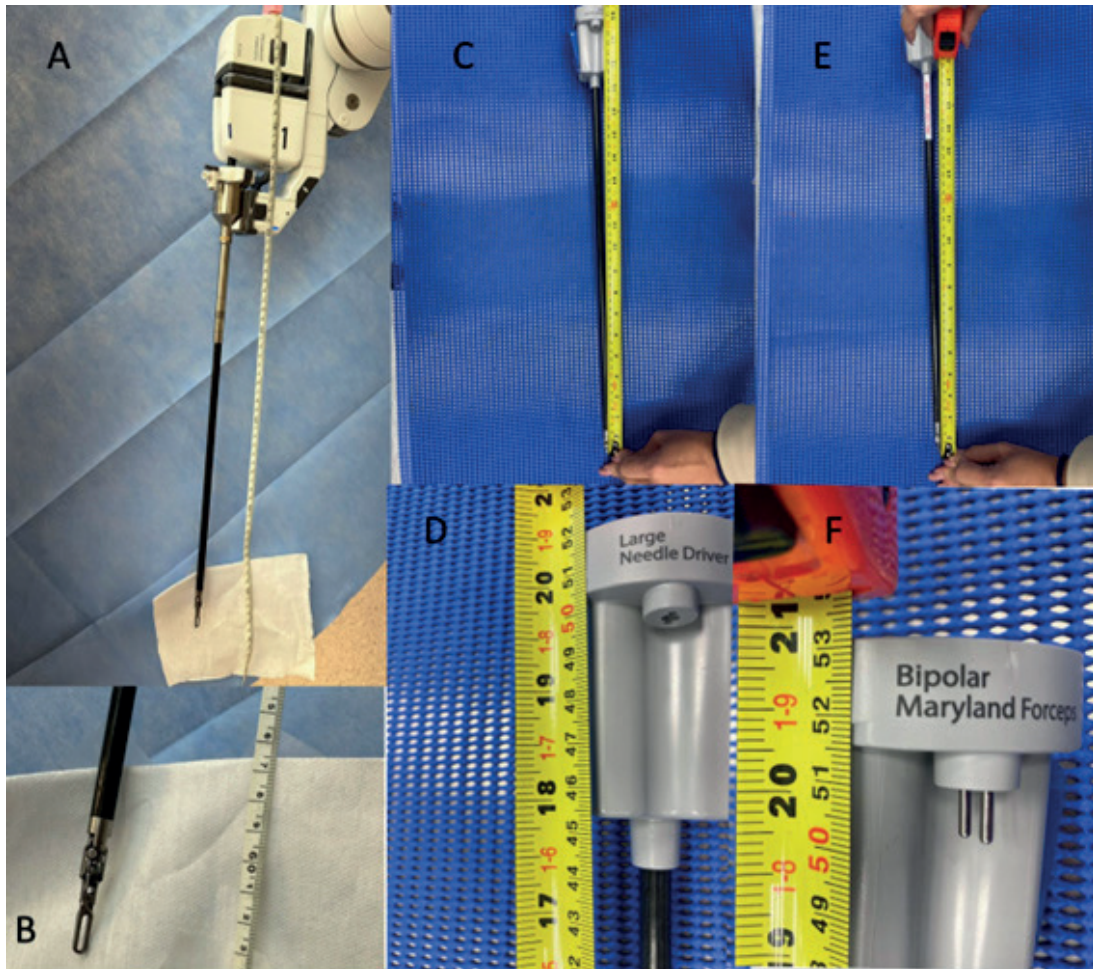
Regarding the traction instruments, it is important to highlight that the Cadere forceps does not have a great traction capacity, making some steps of the procedure difficult, being more recommended to use the “cadere secure” or the “toothed”.

To perform urology surgeries the instrument from DV most missed was the Tenaculum to traction the prostate adenoma during simple prostatectomy. To remedy the lack of this instrument,

Figure 8 - A) Table with Da Vinci instruments; B) Table with HR instruments



Figure 9 - A and B) DV prograsper total length; C and D) HR large needle driver total length; E and F) HR bipolar maryland forceps total length.



the surgical assistant needed to use laparoscopic toothed gripping forceps to help trace the adenoma during the procedure, which we have as a weakness as it impairs the speed and autonomy of the surgeon.

Main Tower

The main tower is very similar to the DV Xi. The components are a HD screen, a Karl Storz Imagem system and a Valleylab energy platform.

The image generated by Storz shows a brilliant tridimensional high-definition view and helps to identify the correct surgical plans during the procedure.

The endoscope can be placed in each one

of all arms carts. This point can be extremely helpful during performing a surgery with steps in different quadrants.

DOCKING

At first moment, as it was a multi-modular platform, we believed that docking could be made easier. However, we believe it is one of the biggest challenges in daily practice.

For each module, a precise positioning in relation to the table is required. Each arm is attached respecting two angles. The first is the tilt angle - inclination of the operative arm compared to the operative bed. The second angle is between

the robotic arm and the head of the patient.

The Medtronic recommends angles for each arm according to the surgery and add that alterations may be necessary according to the patient's body type, the patient's pathology or the surgeon's preference. (Figure-8) In the first cases we try to reproduce exactly what the suggested regarding the docking, trocater's placement and patient suggested position. But in few cases, we realized that, to reproduce our technique some modification must be performed (Figures 9-11). Important to point out is that the angle of the arms can be adjusted according to surgeon preference without compromise the functioning of the arms carts.

