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Correspondence and Editorial Address:

Rua Real Grandeza, 108 - conj. 101 - 22281-034 — Rio de Janeiro — RJ — Brazil
Tel.: + 55 21 2246-4003; E-mail: brazjurol@brazjurol.com.br

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CONTENTS

Volume 51 | number 5 | September . October, 2025 | INT BRAZ J UROL

EDITORIAL IN THIS ISSUE

REVIEW ARTICLE

ORIGINAL ARTICLE

EXPERT OPINION

VIDEO SECTION

LETTER TO THE EDITOR

INFORMATION FOR AUTHORS

EDITORIAL
IN THIS ISSUE

Vol. 51 (5): e20250501, September - October, 2025
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International Brazilian of Urology is the Seventh Biggest Impact Factor (4.5) Among Urology and Andrology Journals in the World

Luciano A. Favorito [1, 2]

[1] Unidade de Pesquisa Urogenital - Universidade do Estado do Rio de Janeiro - Uerj, Rio de Janeiro, RJ, Brasil; [2] Serviço de Urologia, Hospital Federal da Lagoa, Rio de Janeiro, RJ, Brasil

The 2025 September-October number of Int Braz J Urol, is very special. The International Brazilian Journal of Urology new impact factor just been released and we read a spectacular result: 4.5 (Figure-1). This significant increase in the impact factor in the last year is due to the rigorous and technical selection of published articles. Important papers in robotic surgery (1, 2), reconstructive surgery (3), sexual medicine (4), basic research (5), uro-oncology (6, 7), endourology (8) and neurourology (9) contributed greatly to increasing the impact factor due to the large number of citations they received.

With this new impact factor, we are in seventh position among all andrology and urology journals in the world (Figure-2) and if we count the areas of nephrology and urology (which are related) we are the sixteenth largest impact factor among 133 journals analyzed. We are now on the same level as traditional urology journals. In less than six years of our tenure as editor-in-chief, we have achieved through hard and serious work quadripling the journal's impact factor and making the journal one of the most important in the field in the world.

What is striking is that the International Brazilian Journal of Urology is fully open access and does not charge a cent for authors to publish their articles. We are therefore the fully open-access journal with the greatest impact in the world in our area. We must celebrate this achievement and continue with our work. We are on the right track, and we will surely increase even more our impact factor and our relevance in the academic environment.

Figure 1 - The figure shows the International Brazilian Journal of Urology calculation of the impact factor in 2024.

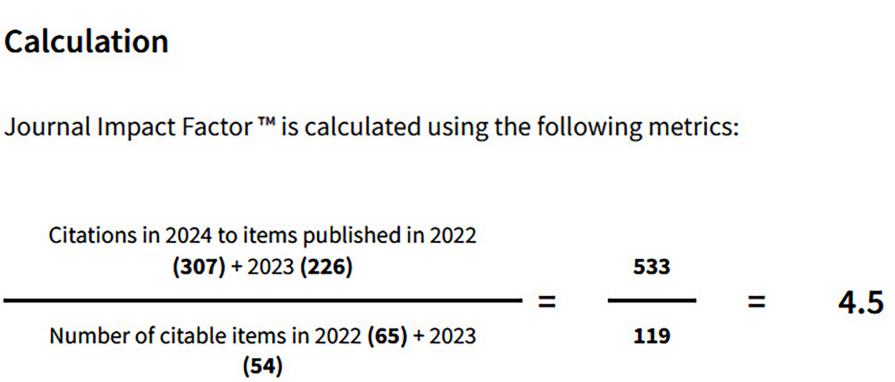

Figure 2 - The figure shows the Jounal Citation Report 2025 (CLARIVATE) in Urology and Andrology. We can observe that the International Brazilian Journal of Urology with the new impact fator (4.5) is in seventh place among the 85 journals in this area, truly a great achievement

JOURNAL CITATION REPORTS™ 2025 (CLARIVATE)
JOURNALS OF UROLOGY AND ANDROLOGY

Journal name	2024 JIF	JIF Quartile	Total citations
EUROPEAN UROLOGY	25.2	Q1	36,969
Nature Reviews Urology	14.6	Q1	7,509
European Urology Oncology	9.3	Q1	4,058
JOURNAL OF UROLOGY	6.8	Q1	41,598
PROSTATE CANCER AND PROSTATIC DISEASES	5.8	Q1	4,813
European Urology Focus	5.6	Q1	5,630
International Braz J Urol	4.5	Q1	2,726
European Urology Open Science	4.5	Q1	1,943
BJU INTERNATIONAL	4.4	Q1	18,324
Minerva Urology and Nephrology	4.2	Q1	1,713
World Journal of Mens Health	4.1	Q1 (U) Q1 (A)	2,134
Therapeutic Advances in Urology	3.5	Q1	1,430
Andrology	3.4	Q1	5,574
Sexual Medicine Reviews	3.4	Q1	2,033
Journal of Sexual Medicine	3.3	Q1	12,861
WORLD JOURNAL OF UROLOGY	2.9	Q2	11,334
UROLOGIC CLINICS OF NORTH AMERICA	2.9	Q2	2,297
Current Urology Reports	2.9	Q2	2,281
JOURNAL OF ENDOUROLOGY	2.8	Q2	8,099
ASIAN JOURNAL OF ANDROLOGY	2.7	Q2 (U) Q2 (A)	4,887
Clinical Genitourinary Cancer	2.7	Q2	3,775
Research and Reports in Urology	2.7	Q2	997
Aging Male	2.6	Q2	1,421
Prostate International	2.6	Q2	656
PROSTATE	2.5	Q2	7,342
INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH	2.5	Q2	3,353
Asian Journal of Urology	2.4	Q2	1,064
LOGIC ONCOLOGY-SEMINARS AND ORIGINAL INVESTIGATI	2.3	Q2	7,101
Current Sexual Health Reports	2.3	Q2	742
Advances in Urology	2.3	Q2	670
INTERNATIONAL JOURNAL OF UROLOGY	2.2	Q2	5,136
CURRENT OPINION IN UROLOGY	2.2	Q2	2,249
Urolithiasis	2.2	Q2	2,164
Systems Biology in Reproductive Medicine	2.2	Q2	1,344
Investigative and Clinical Urology	2.1	Q2	1,200
International Neurourology Journal	2.1	Q2	1,155
Scandinavian Journal of Urology	2.1	Q2	1,030
UROLOGY	2.0	Q2	19,731
ANDROLOGIA	2.0	Q3	6,590
CUAJ-Canadian Urological Association Journal	2.0	Q2	2,684
Sexual Medicine	2.0	Q2	1,606
Basic and Clinical Andrology	2.0	Q3	507
NEUROUROLOGY AND URODYNAMICS	1.9	Q3	7,821

Journal name	2024 JIF	JIF Quartile	Total citat
INTERNATIONAL UROLOGY AND NEPHROLOGY	1.9	Q3	6,997
Journal of Pediatric Urology	1.9	Q3	5,229
BMC Urology	1.9	Q3	3,375
Central European Journal of Urology	1.9	Q3	1,081
BJUI Compass	1.9	Q3	504
INTERNATIONAL UROGYNECOLOGY JOURNAL	1.8	Q3	8,624
Translational Andrology and Urology	1.7	Q3 (U) Q4 (A)	4,561
Urology Practice	1.7	Q3	829
LUTS-Lower Urinary Tract Symptoms	1.5	Q3	713
American Journal of Clinical and Experimental Urology	1.4	Q3	517
UROLOGIA INTERNATIONALIS	1.3	Q3	3,468
Archivio Italiano di Urologia e Andrologia	1.3	Q3	966
Current Urology	1.3	Q3	665
Actas Urologicas Espanolas	1.2	Q3	1,078
Arab Journal of Urology	1.2	Q3	1,060
Bladder Cancer	1.2	Q3	563
Continence	1.2	Q3	118
Urology Research and Practice	1.1	Q3	77
PROGRES EN UROLOGIE	1.1	Q3	1,175
Turkish Journal of Urology	1.1	Q3	896
Kidney Cancer	1.1	Q3	153
Frontiers in Urology	1.1	Q3	152
Indian Journal of Urology	0.9	Q4	1,271
Urology Journal	0.9	Q4	1,167
Canadian Journal of Urology	0.9	Q4	1,114
ARCHIVOS ESPANOLES DE UROLOGIA	0.9	Q4	733
Urology Annals	0.8	Q4	1,018
Revista Internacional de Andrologia	0.8	Q4	195
Urologia Journal	0.7	Q4	631
IJU Case Reports	0.6	Q4	277
Urological Science	0.6	Q4	268
Trends in Urology & Mens Health	0.6	Q4	119
Journal of Clinical Urology	0.5	Q4	385
International Journal of Urological Nursing	0.5	Q4	153
Continence Reports	0.5	Q4	17
Urology Case Reports	0.4	Q4	1,145
Urologie	0.4	Q4	692
African Journal of Urology	0.4	Q4	428
Current Bladder Dysfunction Reports	0.4	Q4	243
AKTUELLE UROLOGIE	0.4	Q4	156
Journal of Urological Surgery	0.2	Q4	90

Legend
Category: Urology
Category: Urology (andrological journal)
Category: Andrology
Category: both Urology and Andrology

The Editor-in-chief expects everyone to enjoy reading the original contributions with a lot of interesting papers in this number.

CONFLICT OF INTEREST

None declared.