SECURITY

The HR system has many more safety features than the DV. When operating with the HR, the

team must get used to triggering different alarms.

The goggle sensor and the pedal drive system make the procedure safer, especially for surgeons at the beginning of the learning curve.

It is important to highlight that, so far, we have not experienced any adverse events with the platform, and we believe that it is a technology that follows all the necessary protocols to perform safe robotic surgery.

SURGICAL TECHNIQUE

In radical prostatectomy, it was possible to perform the same standard of surgical technique since the first procedure, making it possible to perform surgery with the same technical rigor used in surgeries with the DV. It is only necessary to adapt it to the assistant's portal.

Regarding partial nephrectomy, we believe

Figure 10 - A) Medtronic recommendations for prostatectomy. The endoscope trocar (yellow circle) is placed 16 cm or less from the target. The right arm trocar is placed in a line 5 cm below the endoscope line and need stay at least 8 cm distant from the endoscope (black circle). The left arm trocar follows the same instructions of right arm in contralateral side (black circle). The fourth arm of surgeon is placed in the same line of endoscope trocar, with 8 cm or more distant from the right arm. The assistant trocar (orange circle) needs to be placed at least 5 cm distant from the left arm. All trocars need to stay at least 2 cm from bone prominence; **B) Medtronic recommendations for left nephrectomy.** The endoscope trocar (yellow circle) is placed at least 5 cm from the line where will be placed the left and right arm of surgeon. At least 5 cm of distance between the fourth arm trocar and right hand of surgeon. The robotic trocars need to be placed at least 8 cm distant from each other. The assistant trocar should be placed medial to the left and right arms and near the median line of patient, at least 5 cm from the other trocars.

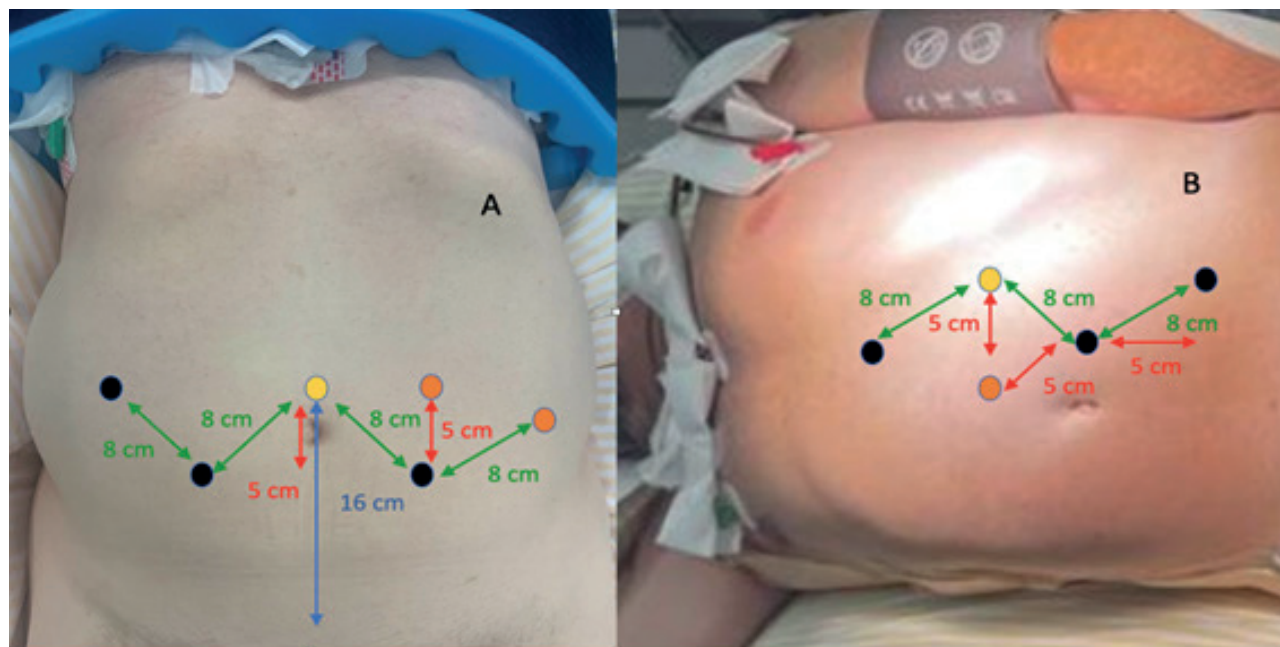
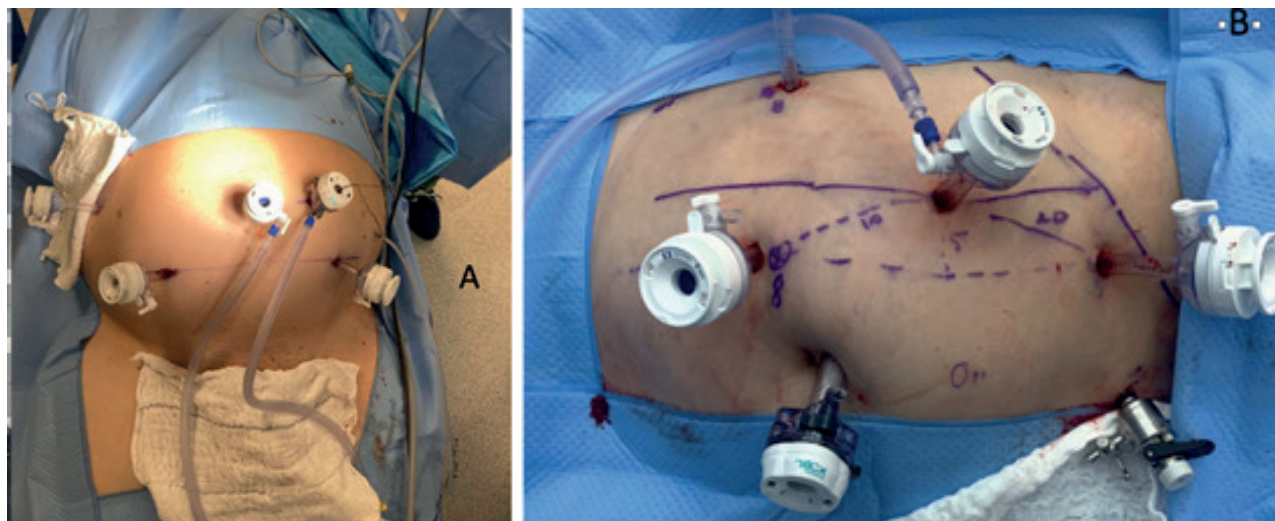


Figure 11 - A) Image of trocars placement - radical prostatectomy with Hugo™ RAS; B) Right parcial nephrectomy with Hugo™ RAS.



that we will need more time for adaptation, the concept of trocar placement changes a lot in relation to the DV. These modifications are necessary to reduce conflict. In this procedure, we found it very difficult for the assistant to carry out some steps, which made it difficult at times for an adequate presentation. The procedures with HR were uneventful, respecting all oncological principles. However, we believe that it is still necessary to improve the standard placement of trocars to facilitate the performance of a procedure with the same standards as the DV.

SIMULATOR AND PERMISSION TO USE

The HR has a simulator with some tasks like manipulation of needle, using of instruments, suture exercises and others. The repetitive exercises in simulators reduce the time necessary in dry and wet lab. For new robotic surgeons it allows get familiar with the platform and acquire a proficiency in some robotic activities.

The quality of simulator and exercises presented is excellent and similar to DV.

About the permission to surgeon use, Medtronic suggests the Hugo™ RAS should be used by medically trained surgeons with a full understanding of the safe operation of the system, in accordance with the hospital's credentialing policies

regarding the use of new equipment. This robot access policy is more flexible and comprehensive compared to DV, delegating to the hospital the function of releasing qualified surgeons for the procedure.

LIMITATIONS AND FUTURES PERSPECTIVES

Some limitations of the Hugo™ platform must be considered here, for example, the lack of glasses and 3D vision to assistant in the surgical field. The 3D glasses for the assistant would allow better image quality and approximation between the surgeon's and assistant's vision. The absence of some auxiliary resources for more complex surgeries, such as firefly with indocyanine green (fluorescence capability that uses near-infrared technology) and the use of robotic ultrasound, which are present on the Da Vinci platform and not on the Hugo™ RAS, is a limitation of the new robotic model.

Indocyanine green is most used in urological surgeries for complex partial nephrectomies - large renal tumors or with multiple renal arteries - and also for vascularization assessment during neobladder surgery. In other specialties such as gynecology, this feature is also important, for example, for identifying sentinel lymph nodes.

Robotic ultrasound on the Da Vinci pla-

tform allows combined intrabdominal vision and ultrasound, helping in various situations such as demarcation of tumor boundaries during complex partial nephrectomies.

CONCLUSIONS

HR has more safety and training features for new surgeons without previous experience with robotic surgery.

The surgeon may realize a training with the simulator until be comfortable with the console and realizing automatic and natural movements. At least 8 hours in simulator training is suggested.

The surgeon training is so important like the team training. A team motivated and familiarized with the robotic assisted system and docking is extremely important to the success of the platforms transition.

For surgeons with experience with the DV, the transition seems to be friendlier in radical prostatectomy, however, for partial nephrectomy, the transition is more challenging, and the team must already have experience with the new platform.

We believe that Medtronic could improve the software to make it more personable. The activation of the energy, the double function of the trigger button and the necessity of keep holding the bottom to change the arms, could be a configuration option according to the preference of the surgeon. Others features that need to be developed are 3D glasses for the surgical assistant, firefly with indocyanine green and robotic ultrasound with vision for the console surgeon.

The size of the Arms module must be reduced the size of the arm as well to facilitate the docking and bed side assistant work.

We need a larger casuistic to be able to construct more solid considerations about this new robotic platform.

CONFLICT OF INTEREST

None declared.

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Systematic review and metanalysis in urology: how to interpret the forest plot

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COMMENT

The systematic review follows rigid rules to find the best scientific evidence. This kind of publication aims to bring evidence together to answer a pre-defined research question. The research needs to make a search in all available databases. Systematic reviews should include a synthesis of the data that have been found. Data synthesis can involve summarizing quantitative and/or qualitative findings (1). Systematic reviews of quantitative data may include meta-analysis. The analysis of quantitative data in meta-analysis is the key to interpret the results of the study (1). In this comment we show the most important topics in the Forest plot interpretation.