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Luciano A. Favorito, MD, PhD
Unidade de Pesquisa Urogenital
da Universidade do Estado de Rio de Janeiro - UERJ,
Rio de Janeiro, RJ, Brasil
E-mail: lufavorito@yahoo.com.br

ARTICLE INFO

Luciano A. Favorito
https://orcid.org/0000-0003-1562-6068

REVIEW ARTICLE

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Management and optimization of chronic renal insufficiency in the setting of kidney cancer A Systematic Review

Jessica K Cobb [1], Hiroko Miyagi [2], Jad Chahoud [2], Claude Bassil [3, 4], Philippe E. Spiess [2]

[1] Department of Internal Medicine, Thomas Jefferson University, Philadelphia, PA, USA; [2] Department of Genitourinary Oncology and Department Onco-Nephrology H. Lee Moffitt Cancer Center, Tampa, FL; [3] Division of Nephrology and Hypertension and Department of Medical Oncology, University of San Raffaele, Milan, Italy, [4] University of South Florida Health Morsani College of Medicine, Tampa, FL, USA.

ABSTRACT

Purpose: There is a bidirectional relationship between chronic kidney disease and the incidence of renal cell carcinoma. Despite the frequency of patients with both chronic kidney disease and renal cell carcinoma, there are limited systematic reviews detailing the nuanced treatment. This review provides comprehensive insights for clinicians for managing chronic kidney disease, and renal cell carcinoma.

Methods and Methods: We reviewed published literature that examined either chronic kidney disease and renal cell carcinoma or an indirect contributor of both.

Results: We compare and contrast renal cell carcinoma treatment with partial and radical nephrectomies, ablative techniques, and radiation and their impact on glomerular filtration rate, recurrence rate, and contraindications. We discuss when and how to intervene with treatment with emphasis on the delicate balance between eradicating malignancy and preserving renal function. Specifically, we detail the appropriate use of renal biopsies in incidentally discovered tumors, active surveillance, and postoperative surveillance including imaging sensitivity and specificity. We offer insight into the limitations of current systemic therapy, including renal toxicity.

Conclusions: Our investigation into the intricate relationship between chronic kidney disease and renal cell carcinoma has many multifaceted challenges for both patients and healthcare providers face. This comprehensive review serves as an extensive synopsis of the current literature and offers patients the best possible long-term renal-based outcomes.

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Jessica Cobb
https://orcid.org/0009-0000-5293-0654

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INTRODUCTION

Chronic kidney disease (CKD) is characterized by persistent abnormalities in kidney function or structure with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 that persist for more than 90 days. CKD has been recognized as a worldwide public health problem as its estimated global prevalence is 9.1%, impacting around 697.5 million individuals (1). CKD is a progressive condition and is typically insidious at milder stages because of the kidneys' compensatory mechanisms; symptoms typically develop when eGFR falls below 30 mL/min/1.73m2. Reduction in eGFR correlates with increased mortality and rate of cardiovascular disease. The incidence of RCC among patients receiving dialysis is more than 3× higher than in the general population (2).

Of all cancer diagnoses, renal cell carcinoma (RCC) makes up 2.4% globally with 400,000 new cases and 180,00 deaths in 2020 (3, 4). The incidence of RCC has increased, which can partially be attributed to extensive use of abdominal imaging to assess various clinical conditions resulting in a decreased in stage of RCC at the time of diagnosis (4). The 5-year survival rates for RCC are stage-dependent, with stage 1 having a rate of 90%, stage 2 at 50%, stage 3 at 30%, and stage 4 at 5% (5). As the prevalence of RCC increases, the bidirectional relationship between CKD and RCC has become more evident (3).

This review explores the balance between eradicating malignancy and preserving renal function. This guide serves as a comprehensive overview of the current literature to equip providers with the necessary information to offer patients the best possible long-term outcomes (Figure-1).

MATERIALS AND METHODS

Inclusion criteria included using keywords in PubMed from accessed from October 2023 through June 2024, considering impact factors and citation frequency. For novel ideas, the team relied on co-authors who are experts in the fields of nephrology, nephron-oncology, and urology. Exclusion Criteria excluded lower-quality publications and those that are not readily available in the English language. Studies included but were not limited to randomized control trials, observational studies, national guidelines, and

Figure 1 - Clinical pearls in diagnosis and management.

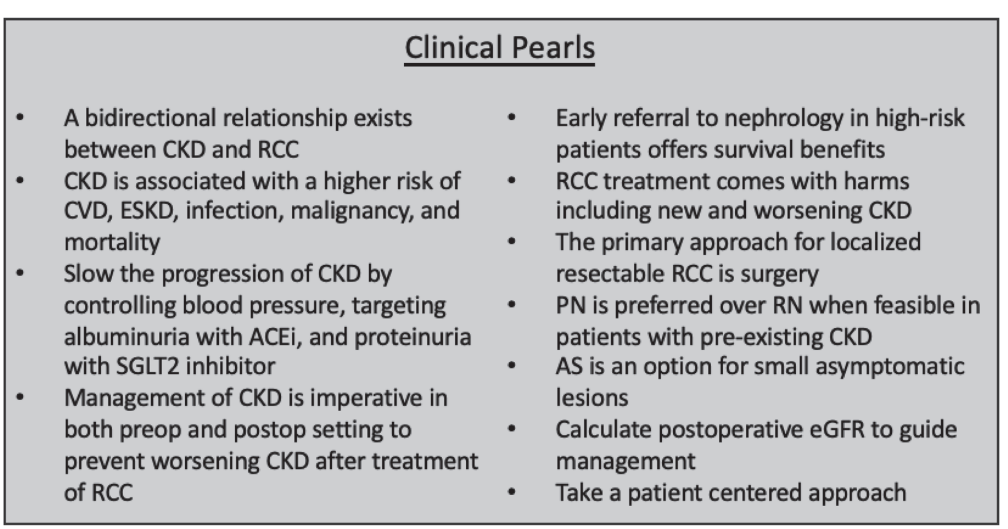

Figure depicting key clinical pearls in diagnosis and management of CKD and RCC. CKD = chronic kidney disease; RCC = renal cell carcinoma; CVD = cardiovascular disease; ESKD = end stage renal disease; ACEi = angiotensin-converting enzyme inhibitors; SGLT2 = sodium-glucose co-transporter 2; preop = preoperative; postop = postoperative; PN = partial nephrectomy; RN = radical nephrectomy; AS = active surveillance; eGFR = estimated glomerular filtration ratio

systemic reviews that examined either CKD, RCC or an indirect contributor of both.

Our search strategy involved combining terms related to CKD (e.g., "postoperative eGFR") and RCC (e.g., "partial nephrectomy," "surgical CKD"). An example search string for PubMed was" ("CKD" OR "ESRD") AND ("RCC" OR "renal cancer"). The list of keywords and dates accessed is available in the supplemental data.

The electronic database used was primarily Pubmed, with supplemental Google Scholar and manual searches of the reference list. Endnote was used to facilitate correct references. No formal risk of bias assessment was completed; however, overt biases and heterogeneity were noted in text when appropriate.

Titles and abstracts identified through the search were screened independently by two reviewers and then further examined by five additional reviewers. Full-text articles of potentially relevant studies were assessed for eligibility based on the inclusion criteria. No disagreements arose during the selection process.

radiation therapy (SBRT), and systemic therapy. Nephrectomy, either partial or radical, is the definitive treatment for RCC. A risk benefit analysis between RN and PN needs to be considered as RN offers improved 5-year cancer-specific survival rates, but PN preserves more renal function; therefore, PNs are preferred over RNs for patients with preexisting CKD and proteinuria, while RN is preferential for patients with concerning oncologic potential (6).

Ablative techniques, such as cryoablation, radiofrequency ablation, and microwave ablation, offer alternative approaches available for small renal masses that are often less invasive and offer greater nephron sparing than conservative treatment (6). While cryoablation's impact on eGFR is comparable to PN (6% decline at 2 years vs 5-8.4% at 1-3 years), the recurrence rate for PN is much preferential (3.2% global recurrence with mean time to recurrence at 47 months) to cryoablation (5% local recurrence at 6-18 months) (Table-1) (6-13). However at this time ablative procedures should only be utilized for patients with stage T1 RCC due to greater local recurrence rate (14).

Table 1 - Table demonstrating impact on eGFR and recurrence rate by treatment. (7-13, 49)

Treatment Type	Impact on eGFR	Recurrence Rate	Mean time to recurrence (months)
RN	32%	11%	100.8
PN	5-8.4%	3.2%	47
Cryoablation	6%	5% *	6-18 *
RFA	3.7%	9.7%	15.6

*Only local recurrence reported. eGFR = estimated glomerular filtration rate; RN = radical nephrectomy; PN = partial nephrectomy; RFA = radiofrequency ablation.

RESULTS

Preoperative counseling for RCC

Management options for RCC

RCC treatment is stage-dependent and may include partial nephrectomy (PN) or radical nephrectomy (RN), ablative techniques, stereotactic body

Although RCC has historically been considered resistant to radiation, technological advances in radiation therapy have allowed SBRT to be efficacious for local tumors or metastatic sites, offering a noninvasive approach without significant treatment-related toxicity. Recently a multicenter phase II trial with SBRT demonstrated with a mean follow-up time of 42 months with

100% cancer-specific survival with a mean decrease eGFR of 14.6 mL/min/1.73² (n=70) (15). The 2025 NCCN guidelines now list SBRT as an option for non-optimal surgical candidates (14).

Risk of post-treatment progressive CKD

Surgical removal of RCC has excellent 5-year cancer-specific survival rates (87% to 90% after PN and 96.7% after RN) (16). However, PN and RN independently contribute to the post-surgical increased risk for the development and progression of CKD.

A randomized phase III trial demonstrated patients with T1 RCC and a normal contralateral kidney did not have overall survival (OS) advantages or improvements in rates of kidney failure (eGFR <15mL/min1.73m2) with PN compared to RN (17). However, study limitations include small sample size, poor accrual, and substantial loss to follow-up. Data from a systematic review and meta-analysis for T2 or higher masses have shown improved preservation of kidney function and lower decline in renal function after PN than RN (16). Patients who received PN experienced improved OS (n=5,056; HR: 0.77; 95% CI: 0.65-0.90; p = 0.002; I2=0%). Based on the evidence that renal function is better preserved following PN than RN, there has been growing interest in the use of PN to treat larger masses (Table-1).