When studying we must be familiar with the various types of graphs used in a meta-analysis. In the left column of a quantitative data the author's name of the studies included in meta-analysis are registered (Figure-1) (2).

In the right column of the figure 2 we can observe the confidence intervals (CI) registered in the quantitative data of a meta-analysis. Some forest plots may also provide information about the weights assigned to each study or independent variable in the analysis (Figure-2). These weights can be represented by the size of the "boxes" on the plot or by a number associated with each study. In some situations, the authors can include the values of the mean, standard deviation (SD) and the mean difference assigned to each group studied in meta-analysis in the center of the graphic (Figure-3) (3).

The vertical axis of the forest plot typically represents the independent variables or individual studies included in the analysis. Each study or independent variable is represented by a line on the plot (Figure-4). The horizontal axis usually represents the outcome measure or estimated effect. It can be a measure of risk, such as odds ratio or hazard ratio, or a measure of difference, such as mean difference or proportion difference (Figure-4). The vertical lines represent the confidence intervals for each study or independent variable. The length of the line indicates the precision of the estimate. The longer the line, the less precise the estimate. The central line in each "box" represents the point estimate for each study or independent variable. It can be the point estimate or the weighted average of the studies (Figure 4). If the confidence intervals of different lines do not overlap, it suggests that there is a statistically significant difference between the represented studies or independent variables. If the lines cross the null vertical line (typically a vertical line at a value of 1 or 0), it indicates that there is no statistically significant difference between the compared interventions or independent variables (Figure-4).

The value of each study depends on the sample size and precision, which will receive weight values. These weight values will be evaluated to compound the diamond represent the final result. Diamond size determined by 95% CI if not

touching the vertical line represents that the final result is statistically significant (left – better intervention/ Right – better control group) If the diamond touches the line represents the studies do not have statistical significance (Figure-5).

Figure 1 - The figure shows the quantitative data in a meta-analysis. In the left column (red square) we can observe the author's name of the studies included in meta-analysis.

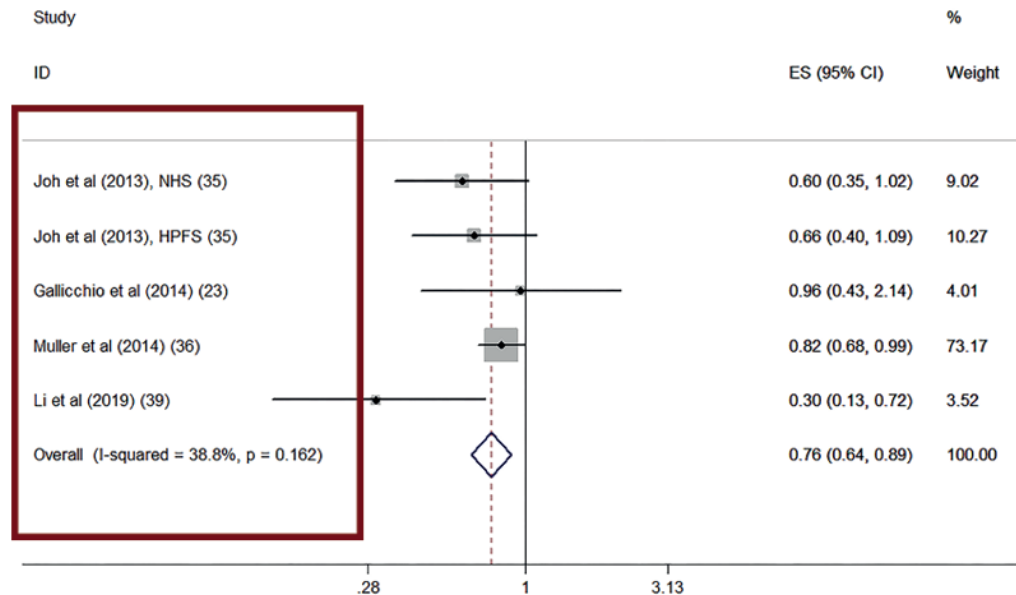


Figure 2 - The figure shows the quantitative data in a meta-analysis. In the right column (red square) we can observe the confidence intervals (CI) and the weights assigned to each study.

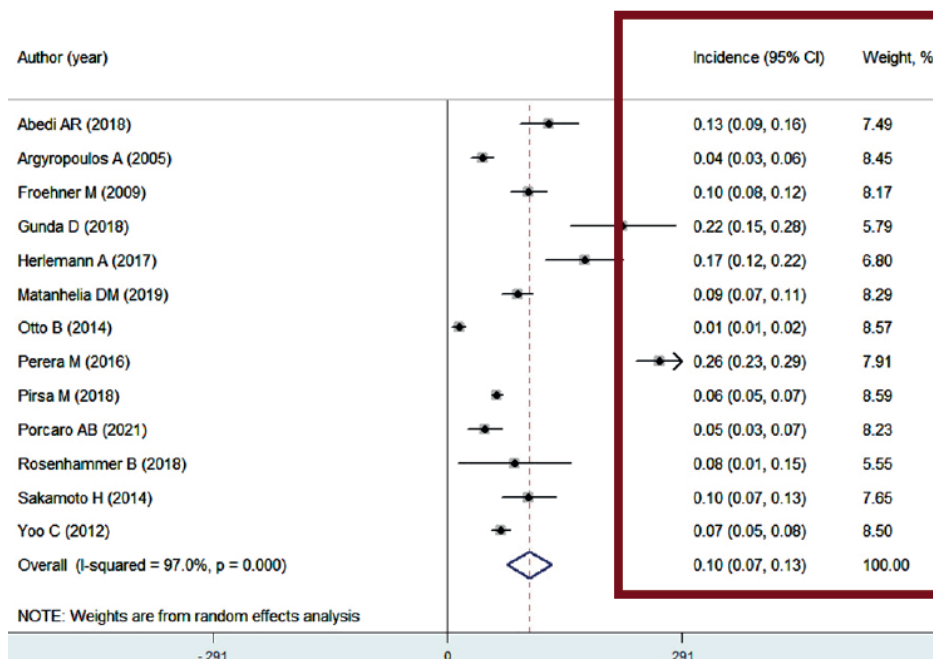


Figure 3 - The figure shows the quantitative data in a meta-analysis. In column highlighted by the red square we can observe the mean, standard deviation (SD) and the mean difference assigned to each group studied in meta-analysis (2).

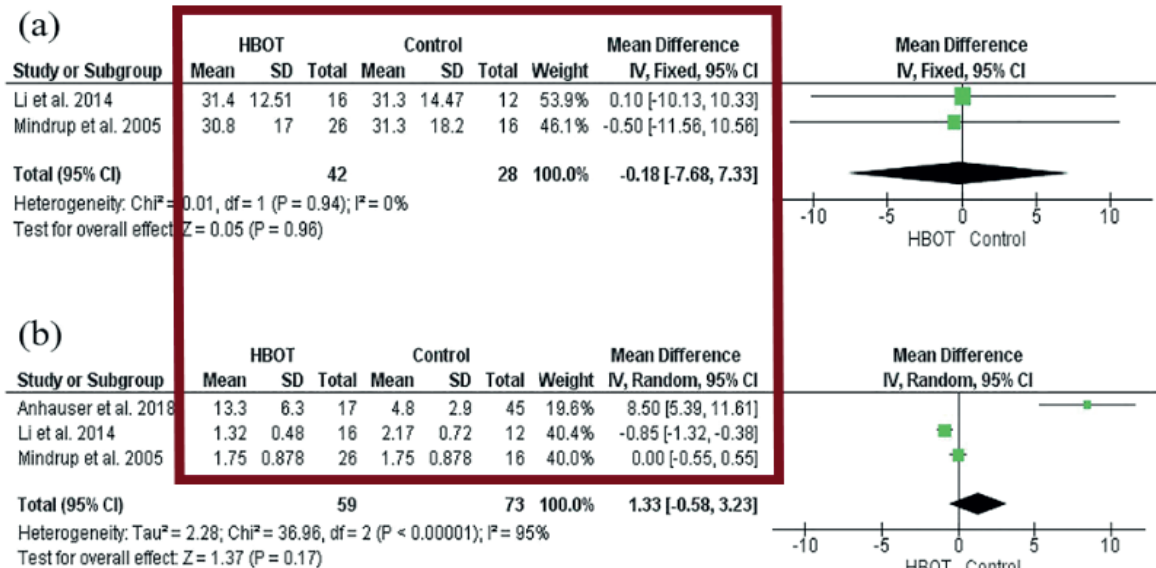


Figure 4 - The figure shows the quantitative data in a meta-analysis – the Forest plot. In the column highlighted by the red square we can observe the vertical axis of the forest plot (independent variables or individual studies included in the analysis) and the horizontal axis (represents the outcome measure or estimated effect). The vertical lines represent the confidence intervals for each study or independent variable. The central line in each “box” represents the point estimate for each study or independent variable. If the confidence intervals of different lines do not overlap, it suggests that there is a statistically significant difference between the represented studies or independent variables. If the lines cross the null vertical line (typically a vertical line at a value of 1 or 0), it indicates that there is no statistically significant difference between the compared interventions or independent variables (2).