In patients undergoing PN for a renal mass in a solitary kidney, the main factor determining postoperative renal function is the parenchymal volume preservation (18). Other factors have been demonstrated to correlate with postoperative renal function, including AKI, type/duration of ischemia, complexity of tumor, and comorbidities; however, their influence was less than that of parenchymal volume preservation (n=841, r = 0.84, p < 0.001).

Medical vs surgical CKD

Though CKD secondary to medical causes (CKD-m) is associated with an annual reduction in renal function of 2% to 5%, surgically-induced CKD (CKD-s) related to the removal of functioning nephrons does not have the same decline (0.7%/ year decline)(n=44,808, p <0.001) (19). The distinct absence of ongoing decline has been attributed to a lack of so-called "drivers of CKD," most notably diabetes and hypertension (Table-2) (20). Postoperative data has shown that patients with both CKD-m and CKD-s experienced the highest overall mortality (19). Furthermore, the risk of death after surgery was significantly higher for patients with preoperative

Table 2 - Relative risk of CKD by risk factor. (47, 48)

Risk Factors	Relative Risk
HTN only[1]	2.0 (95% CI 1.8-2.2)
HTN, HLD, and high BMI	2.6 (95% CI 2.2-2.9)
HTN and DM	3.3 (95% CI 2.9-3.8)
HTN, HLD, high BMI, and DM	5.5 (95% CI 4.9-6.2)
Obesity (BMI >30 kg/m²)	1.77 (95% CI 1.47-2.14)
Smoking[2]	1.52 (95% CI 1.13-2.06)
Physical inactivity[3]	2.14 (95% CI 1.39-3.30)
Obesity, smoking[2], and physical inactivity[3]	5.10 (95% CI 2.36-11.01)

CKD = chronic kidney disease, HTN = hypertension; CI = confidence interval; HLD = hyperlipidemia; BMI = body mass index; DM = diabetes mellitus. [1] = without other risk factors.
[2] = >25 pack-years. [3] = no or some physical activity in leisure time.

CKD-m than patients with normal preoperative renal function (2.7×, 3.5×, and 4.4× higher for stage 3, 4 and 5 CKD respectively)(n=4,180, CI 1.8-5.0; CI 2.4-5.9; CI 2.8-7.0 respectively) (20). Among patients without CKD-m, preoperative eGFR was not a predictor of OS. The survival curve for patients who developed CKD-s was similar to those with normal postoperative eGFR levels, as long as new baseline eGFR is > 45 mL/min/1.73^2. If the GFR fell below this threshold the mortality and risk of functional decline increased significantly. This suggests that patients with CKD-s experience much better outcomes than those with CKD-m, and the two disease subtypes should be treated as separate entities.

Predicting postoperative renal function

Given the increased risk of CKD following RN compared to PN, careful preoperative renal function and contralateral renal status is imperative. A cutoff line exists for estimated postsurgical baseline GFR above 45 mL/min/1.732; if estimated below the cutoff, even if RN is preferred, then PN is recommended. This cutoff is strongly associated with improved survival outcomes (n=1,479; HR: 2.8; p<0.001) (6, 19, 21). Additionally, actual postoperative eGFR <65mL/min/1.73m^2 were associated with increased cancer-specific mortality for PN or RN with a significant increase in the subdistribution hazard ratio for every 10mL/min reduction in eGFR (n=3,457; HR: 1.25; 95% CI:1.07–1.44, p = 0.003) (22). Therefore, there has been increased research in developing tools to predict postoperative eGFR, called new baseline GFR (NBGFR).

Currently, the most reliable way to predict NBGFR after RN involves a model to determine parenchymal volume analysis (PVA) based on preoperative GFR, split renal function (SRF), and renal function compensation (RFC). Historically, SRF has been determined by nuclear renal scans; however, PVA via software analysis has been shown to provide more accurate and precise SRF and preclude the need for renal scans (n=187; r=0.85; p<0.05) (21, 23).

Competing risks

Life-preserving and life-limiting dialysis

The incidence of RCC among patients receiving dialysis is 3× higher than in the general population (n=831,804; SIR 3.6; CI 3.5 to 3.8; P < 0.0001) (2). This risk, along with carcinoma aggressiveness, further increases after a decade of dialysis use; therefore, periodical screening for RCC should be considered. There are not current guidelines for this population, as cancer screening guidelines are created to improve health outcomes via early detection; however, the 5-year survival rate for patients after initiation of maintenance dialysis is approximately 40%. Given the limited life expectancy of many of these patients, screening needs to be individually tailored to those who are most likely to benefit from early detection, such as in younger patients with a longer anticipated life span (24).

Systemic treatment of RCC

Systemic treatments, utilized in the context of metastatic RCC (mRCC), unresectable RCC, or adjuvant therapy, include immune checkpoint inhibitors (ICIs) and targeted molecular therapy (e.g., VEG-F-TKIs and mTOR inhibitors). Though these systemic treatments have offered improvements in OS, they may be associated with nephrotoxicity and worsening renal function. All patients should be closely followed for nephrotoxicity after treatment with systemic therapy.

ICI associated AKI (ICI-AKI) is a rare but potentially serious complication, with a meta-analysis demonstrating an incidence of 2.2% (n=11,482; 95% CI 1.5-3.0%; I^2=68%); a multicenter study indicated that up to 15% of patients who develop AKI will not experience renal recovery (n=138; HR 3.91; 95% CI 1.22-12.59) (25, 26). For patients that experience ICI-AKI, clinicians should hold ICIs and initiate treatment with glucocorticoids. Patients may be rechallenged with ICI after kidney function improves. An observational study noted 84% of patients with ICI-AKI, rechallenged did not redevelop ICI-AKI (n=429) (27).

Anti-VEGF agents and TKIs are associated with proteinuria and rarely associated with nephrotic syndrome. A meta-analysis demonstrated proteinuria with VEGF-TKIs as 18.7% and 2.4% for all-grade and

high-grade proteinuria respectively (n=6,682; all grade: 95% CI, 13.3%-25.6% Q=400.96; *P<0.001; I* ^{2}=94%; high grade Q=72.46; *P<0.001; I* ^{2}=64%; 95% CI, 1.6%-3.7% respectively); the severity of proteinuria is increased in patients with preexisting renal disease (28-31). Stopping the offending agent often results in significant reduction in proteinuria, although persistence is common which may be treated with angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARB) (32).

Of note, the risk of CKD in the setting of adjuvant setting is likely higher than reported as many trials exclude patients with low eGFR (e.g. KEYNOTE 564 excluded patients with eGFR < 40 mL/min/1.73m^2), while this is not a guideline recommended cutoff for pembrolizumab (32). Additionally, patients in this trial had labs every 3 weeks monitoring for urinary protein/creatinine ratio with clear cut off guidelines, while urinalysis is more commonly ordered every 6-8 weeks with termination of therapy at physician's discretion (33).

Risk stratification should be completed prior to starting chemotherapy. International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) is a risk model for mRCC which uses clinical and laboratory parameters to risk stratify the patient (intermediate/poor versus favorable) (34, 35). The NCCN guidelines recommend preferred regimen based on the favorability determined by the IMDC (14).

Postoperative treatment surveillance

Surveillance guidelines & impact on renal function

Posttreatment surveillance imaging allows for early local recurrence detection and metastases identification, improving survival rates with timely re-intervention (Table-3). Long-term follow up is imperative as 30% of recurrences are discovered over 5 years after treatment (36). However, contrast enhanced imaging is not without possible renal implications.

Per the American College of Radiology (ACR) Committee on Drugs and Contrast Media, IV iodinated contrast media is not an independent nephrotoxic risk factor in those with a stable baseline eGFR ≥45 mL/min/1.73m^2 (37). In patients with eGFR 30-44 mL/min/1.73m^2 it is either rarely or not nephrotoxic. However research on those with eGFR <30 mL/min/1.73m^2 have conflicting results. Two studies which were propensity-score matched showed IV iodinated contrast material as an independent nephrotoxic risk factor while two others found no such evidence. Studies in support demonstrated that these patients have a 3x increased risk of iodinated contrast induced AKI (CI-AKI) (38-42). Persistent renal damage from CI-AKI is proposed to occur among 18.6% of patients with moderate to severe baseline renal impairment (n=3,986) but only 1.2% of the general population (n=4,418) (43, 44).

Table 3 - Diagnostic imaging modalities for patients with respective sensitivity and specificity (49).

Imaging Type	Sensitivity	Specificity
Contrast enhanced CT	88%	75%
Unenhanced US	56%	71%
Contrast enhanced US	93%	72.5%
Contrast enhanced MRI	87.5%	89%
FDG/PET	88%	87.5%

CT = computed tomography; US = ultrasound; MRI = magnetic resonance imaging; FDG = fluorodeoxyglucose; PET = positron emission tomography.

Anuric patients with ESRD may receive IV iodinated contrast; however, oliguric patients on dialysis should be treated as similar to patients with eGFR <30 mL/min/1.73m2, and a contrast risk-benefit analysis should be considered (45). While there is data demonstrating a dose-toxicity relationship, if the risk-benefit ratio favors contrast-enhanced imaging, it is not recommended to reduce contrast doses in attempts to mitigate risk of CI-AKI as this may result in suboptimal imaging (45).

MRI Contrast

MRI imaging with gadolinium contrast is preferential for patient who cannot tolerate any conventional contrast (36). For patients with ESRD on chronic dialysis, it is recommended to undergo GBCA-enhanced MRI before regularly scheduled dialysis although the evidence is lacking proving improved safety as dialysis does not improve GBCA clearance (45). Patients' ineligible for CT contrast and MRI should be considered for contrast enhanced ultrasound.