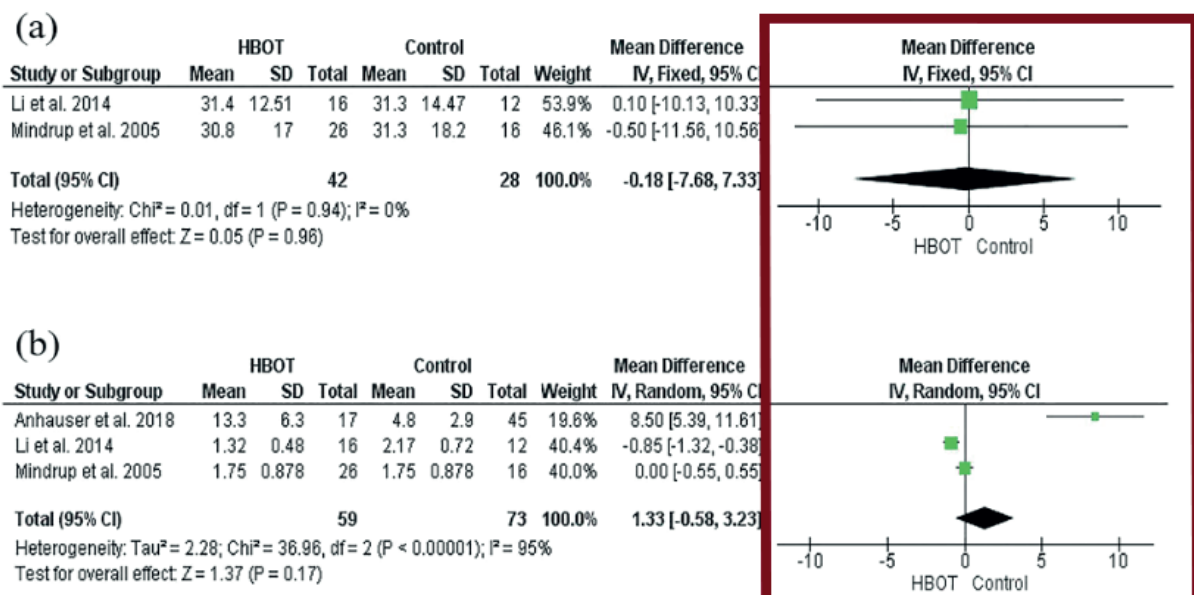
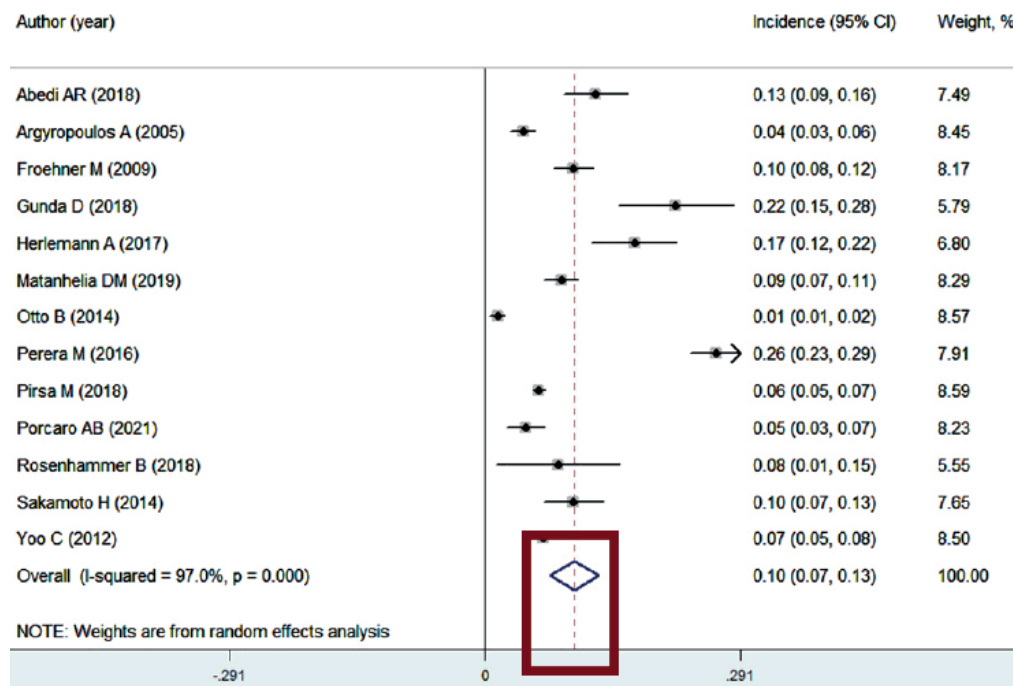


Figure 5 - The figure shows the Diamond in a Forest plot. The diamond represents the value of each study (size determined by 95% CI). If the diamond is not touching the vertical line represents that the final result is statistically significant. If the diamond touches the line represents the studies do not have statistical significance.



The legends and annotations in the plot may provide additional information about the studies or independent variables included in the analysis, the outcome measures used, and other relevant statistics. Remember that the precise interpretation of the forest plot may depend on the specific context of the study or analysis. If you have any doubts about a specific forest plot, it's always advisable to consult the cited references or seek the assistance of an expert in the field.

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CONFLICT OF INTEREST

None declared.

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Editorial Comment: Prediction Model for Neurogenic Bladder Recovery One Year After Traumatic Spinal Cord Injury

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COMMENT

El Sammak S. et al. have aimed to build a prediction model for neurogenic lower urinary tract dysfunction (NLUTD) recovery 1 year after traumatic spinal cord injury (SCI). A multivariable odds logistic regression model was applied to the National Spinal Cord Injury Model Systems (NSCIMS) database, which prospectively collects demographic, functional, medical, and other outcomes of people with SCI. From 2000 to 2016, 2515 patients with NLUTD after acute SCI were identified, of whom 417 patients (16.6%) recovered bladder function within 1 year. Patients aged 30-44 made up the majority of the population (26.5%). Most patients (79.8%) were male, and the three most frequent traumatic etiologies were violence (11.7%), falls (28.4%), and car accidents (43.3%). Sacral sensation, American Spinal Injury Association (ASIA) impairment score, bowel function at baseline, voluntary sphincter contraction, anal sensation, S1 motor scores, and the number of days in the rehabilitation facility were identified as predictors of bladder recovery, with a discriminative capacity of 90.5%.

For the purpose of maximizing patient care, managing patient expectations, and promoting individualized rehabilitative efforts, it is essential to understand the trajectory of bladder recovery in SCI patients. This prediction model may ultimately help us counsel our patients through the first year of rehabilitation and provide good arguments in favor of assisted bladder emptying options. Although this prediction model

provides relevant information, one should emphasize the role of invasive urodynamics to assess the risk of upper urinary tract deterioration among patients with traumatic SCI, particularly for those with suprasacral lesions. According to the European Association of Urology (EAU) guidelines on Neuro-Urology, urodynamic investigation should be performed as a mandatory baseline diagnostic intervention and at regular intervals in high-risk patients (1).

CONFLICT OF INTEREST

None declared.

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Editorial Comment: Management of sphincter insufficiency in patients with neurogenic bladder and bladder augmentation

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COMMENT

This is a retrospective study over 29 years at a single institution, which evaluated the need and effectiveness of bladder neck procedures (BNPs) in patients with neurogenic lower urinary tract dysfunction (NLUTD) undergoing bladder augmentation. Patients were evaluated preoperatively with urodynamics, urinary tract ultrasound, renal function tests, and cystoscopy. In total, 87 patients were included in the analysis, with a median follow-up of 10.7 years. Urinary continence was achieved by 64 patients (74%), while occasional episodes of urinary incontinence were reported by 19 (22%) patients, and 4 patients (5%) remained incontinent (pad usage). Overall, 37 patients (43%) were treated by BNPs, including bladder neck injections (BNI) in 28 patients, fascial sling operation in 14 patients, and bladder neck closure (BNC) in five females. BNI and fascial sling procedures had comparable results for both sexes. Full continence was achieved in 10/28 (36%) patients with one or repeat BNIs and 9/14 (64%) with sling operation. The four female patients requiring BNC achieved urinary continence. In this cohort, myelomeningocele was the most common diagnosis and incontinence was mostly caused by neurogenic sphincter underactivity.

The primary goals for management of patients with NLUTD include protecting the upper urinary tract, achieving a safe situation in the lower urinary tract, providing a reservoir of sufficient volume and improving quality of life (1). In high-risk patients, bladder augmentation techniques have an established role despite inherent perioperative morbidity. Taskinen et al considered BNPs in two circumstances: if the patients remained incontinent despite an adequate size and low-pressure bladder, or concomitantly with bladder augmentation when sphincter underactivity was evident. Timing for BNPs may be challenging due

to diagnostic uncertainties related to borderline urodynamic findings and low adherence to intermittent catheterization.

CONFLICT OF INTEREST

None declared.

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En Bloc Resection of Bladder Tumors (ERBT) using different lasers – Hybrid and Holmium Laser

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ABSTRACT

Introduction: The En-bloc Resection of Bladder Tumors (ERBT) is a method that offers more benefits compared to the traditional Transurethral Resection of Bladder Tumor (TURBT) (1, 2). Recent studies have shown that ERBT offers better pathological analysis and oncological outcomes (3-6). Thulium and holmium are the most frequently used lasers for this procedure, with the hybrid laser being a new addition that combines thulium and diode to improve hemostatic properties (5, 7-9).

Objective: This report aims to discuss the use of two types of lasers, hybrid and holmium, for ERBT. **Material and Methods:** Two case studies were conducted. The first case featured a 68-year-old male with two tumors measuring 1.5cm and 2cm. The hybrid laser was used for the procedure. The second case involved a 70-year-old female with a 5cm tumor on the posterior bladder wall, and holmium laser was used with morcellation of the tumor. The quality of histopathological analysis was evaluated. The perioperative data and the entire procedure of the two cases were documented in a step-by-step video.

Results: Both lasers demonstrated excellent results without technical difficulties. There was no bleeding, and both patients were discharged with one day of hospitalization. The detrusor muscle was present without artifacts, and the morcellation did not affect the analysis. The first case showed a pT1G3, and the second case showed a pT2 urothelial carcinoma. The hybrid laser exhibited superior hemostatic capacity compared to the holmium laser.

Conclusion: ERBT can use hybrid or holmium lasers without affecting histopathological analysis, even with morcellation.

CONFLICT OF INTEREST

None declared.

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Modified biplanar (0-90°) endoscopic-guided puncture technique for percutaneous nephrolithotomy: refinement with endoscopic combined intrarenal surgery to reduce fluoroscopy and operative time

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ABSTRACT

Introduction: We aim to publish our innovative modified biplanar 0-90 endoscopic guided puncture technique for percutaneous nephrolithotomy in supine recorded with a GoPro® camera for standardization of the technique. It solves drawbacks of the fluoroscopic technique, i.e., in kidneys with complex anatomy, it may be challenging to distinguish calyces as they are often superposed, and it does not allow for all benefits of a combined endoscopic approach (1, 2). Our technique shortens puncture and fluoroscopic time and is easy to teach and reproduce.