DISCUSSION

The bidirectional relationship between CKD and RCC is established, and they are both relatively frequent diagnoses; however, systematic reviews detailing the nuanced treatment with respect to both are lacking.

We discussed the pros and cons for PN, RN, ablative techniques, SBRT, and systemic therapy. Each has strengths and weaknesses, and the risk of further renal damage must be part of the patient/provider discussion. RN offers improved 5-year cancer-specific survival rates, while PN preserves more renal function. Ablative techniques offer greater nephron sparing than conservative treatments at the cost of increased recurrence rates, and therefore, they are only recommended for low-stage RCC.

A cutoff line exists for estimated postsurgical baseline GFR above 45 mL/min/1.732, which is strongly associated with improved survival outcomes. Currently, providers should predict NBGFR with PVA, and RNs are not advised if NBGFR is less than 45 mL/min/1.732.

Providers should monitor patients on systemic therapy for renal toxicity, which may necessitate stopping the offending agent. Providers should be wary that the risk of CKD in the adjuvant setting is likely underreported, as many trials' requirements do not reflect real-world conditions (excluding patients with low eGFR and increased post-treatment lab frequency). To guide the selection of systemic therapy and estimate the median survival of patients with mRCC, providers should use risk stratification with IMDC.

Limitations of our systematic review may include publication bias, heterogeneity, possibly poorer quality of studies than initially anticipated, and time lag bias.

CONCLUSIONS

In conclusion, our investigation into the intricate relationship between CKD and RCC has many multifaceted challenges for both patients and healthcare providers face. When considering treatment modalities for RCC providers must consider the delicate balance between eradicating malignancy and preserving renal function. An individualized approach, coupled with ongoing research to refine guidelines and strategies, is crucial for optimizing patient outcomes.

Disclosure of interests

Dr. Jad Chadhoud has provided advising for Aveo, Pfizer, Eelixis, Eisai, Mycaregorithm and has received institutional research grant funds from Pfizer. All other authors have no competing interests.

Ethics Statement

This study did not require Institutional Review Board (IRB) approval as it did not involve human subjects, animal subjects, or any other activities that fall under the purview of IRB oversight. The research was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and relevant institutional guidelines.

No personal data or identifiable information was collected or used in this study. All data sources were publicly available and did not involve any intervention or interaction with individuals. All efforts were made to ensure the integrity and ethical conduct of the research.

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CONFLICT OF INTEREST

None declared.

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Correspondence address:
Philippe E. Spiess, MD
Department of Genitourinary Oncology and
Department Onco-Nephrology
H. Lee Moffitt Cancer Center
12902 Magnolia Drive, office 12538, Tampa, FL 33612
Telephone: + 1 813 745-8343
E-mail: philippe.spiess@moffitt.org

REVIEW ARTICLE

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Asymptomatic Leukocytospermia and Assisted Reproductive Technology Outcomes: Reason for concern?

Marie-Christin Reich [1], Natalie Heide [1], Peter Humaidan [1, 2], Sandro C. Esteves [2, 3, 4]

[1] Skive Regional Hospital, Fertility Unit, Skive, Denmark; [2] Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark; [3] ANDROFERT, Clínica de Andrologia e Reprodução Humana, Campinas, SP, Brasil; [4] Departamento de Cirurgia, Disciplina de Urologia, Universidade Estadual de Campinas - UNICAMP, Campinas, SP, Brasil

ABSTRACT

Leukocytospermia, defined as ≥1×10^6 white blood cells (WBC)/ml of semen, is a condition frequently observed in infertile men. While symptomatic leukocytospermia is often associated with genital tract infections and managed accordingly, the clinical significance of asymptomatic leukocytospermia remains uncertain—particularly in the setting of Assisted Reproductive Technology (ART). Seminal leukocytes, primarily neutrophils, play a physiological role in immune surveillance and tissue homeostasis. However, when excessively activated, they may generate high levels of reactive oxygen species (ROS), contributing to oxidative stress, sperm dysfunction, and DNA damage. This narrative review critically examines whether asymptomatic leukocytospermia adversely affects ART outcomes, including fertilization, embryo development, clinical pregnancy, and live birth rates. A synthesis of current evidence—including meta-analyses and large retrospective studies—suggests that asymptomatic leukocytospermia does not negatively impact these outcomes. Moreover, standard sperm preparation techniques and the widespread use of ICSI appear to neutralize any potential deleterious effects from seminal leukocytes. Given the absence of compelling evidence supporting its harmful impact on ART success, routine treatment of asymptomatic leukocytospermia—particularly with empiric antibiotics—is not recommended. Such interventions may disturb the natural immune balance, promote antibiotic resistance, and increase healthcare burdens without demonstrable benefit. Nonetheless, selective treatment may be justified in specific scenarios, such as recurrent implantation failure or early pregnancy loss. Further research is warranted to standardize leukocyte detection methods and to clarify the role of adjunctive therapies. Until more definitive data emerge, an individualized, evidence-based approach remains the most appropriate strategy for managing asymptomatic leukocytospermia in infertile men pursuing ART.

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Esteves SC
https://orcid.org/0000-0002-1313-9680

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INTRODUCTION

Infertility affects about 17% of couples worldwide (1), with male factors contributing to 20-30% of the cases (2, 3). Among the potential causes of male infertility, leukocytospermia –defined as an increased concentration of white blood cells (WBCs) in semen– remains a subject of debate. The reported prevalence of leukocytospermia varies widely, ranging from 2 to 40% among infertile men, depending on the study population, detection method, and diagnostic threshold used (4-6).

The World Health Organization (WHO) defines leukocytospermia as the presence of $\geq 1 \times 10^6$ WBC/mL of semen (4, 7). It can result from an infection, such as male genital tract infection (MGTI), including male accessory gland infection (MAGI), which is typically managed with antibiotics and frequent ejaculation (8, 9). However, non-infectious causes –including non-bacterial inflammation, autoimmune disease, varicocele, and unhealthy lifestyle factors such as tobacco use or chronic alcohol consumption– are also implicated (5, 8, 10-13). In such cases, treatment strategies may involve anti-inflammatory medications, antihistamines, antioxidants, and lifestyle modifications (5, 14-16).

The term seminal leukocytes collectively refers to WBCs found in semen, which consist of 2-5% T-lymphocytes, 20-30% macrophages, and 50-60% granulocytes, primarily neutrophils (17, 18). These cells originate from the testis, epididymis, and prostate (19-21). Under normal physiological conditions, seminal leukocytes play a key role in immune surveillance, helping to regulate inflammatory responses by releasing cytokines and proinflammatory mediators. This immune activity facilitates pathogen elimination and supports reproductive health by removing abnormal and immature sperm cells through phagocytosis and the release of reactive oxygen species (ROS) (22, 23).

In cases of infection or inflammation, leukocytes are actively recruited through chemotaxis, which directs them from the bloodstream to affected tissues (24). Once at the site of inflammation, leukocytes become activated by integrins and cytokines, including tumor necrosis factor alpha (TNFα) and interleukins (25, 26). This activation leads to the release of large amounts of proinflammatory cytokines and ROS, resulting in oxidative stress, which can damage sperm plasma membranes and DNA, ultimately compromising sperm quality and contributing to male infertility (27-30).

A key distinction must be made between symptomatic and asymptomatic leukocytospermia. Symptomatic leukocytospermia is associated with MGTI or MAGI and is often accompanied by clinical symptoms like urogenital pain, dysuria, pollakiuria, or other urine tract disturbances (31-33). Diagnosis typically involves identifying the causative pathogens to guide targeted antibiotic therapy (31-33). Conversely, asymptomatic leukocytospermia presents without overt clinical symptoms and may have infectious and non-infectious origins (6, 34). Consequently, the necessity for treatment in cases of asymptomatic leukocytospermia remains a topic of ongoing debate (6, 35), particularly when evaluating its role in the context of Assisted Reproductive Technology (ART) outcomes (36).

European and American Urological guidelines provide no clear recommendations on managing asymptomatic leukocytospermia in men with infertility (37, 38). In modern healthcare systems, the cost-effectiveness of ART, including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), depends on treatment expenses, success rates, and risk of multiple pregnancies (39, 40). Given that leukocytospermia has been associated with impaired semen quality, it is crucial to determine whether treatment improves ART outcomes and enhances the cost-effectiveness of fertility care for affected couples.

This article critically assesses whether an evidence-based rationale exists for treating asymptomatic leukocytospermia in the context of ART, specifically in IVF and ICSI cycles. By systematically examining the existing literature, we seek to clarify whether intervention is necessary to optimize ART success or whether asymptomatic leukocytospermia poses minimal concern.

LEUKOCYTOSPERMIA AND MALE INFERTILITY

Inflammation, Leukocytospermia, and the Impact on Sperm Function

Infection-induced inflammation triggers an immune response that activates local macrophages and recruits leukocytes from the bloodstream to the site of infection (41). The testicular immune defense protects male germ cells while allowing an inflammatory response to combat infections (42).

Macrophages play a key role in immune regulation through phagocytosis and the secretion of pro-inflammatory and anti-inflammatory cytokines (25, 43). These antigen-presenting cells are critical for immune homeostasis, spermatogenesis, and regulation of autoimmunity against testicular antigens (44, 45).

Another part of the natural immune defense system is leukocytes, especially neutrophil granulocytes. In a healthy state, circulating neutrophils are resting and most are eliminated without receiving an activating signal (46). However, when infections or injuries occur, they must be able to respond appropriately as multifunctional first responders (46). Neutrophils that encounter a series of agonists enter a pre-activated or primed state that sets them on high alert, enabling them to respond aggressively (e.g., through degranulation, respiratory burst activity, increased phagocytosis, release of ROS, and bioactive mediators) if another activation stimulus occurs (46). Due to the variety of host- and pathogen-derived mediators, priming can be induced by multiple signaling pathways and intracellular processes, such as chemokines, cytokines, alarmins, integrins, pathogen-derived molecules, and mechanical forces (46). The signaling pathways and the resulting cellular phenotype depend on the priming agent acting on the neutrophils and the specific environment (46).

Despite their critical role in the defense system, leukocytes can also become detrimental when activated as they produce 1,000 times more ROS than spermatozoa (47). While controlled ROS levels are essential for sperm maturation, capacitation, acrosome reaction, and chromatin condensation (48), excessive ROS generation by activated seminal leukocytes depletes seminal antioxidants (49) such as catalase, glutathione, and superoxide dismutase, which scavenge free radicals (49-51). This imbalance leads to oxidative stress, potentially damaging spermatozoa (52).

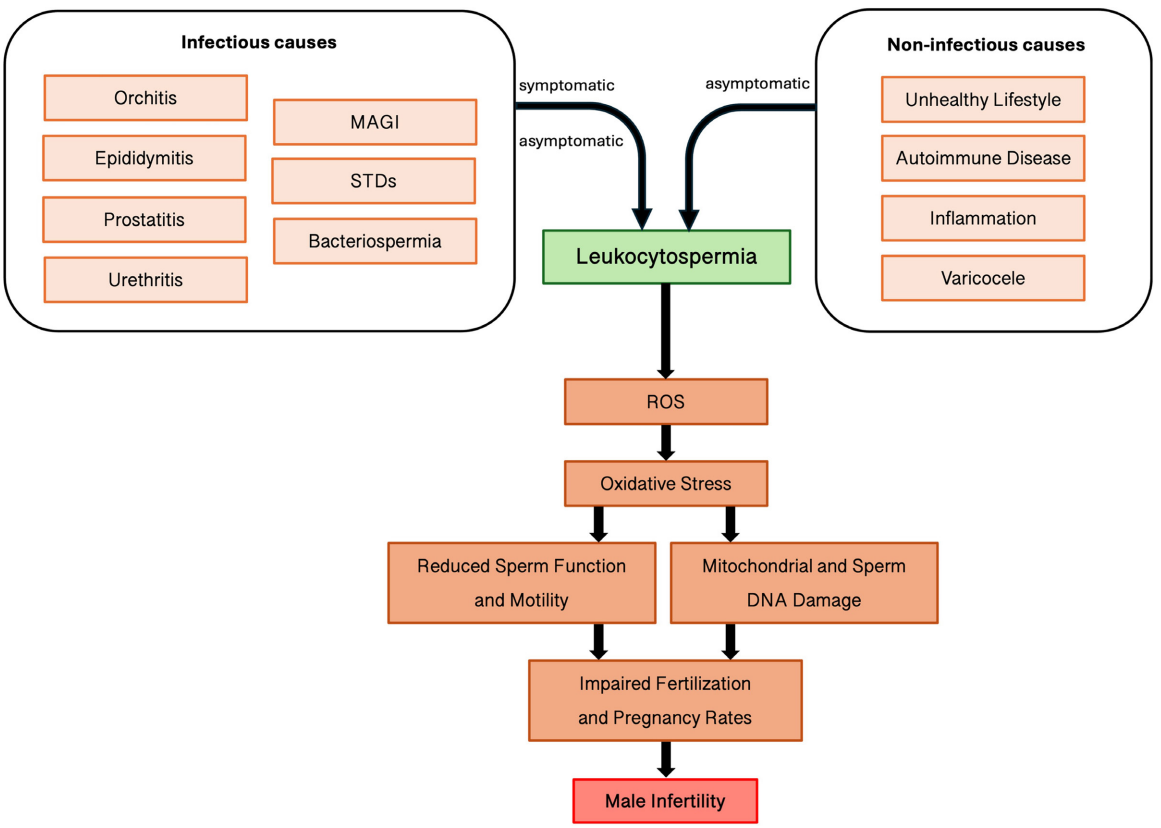
ROS, including hydroxyl radicals (-OH), superoxide anions (O2-), and hydrogen peroxide (H2O2), are potent oxidants (53-57). Importantly, spermatozoa are particularly vulnerable to oxidative stress due to the high content of polyunsaturated fatty acids in their plasma membrane (53). While H2O2 can penetrate plasma membranes and cause intracellular damage, O2- and -OH primarily induce lipid peroxidation, disrupting membrane integrity and impairing sperm function (28, 58-60). ROS-mediated intracellular damage ranges from chromatin cross-linking and protein impairment to DNA modifications and fragmentation (56, 61-65).

Oxidative stress further compromises sperm function by reducing acrosine activity, impairing sperm-oocyte fusion (66-69), and damaging mitochondrial function (62, 70, 71). Since mitochondria are crucial for adenosine triphosphate (ATP) production in the sperm cell, oxidative damage to mitochondrial DNA (mtDNA) can impair sperm motility and overall fertilization potential (62, 70-76). Additionally, ROS-induced axonemal damage directly affects sperm motility (43, 77) (Figure-1).

Maintaining sperm DNA integrity is essential for successful fertilization, embryo development, and ongoing pregnancy (78). Increased sperm DNA fragmentation is associated with prolonged time to pregnancy in fertile couples (79). While sperm with fragmented DNA can fertilize oocytes, early embryonic development often arrests when paternal genes are not correctly functional (80). Additionally, sperm DNA damage may increase the risk of chromosomal abnormalities and miscarriages (81), reducing success rates of both natural conception and ART (82-88).

Given that leukocytospermia might increase the proportion of spermatozoa with impaired DNA compared to non-leukocytospermic samples (78), a question to ask is: should screening for leukocytospermia become a routine part of infertility assessments for couples undergoing ART? This question is relevant to refine clinical guidelines for male infertility evaluation and ART decision-making.

Figure 1 - Pathophysiological Pathways Linking Infectious and Non-Infectious Causes of Leukocytospermia to Male Infertility via Oxidative Stress. MAGI, male genital infections; STDs, sexually transmitted diseases; ROS, reactive oxygen species.



Detection Methods of Seminal Leukocytes

Several techniques are available for detecting seminal leukocytes, each with varying levels of specificity and practicality. One traditional method involves staining a sperm smear using the Papanicolaou technique, which distinguishes leukocytes from spermatids and spermatocytes based on differences in staining properties, size, and nuclear morphology (89). However, the method is prone to morphological misidentification, making it less reliable (89).

A more commonly used approach is the histochemical peroxidase test, which quantifies leukocytes containing the peroxidase enzyme –a characteristic feature of granulocytes (89). This test is quick, inexpensive, and widely used for initial screening. However, it has limitations: it cannot detect activated polymorphonuclear cells that have already released their granules or peroxidase-negative leukocytes such as lymphocytes, macrophages, and monocytes (89). Therefore, the number of total leukocytes in semen may be underestimated, though peroxidase-positive granulocytes remain the predominant leukocyte type in semen (89).

A more precise alternative is the immunocytochemical method, which uses monoclonal antibodies targeting the CD45 antigen, a pan-human leukocyte marker (89). This approach enables the detection of all leukocyte subtypes, including granule-released polymorphonuclear leukocytes and peroxidase-negative cells such as lymphocytes, macrophages, and monocytes. However, while more accurate, immunocytochemical staining is also more time-consuming and expensive compared to histochemical methods (89).

LEUKOCYTOSPERMIA AND ART OUTCOMES: INSIGHTS FROM META-ANALYSES AND RECENT STUDIES

Meta-analysis

A 2020 systematic review and meta-analysis examining the impact of leukocytospermia on sperm quality and ART outcomes analyzed 28 case-controlled retrospective studies. The findings revealed no significant differences in fertilization rates (FR) or clinical pregnancy rates (CPR) between couples with and without leukocytospermia undergoing conventional IVF or ICSI (90). However, males with leukocytospermia exhibited significantly lower sperm concentration and reduced progressive motility, indicating a negative impact on sperm parameters. Notably, two-thirds of the included studies (n=18) did not differentiate between symptomatic and asymptomatic leukocytospermia (90). The ten remaining studies specifically compared asymptomatic leukocytospermia to non-leukocytospermic controls. The meta-analysis indicated a considerable inter-study heterogeneity due to differences in the distinction between symptomatic and asymptomatic cases and in the detection methods across studies, which introduced potential inconsistencies in reliability and accuracy, limiting the generalizability of the findings (90).

To address this heterogeneity, the meta-analysis included a subgroup analysis based on leukocyte detection methods, categorizing studies into those using CD45-based immunocytochemistry or flow cytometry, peroxidase staining, and morphological evaluation of stained semen smears (90). Another subgroup analysis included only studies assessing asymptomatic leukocytospermia without genital tract infections (90). After adjusting for these variables, the previously observed association between leukocytospermia and reduced sperm concentration and progressive motility was no longer significant, suggesting that methodological differences and confounding factors contributed to the initial findings (90). Moreover, most studies did not account for key variables such as duration of sexual abstinence and patient age, both of which are known to influence semen quality (90).

Ultimately, after controlling for confounding factors, the meta-analysis concluded that asymptomatic leukocytospermia did not negatively impact basic semen parameters or sperm DNA integrity (90). Furthermore, subfertile couples with asymptomatic leukocytospermia did not exhibit reduced reproductive outcomes after ART, reinforcing the notion that leukocytospermia alone may not be a critical determinant of ART success (90).

Large-Scale Retrospective Studies

The largest retrospective study included in the meta-analysis discussed above had some divergent findings (91). The authors compared conventional IVF and ICSI outcomes among three groups: non-leukocytospermia (n=3,026), low-level leukocytospermia ($<10^6$ WBC/mL, n=344), and high-level leukocytospermia ($\geq 10^6$ WBC/mL, n=138) (91). No significant differences were found in pregnancy complications or congenital malformations across the groups (91). However, leukocytospermic patients underwent significantly more ICSI cycles than non-leukocytospermic patients (91). Interestingly, couples with leukocytospermia had more cycles with at least one high-quality embryo and more two pronuclei (2PN) zygotes than those without leukocytospermia (91).