Methods: A 77-year-old female patient had previous double J insertion due to an obstructing stone in the right distal ureter. She managed to pass the distal stone but remained with the double J and a 20mm stone (1300HU) in the right renal pelvis. The shared decision was for the actual standard of care (3, 4) endoscopic combined intrarenal surgery (ECIRS). The MiniECIRS started with flexible ureteroscopy and a posterior calix which gave direct access to the stone was chosen. The tip of the flexible scope was used to mark point A with the C-arm in the 0-degree position and line B in the 90-degree position. Puncture was fast and the MiniECIRS was uneventful with a single mid-pole access guided by the flexible scope. The surgeon had a Full-HD GoPro® camera mounted on his head, controlled by the surgical staff. All essential surgical steps were recorded.

Results: The quality of the recorded movie was graded as excellent, and the camera did not cause any discomfort to the surgeon. Operative and X-Ray time were 120minutes and 2minutes (7.64mGy). Hemoglobin drop was 0.8g/dL. The post-operative day-1 computed tomography scan was stone-free. The patient was discharged 24h after surgery. Kidney stent was left with a string and removed after 5days. The patient remained asymptomatic and metabolic evaluation revealed a calcium oxalate stone, low urinary volume and hypocitraturia which were treated with potassium citrate and hydration.

Conclusion: The Modified Biplanar (0-90 degree) Endoscopic-Guided Puncture Technique for Percutaneous Nephrolithotomy joins the reproducibility of the same technique under fluoroscopy with advantages regarding safety and efficiency of ECIRS.

CONFLICT OF INTEREST

None declared.

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Robot-assisted radical cystectomy and ileal conduit with Hugo™ RAS system: feasibility, setting and perioperative outcomes

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ABSTRACT

Introduction: Robotic approach has shown its feasibility and safety with respect to open approach for radical cystectomy (1). The performances of Hugo™ RAS system (Medtronic, Minneapolis, USA) have been demonstrated in several clinical scenarios (2-5). We report the feasibility and surgical settings of the first series of robot-assisted radical cystectomy (RARC) with intracorporeal ileal-conduit performed with Hugo™ RAS system.

Methods: Two patients were submitted to RARC with ileal conduit at our institution. The trocar placement scheme and the operating room setting with docking angles of the four arms were already described (6). A 12-mm and a 5-mm trocar for the assistant were placed. In both cases, an ileal-conduit with a Wallace type-1 uretero-enteric derivation was performed intra-corporeally.

Results: The first patient was a 71-year-old male with a very-high risk non-muscle invasive bladder cancer(BC), and the second patient was a 64-year-old male with a diagnosis of T2 high-grade BC. Operative times were 360 and 420 minutes with a docking time of 12 and 9 minutes, respectively. No intraoperative complications occurred. The estimated blood loss was 200ml and 400ml, respectively. The second patient developed an ileus on postoperative day 4 (Clavien-Dindo grade 2). No positive surgical margins were recorded. No recurrence nor progression occurred during follow-up.

Conclusion: RARC with intracorporeal ileal conduit urinary diversion is feasible with Hugo™ RAS system. We provided insight into the surgical setting using this novel robotic platform to help new adopters to face this challenging procedure. These findings may help a wider distribution of robotic programs for BC treatment.

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CONFLICT OF INTEREST

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An insight into the Nomogram of Percutaneous Nephrolithotomy

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To the editor,

A study by Xie et al. (1). presented an excellent investigation of the practical nomogram design and the implementation of mini percutaneous nephrolithotomy (PCNL) and laser techniques to reduce complications and improve stone clearance. We want to raise a few additional considerations regarding the methodology and potential variables that could influence the study outcomes. Firstly, while the study reported the use of nephrostomy, no explanation was provided regarding implementing a double-J stent or ureteral stent. These stents may induce passive dilatation and facilitate stone expulsion during the follow-up period. It would be worthwhile to explore the effect of double-J and ureteral stents on stone clearance rates and assess their potential impact on the results (2). Considering these variables might provide further insights into optimizing patient outcomes.

Secondly, in the group of patients who had previously undergone surgery, careful attention should be given to analyzing the characteristics of the prior stones in terms of their hardness. The degree of stone hardness can significantly influence the effectiveness of PCNL and contribute to variable outcomes (3). By incorporating the analysis of stone hardness, future studies can better understand the relationship between stone characteristics and treatment success rates, enabling the development of more tailored treatment strategies. Additionally, the positioning of patients, both prone and supine, could potentially have an impact on treatment outcomes (4). Exploring the effect of a patient's position as one of the variables could provide valuable insights into the optimal positioning for achieving successful stone clearance in future studies.

In conclusion, we appreciate the valuable contributions made by Xie et al. on developing a nomogram for predicting the risk of adverse outcomes in patients with residual stones following PCNL. However, we suggest further investigations consider the impact of double-J and ureteral stents on stone expulsion rates, analyze the degree of stone hardness in patients with prior surgeries, and explore the effect of the patient's position on treatment outcomes. By addressing these considerations, we will enhance the accuracy and applicability of predictive models and contribute to advancing personalized treatment approaches.

The Author

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We use ChatGPT to improve the language of the manuscript.

CONFLICT OF INTEREST

None declared.

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- The photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, not embed in Word or PowerPoint.
- A list of abbreviations is provided.