Despite these favorable laboratory parameters, total sperm concentration and total sperm count were significantly lower in leukocytospermic men, although sperm vitality was slightly higher in the low-level leukocytospermic group (91). Notably, FR and CPR were significantly higher in the presence of leukocytospermia (91). Based on these findings, the authors suggested that leukocytospermia may be physiologically advantageous to a certain extent (91). They further hypothesized that ROS play a dual role, being essential for various physiological processes such as DNA condensation, sperm capacitation, and acrosome reaction, but potentially detrimental when present at excessively high concentrations over prolonged periods (91).

However, a notable finding was that high-level leukocytospermia was associated with increased early pregnancy loss and a three-fold higher risk of ectopic pregnancy compared to the non-leukocytospermia group (91). These differences remained significant even

after excluding women with reproductive tract anomalies and ovarian dysfunction, though only the increase in early miscarriages reached statistical significance (91). The authors suggested that while ROS can impair various sperm functions, they do so to various degrees. Although high ROS levels contribute to DNA fragmentation, both sperm fusion and motility remain primarily unaffected, potentially explaining the increased fertilization rates alongside higher early pregnancy loss rates in the high leukocytospermia group (91).

Overall, the study suggested that low-level leukocytospermia may enhance sperm fertilization capacity and pregnancy outcomes, while high-level leukocytospermia, despite not impairing sperm fertilizing ability, may compromise early pregnancy (91). Yet, the study had several limitations. It made no distinction between symptomatic and asymptomatic leukocytospermia, relied on the peroxidase test for WBC detection, and had a retrospective design (91). Despite these limitations, male and female ages and indications for IVF/ICSI were comparable across groups, supporting the validity of the findings (91).

Additional Retrospective Studies on ART Outcomes

Another retrospective study comparing IVF, ICSI, and split insemination outcomes between leukocytospermic and non-leukocytospermic men reported no significant differences in FR, CPR, or live birth rates (LBR) (92). However, in conventional IVF cycles, sperm concentration and progressive motility were significantly lower in leukocytospermic men (92). Similarly, leukocytospermic patients undergoing ICSI exhibited reduced progressive motility (92).

The study further analyzed split insemination cycles (i.e., using IVF and ICSI simultaneously) to determine whether the insemination method influenced ART outcomes in the presence of leukocytospermia. No differences were observed in FR, CPR, and LBR between IVF and ICSI within the leukocytospermia group. However, ICSI resulted in more 2PN zygotes, available embryos, and good-quality embryos compared to IVF (92).

While informative, the study had limitations, including its retrospective design and relatively small sample size (n=133; leukocytospermic men: 63 IVF, 38 ICSI, 32 split insemination cycles) (92). Moreover, the peroxidase test was used for WBC detection, and there was no differentiation between symptomatic and asymptomatic leukocytospermia (92). Semen samples were collected after a wide range of ejaculatory abstinence intervals (2-7 days). Nevertheless, all included patients underwent their first ART cycle and had a normal karyotype. Women older than 40 years and those with uterine malformations, coagulation, or thrombophilia disorders were excluded (92). The study supported that leukocytospermia does not compromise ART success, though ICSI may provide certain embryological advantages over conventional IVF (92).

Leukocytospermia and Preimplantation Genetic Testing Outcomes

A 2024 retrospective study examined the impact of leukocytospermia on ICSI outcomes with preimplantation genetic testing for aneuploidy (PGT-A). Among 5,435 fertilization cycles, no significant differences were observed in LBR, FR, 2PN rate, or embryo aneuploidy rates between couples with and without leukocytospermia (93). Moreover, leukocyte concentrations did not predict LBR, thus also suggesting that leukocytospermia does not negatively impact ART outcomes (93).

The authors proposed that the unique setting of ICSI with PGT-A might have mitigated any potential adverse effects of leukocytospermia, as sperm selection during ICSI could reduce the influence of leukocyte-mediated oxidative stress (93). However, they cautioned that these findings might not directly translate to conventional IVF treatments (93).

As with prior studies, leukocytospermia was detected using the peroxidase test, and no distinction was made between symptomatic and asymptomatic cases (93). However, semen samples were collected after a well-defined 2-5 days of ejaculatory abstinence, and female age did not significantly differ between groups, ensuring comparability (93).

The Case Against Routine Treatment of Asymptomatic Leukocytospermia

Given the lack of conclusive evidence linking asymptomatic leukocytospermia to impaired ART outcomes, routine treatment remains controversial. Below are the primary arguments against intervention.

1. There is no significant influence on ART success
   - Studies show no significant differences in ART success rates between men with and without asymptomatic leukocytospermia (90).
   - Sperm preparation methods (e.g., density gradient centrifugation) can eliminate leukocytes, reducing their potential impact on fertilization and embryo development (94, 95).
   - ICSI appears to circumvent potential sperm quality issues, reducing any need for routine treatment (89, 92, 93).
   - Asymptomatic leukocytospermia may resolve naturally over time without medical intervention (35).
   - There is no evidence that treating asymptomatic leukocytospermia improves conception rates (38, 96).
2. The Immune Surveillance Hypothesis
   - Seminal leukocytes may serve a beneficial function, defending against subclinical infections and oxidative stress (17, 20).
   - Treating asymptomatic cases could disturb the natural immune balance without offering clear reproductive benefits (97).
3. Risks of Overtreatment
   - Unnecessary antibiotic use contributes to antimicrobial resistance (97).
   - Antibiotics may alter the seminal microbiome, potentially affecting fertility (35, 94, 98, 99).
   - Overdiagnosis and overtreatment can lead to increased costs and unnecessary stress for couples undergoing ART (100).

Clinical Justification for Targeted Treatment

While routine treatment is not recommended, selective intervention may be justified in specific cases (Figure-2, Table-1), as listed below.

1. Symptomatic Male Genital Tract Infections (MGTI)
   - Antibiotic therapy is recommended if bacterial infection is confirmed as the likely cause of leukocytospermia (37, 38, 97).
   - In cases of sexually transmitted infections, partner treatment should also be considered (38, 101, 102).
2. Adjunctive Therapies
   - Antioxidants (e.g., Vitamin C, E, Selenium, Coenzyme Q10) may help reduce oxidative stress without the risks of antibiotics (14, 103, 104), though their impact on fertility outcomes remains uncertain (37, 38).
   - Anti-inflammatory therapy (e.g., COX 2 inhibitor) may improve semen parameters and reduce leukocytospermia, but the effect on pregnancy rates remains inconclusive (5, 15).
3. Recurrent ART Failure
   - We suggest that in cases of recurrent early pregnancy loss and implantation failure, it may be justifiable to alleviate leukocytospermia using antibiotics, anti-inflammatory drugs, or antioxidants.

Future Directions

Despite advancements in understanding leukocytospermia, several knowledge gaps remain, particularly in distinguishing symptomatic from asymptomatic cases and assessing the possible impact on reproduction by comparing asymptomatic leukocytospermic infertile men with fertile controls. Future research should prioritize the standardization of leukocyte detection methods, such as flow cytometry versus peroxidase staining, to enhance diagnostic accuracy and clinical relevance. Additionally, further studies are needed to evaluate the efficacy of target-

Figure 2 - Clinical Management Algorithm for Leukocytospermia in Couples Undergoing Assisted Reproductive Technology.

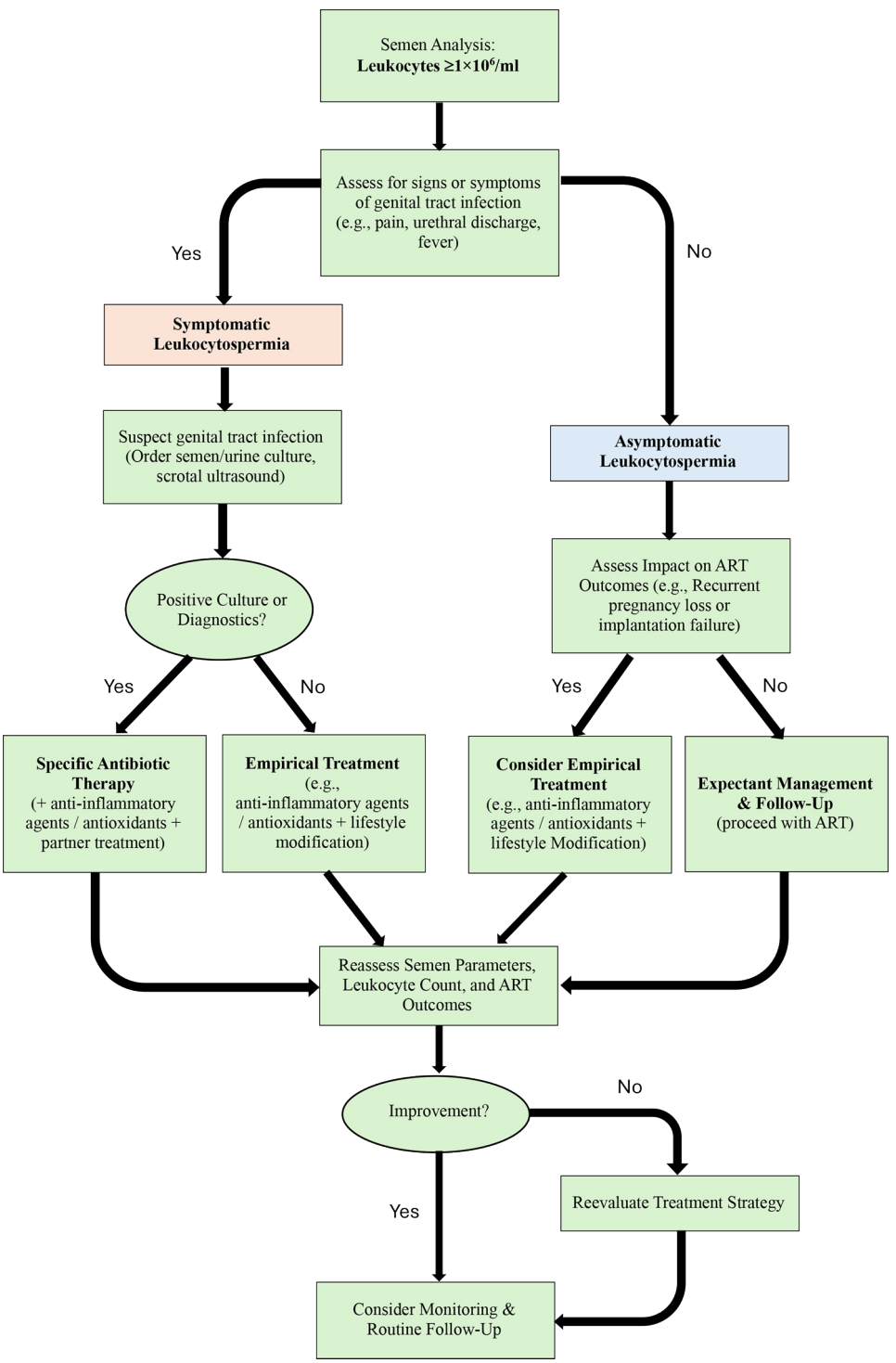


Table 1 - Management of Leukocytospermia in Male Partners of Couples Undergoing Assisted Reproductive Technology.

Parameter	Symptomatic Leukocytospermia	Asymptomatic Leukocytospermia
Diagnostic Approach	Detailed medical history and physical examination	Detailed medical history and physical examination
	Comprehensive evaluation of symptoms (e.g., pain, fever, dysuria, swelling), urine analysis, and imaging studies as appropriate	Screening* based on semen analysis during fertility evaluation
	Microbiological analysis to determine the causative pathogen (e.g., semen culture, Gram staining, PCR) (38, 97)	
Primary Treatment	Antibiotic therapy based on identified pathogen and infection site (37, 38, 97)	Expectant management
		Consider lifestyle modifications (e.g., smoking cessation, weight loss) (97)
Anti- inflammatory Treatment	NSAIDs or COX-2 inhibitors may be considered (99) alongside antibiotic therapy, particularly if symptoms	NSAIDs or COX-2 inhibitors may be considered to improve sperm parameters (5, 15)
Antioxidants	May be considered alongside antibiotic therapy (14, 103), particularly if markers of oxidative stress present (e.g., high sperm DNA fragmentation levels)	May be considered to improve sperm parameters (97), particularly if markers of oxidative stress present (e.g., high sperm DNA fragmentation levels)
Surgical Treatment	Treatment of obstructive causes should be considered (e.g., partial ejaculatory duct obstruction) (13, 97)	May may be considered if clinical varicocele is present (13, 97)
Duration of Treatment	Depends on etiology; typically, 1–4 weeks for antibiotic therapy (8)	Not determined
Follow-up	Repeat semen analysis* and microbiological analysis post- treatment to confirm leukocytospermia and infection resolution	Repeat semen analysis to confirm leukocytospermia resolution*
		Consider microbiological analysis to assess subclinical infection if ART failure or miscarriage

ART = assisted reproductive technology; PCR = polymerase chain reaction; ROS = reactive oxygen species; IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection; NSAIDs = non-steroidal anti-inflammatory drugs; COX = cyclooxygenase; reference numbers are shown in parentheses.

* Screening tools such as the peroxidase test or immunocytochemical staining with CD45 may be used.

ed treatment approaches, if any, including antioxidants and anti-inflammatory therapies, in improving ART outcomes for leukocytospermic patients.

CONCLUSIONS

Current evidence suggests that among couples undergoing ART, asymptomatic leukocytospermia does not compromise the outcomes and should, therefore, not be routinely treated, mainly when semen processing methods are used (e.g., density gradient centrifugation), and ICSI is the fertilization method. While some studies indicate a potential association between leukocytospermia and an increased risk of early pregnancy loss and ectopic pregnancy, these findings are based on low-quality evidence and require further investigation. For now, we suggest that clinical decisions regarding the treatment of asymptomatic leukocytospermia should be individualized, particularly in cases of recurrent early pregnancy loss and unexplained ART failure. Until more robust data emerge, a pragmatic, evidence-based approach remains crucial in balancing the potential risks and benefits of treatments to alleviate leukocytospermia in the context of ART.

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CONFLICT OF INTEREST

None declared.

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Correspondence address:
Sandro C. Esteves, MD, PhD
ANDROFERT, Clínica de Andrologia e Reprodução Humana
Av. Dr. Heitor Penteado, 1464
13075-460, Campinas, SP, Brasil
E-mail: s.esteves@androfert.com.br

REVIEW ARTICLE

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Management of Small Renal Masses: Literature and Guidelines Review

Antonio Silvestri [1], Filippo Gavi [1], Maria Chiara Sighinolfi [1], Simone Assumma [1], Enrico Panio [1], Daniele Fettucciari [1], Giuseppe Pallotta [1], Or Schubert [1], Cristina Carerj [1], Mauro Ragonese [1], Pierluigi Russo [1], Riccardo Bientinesi [1], Nazario Foschi [1], Chiara Ciccarese [2], Roberto Iacovelli [2], Bernardo Rocco [1]

[1] Department of Urology, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy; [2] Department of Oncology, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy

ABSTRACT

Renal cell carcinoma (RCC) ranks among the most prevalent malignancies worldwide, with a rising incidence attributed largely to the incidental detection of small renal masses (SRMs ≤ 4 cm) through widespread abdominal imaging. Historically managed with radical nephrectomy, treatment of SRMs has evolved significantly over recent decades. Partial nephrectomy has become the standard surgical approach, while active surveillance (AS) has emerged as a viable alternative for select patients, particularly those with comorbidities or limited life expectancy. AS involves serial imaging to monitor tumor progression, reserving intervention for signs of clinical advancement.

This review synthesizes oncological outcomes and current management strategies for SRMs, comparing AS with immediate intervention. A comprehensive literature search (2005–2024) was performed across PubMed, Web of Science, and Scopus, complemented by an analysis of major international guidelines (EAU, AUA, ESMO, CUA, and Latin American Renal Cancer Group). All guidelines support AS for selected patients with cT1a tumors, though criteria vary. The AUA limits AS to tumors <2 cm, while only its guidelines define clear triggers for transitioning from AS to treatment. Imaging surveillance intervals and biopsy indications also differ, with broader support for renal mass biopsy prior to ablation but more selective use during AS.

This review underscores the importance of individualized decision-making in SRM management and highlights areas of consensus and divergence among contemporary guidelines.

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Antonio Silvestri
https://orcid.org/0009-0008-2285-8231

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INTRODUCTION

According to the Global Cancer Observatory, renal cell carcinoma is the 14th most common malignant tumor, precisely the 9th most common cancer among men and the 14th among women, with 431,288 cases in 2020 (1). RCC incidence is higher in Europe and North America and has been increasing in the last decades. Simultaneously the mortality rate in developed countries has declined. It has been hypothesized that this phenomenon is related to the widespread use of abdominal imaging for nonspecific musculoskeletal or gastrointestinal complaints, leading to the incidental detection of otherwise asymptomatic small renal masses (≤ 4 cm) (2, 3). Traditionally, RCC was treated with radical nephrectomy (RN), regardless of renal mass dimensions. However, the management of small renal masses (SRMs) has undergone a significant transformation over the past decades. Nephron sparing surgical approach, such as partial nephrectomy (PN), has become the standard treatment, and active surveillance (AS) has moved from being a niche approach to an established treatment option for a specific patient population. AS is defined as the initial monitoring of tumor size by serial abdominal imaging (US, CT, or MRI) with delayed intervention reserved for tumors showing clinical progression during follow-up (4). This review aims to resume oncological results on the management of small SRMs with either AS or immediate treatment, focusing on the key factors influencing the choice between these two strategies.

MATERIALS AND METHODS

A comprehensive literature review was conducted to identify studies published in English between 2005 and 2024 focused on the management of small renal masses (SRMs). PubMed, Web of Science, and Scopus databases were queried using the following key words: "small renal mass", "active surveillance", "treatment" and "renal mass biopsy". A review of international available guidelines was performed as well, to depict the definition of SRM, guidelines' position on active surveillance, definition of active surveillance monitoring.

SUMMARY OF THE CURRENT GUIDELINES

At present, EAU, ESMO and CUA consider active surveillance in cT1a RCC, while AUA recommends active surveillance only for SRM < 2 cm. EAU, AUA, ESMO, CUA and Latin American Renal Cancer group agree on the patient selection, suggesting active surveillance to frail and comorbid patients, with the rationale that primary intervention would overweigh oncological benefits. AUA, CUA and Latin American Renal Cancer group suggest repeated imaging every 3-6 months during the first year, then every 6-12 months. Instead, EAU and ESMO do not specify any imaging protocol for active surveillance. Only the AUA guidelines provides specific triggers for a change in the disease management from AS towards intervention, which are tumor size > 3 cm, stage progression, growth kinetics > 5 mm/year, clinical changes in patient/tumor factors, additional biopsy results. Recommendations for renal mass biopsy (RMB) vary among the guidelines. EAU, AUA and CUA agree on practicing RMB before ablation treatment in SRM. RMB is recommended in AS, according to EAU and ESMO, only for selected patients, and according to AUA, only in the suspicion of non-malignant lesions. An overview of the summary of the current guidelines is presented in Table-1.

EVOLUTION OF THE USE OF ACTIVE SURVEILLANCE

Initially, SRMs were almost exclusively managed with an interventional approach, which included RN or PN. However, as the incidental diagnosis of SRM increased through advanced imaging techniques such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), it became apparent that many of these masses had indolent or even benign behavior. This awareness led to a reconsideration of the management of SRM and the

Table 1 – Overview of the summary of the current guidelines.

	Inclusion criteria	Patient selection	Imaging	Triggers for intervention	Renal mass biopsy
EAU	cT1a RCC	Frail and comorbid patients	No imaging protocol	/	Before ablation treatment
AUA	SRM < 2cm	Frail and comorbid patients	Every 3-6 months during the first year, then every 6-12 months	Tumor size > 3 cm, stage progression, growth kinetics > 5 mm/year, clinical changes in patient/tumor factors, additional biopsy results	Before ablation treatment and in suspect of non malignant lesions
ESMO	cT1a RCC	Frail and comorbid patients	No imaging protocol	/	Only in selected patients
CUA	cT1a RCC	Frail and comorbid patients	Every 3-6 months during the first year, then every 6-12 months	/	Before ablation treatment
Latin American Renal Cancer Group	Small tumors	Frail and comorbid patients	Every 3-6 months during the first year, then every 6-12 months	/	/

gradual introduction of AS as an alternative option. In the 2000s, early retrospective studies began to examine the natural history of SRM and the outcomes of conservative management. These studies showed that many SRM grow slowly and have a low risk of metastasis, paving the way for AS as a viable option (5-7). Since the 2010s, several prospective studies have further consolidated the role of AS. The Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry, a multicenter prospective study, has shown that AS is non-inferior to primary intervention in terms of cancer-specific survival (CSS) at an intermediate follow-up of 5 years (8). Initially AS was considered primarily for elderly patients with significant comorbidities, in whom the risks associated with surgery may outweigh the benefits (9-11). Few years later Metcalf et al. focused the attention on AS in young and healthy patients, showing that even in patients aged less than 60 years AS in SRMs is not inferior to immediate intervention in terms of overall and cancer-specific survival. Nowadays the management of SRMs through AS is widely recognized by international guidelines.

ACTIVE SURVEILLANCE VS. IMMEDIATE TREATMENT

The rationale for managing RCC with AS derives from the observation that up to 20-30% of RM < 4 cm are histologically benign, and those that are malignant often exhibit a low degree of aggressiveness (12, 13), characterized by a slow growth rate and a low metastatic potential, with a progression to metastatic disease observed in only 1-2% of cases (14). Initial tumor size at diagnosis does not reliably predict the natural history of renal masses, although malignant lesions may exhibit a higher growth rate (14). Kouba et al. demonstrated that, among SRMs managed with AS, those who underwent delayed intervention exhibited a higher tumor growth rate (6).

Delayed intervention does not result in an increased risk of disease progression, is not associated with added surgical morbidity, and does not preclude patients from undergoing definitive surgery via a minimally invasive approach with comparable oncological outcomes (5, 7). Therefore, a deferred intervention is a safe approach in the management of SRMs (15, 16). Delayed intervention may include PN, RN or image-guided percutaneous ablation, such as cryoablation (PCA), radiofrequency ablation (RFA) or microwave ablation (MWA) (17, 18). Five studies concur on establishing a growth rate > 0.5 cm/year as a threshold for delayed intervention (8, 11, 19-21), while three of these also consider a tumor diameter > 4 cm as an additional criterion for intervention (8, 19, 21).

The Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry is a prospective study designed for patients with SRMs undergoing either AS or primary intervention. The DISSRM protocol advises serial imaging every six months for two years, followed by annual imaging thereafter. Axial imaging, utilizing either computed tomography (CT) or magnetic resonance imaging (MRI), is performed within six months of enrollment in the registry. Contrast-enhanced imaging is employed in patients with adequate renal function (11). Ultrasound may be considered every twelve months for a duration of three years. The use of CT or MRI remains at the discretion of the physician in cases of ambiguous ultrasound findings or observed changes (8). Similar protocols have been adopted by other investigators; for example, Marchioni et al. implemented abdominal imaging every four to six months for two years, succeeded by imaging every six to twelve months (9). An overview of the included studies to evaluate the efficacy of AS in SRMs is presented in Table-2.

Survival analysis

A consensus among most authors suggests that AS provides equivalent short- and medium-term oncologic efficacy to partial or radical nephrectomy for SRMs. Within the reviewed literature, six prospective studies (8, 18, 19, 21-23) and three retrospective studies (20, 24, 25) have examined either OS, CSS, or both in patients with SRMs managed with AS. The specific inclusion criteria, as well as the values of OS and CSS, are detailed in Table-1. Based on the included studies, CSS at 5 years for patients initially managed with AS is not significantly different compared to that of patients managed with immediate treatment. However, three of these studies highlighted a lower OS at 5 years in patients managed with AS compared to those managed with immediate treatment. This difference can likely be attributed to older age and a higher burden of comorbidities in the patients selected for AS (8, 18, 22), emphasizing how older patients undergoing AS will primarily die from causes other than renal cancer (22). Regarding mortality from non-RCC causes, cardiovascular events represent the leading cause of death in patients older than 75 years. Furthermore, nephrectomy is associated with accelerated renal dysfunction, which, in turn, increases cardiovascular mortality (26). Consequently, in the elderly population, active treatment is not linked to improved OS, and cardiovascular mortality surpasses cancer-specific mortality (27). According to Metcalf et al., even in a cohort of patients aged 60 years or younger at the time of diagnosis of a SRM, AS demonstrates non-inferiority to primary intervention with regards to both OS and CSS. This finding supports the possibility to expand AS to younger and healthier patients, provided they are carefully selected and monitored (19). However, the prevalent consensus suggests that active surveillance (AS) represents a reasonable strategy for elderly patients with comorbidities, whereas immediate surgical intervention, particularly partial nephrectomy (PN), may be more suitable for younger, healthier individuals (28).

Only two authors disagree on the oncological efficacy of AS in SRMs. Zini et al. report that RCC-specific mortality rates in nonsurgical management (NSM) significantly exceeds that of nephrectomy group. It is important to note that this study was not randomized, and this may limit the comparability of the NSM and nephrectomy groups due to potential selection bias and confounding factors (29). Patel et al. instead indicated that, when comparing

NSM and surgical intervention, CSS was equivalent among treatment groups for patients younger than 75 years, but significantly worse for patients aged 75 years or older undergoing NSM. This discrepancy could suggest that younger patients are more effectively selected for NSM (30).

Role of the histological diagnosis

According to several authors, the initial management of SRMs can be guided by histological diagnosis. Surgical intervention or ablation may be favored for SRMs diagnosed as renal cell carcinoma (RCC), whereas active surveillance (AS) might be preferred for indolent or benign SRMs. Consequently, renal mass biopsy (RMB) could potentially reduce overtreatment, guiding the decision to opt for AS rather than immediate treatment (31, 32). Furthermore, significant differences exist in diameter growth rate and metastatic potential between clear cell and papillary type 1 RCC SRMs, with clear cell RCC exhibiting a faster growth rate and higher metastatic potential. This highlights the potential importance of RMB in counseling patients and personalizing SRM management (33).

Cost analysis

An analysis by Su et al. provides valuable insights into the cost-effectiveness of different management strategies for small renal masses (SRMs). The study demonstrates that the 10-year all-cause mortality rates are similar among patients managed with PN, RN, PCA, and that AS, with the option of timely delayed intervention, appears to have the lowest total cost per patient, suggesting that this strategy offers a safe and cost-effective approach to the management of patients with SRMs (28).

Quality of life

AS patients report worse physical quality of life (QoL) than primary intervention patients, mainly due to lower scores in the physical health component (9). However, mental health scores are similar between the groups and improve over time, regardless of management strategy. This suggests that while AS may be associated with initial concerns, the mental health-related components (which include anxiety and depression) tend to improve over time, suggesting that well-selected and counseled patients may experience improved QoL. Patient selection and counseling, including a shared decision-making process, are crucial prior to initiating an AS protocol to ensure comprehensive patient understanding of the risks and benefits associated with each management option. Notably, approximately 50% of patients who elect for delayed intervention do so due to anxiety, even in the absence of significant tumor growth (11).

CONCLUSIONS

The management of SRMs represents an evolving field, with AS emerging as a viable and safe option for selected patients. The choice between AS and immediate treatment must be individualized, considering age, comorbidities, tumor size, growth rate, and patient preferences. AS allows avoidance of unnecessary interventions and associated risks, while maintaining a safe and close monitoring to intervene promptly in case of progression. Immediate treatment remains the preferred option for young, healthy patients with fast-growing tumors or those with suspected malignancy. Renal biopsy can play a crucial role in guiding decision making by providing histologic information that can help distinguish between benign and malignant lesions and predict tumor behavior. However, it is critical to carefully consider the risks and benefits of biopsy as well as its diagnostic accuracy.

Further research, including prospective randomized controlled trials, is needed to better define the selection criteria for AS and to evaluate the long-term outcomes of different management strategies. Ultimately, the goal is to provide each patient with the most appropriate management, balancing the risks and benefits of AS versus immediate treatment, with the goal of maximizing both survival and quality of life.

Table 2 – Characteristics of the studies included in the review to evaluate the efficacy of AS in SRMs.

First Author (Year)	Study Type	N (Patients with RM)	N (AS Group)	Mean Age	Inclusion Criteria	Follow-up (Years)	N of patients who underwent renal mass biopsy	N of AS patients who underwent delayed intervention	Growth Rate (cm/year)	Development of Metastatic Disease	5-Year OS (%) in AS	5-Year CSS (%) in AS	Key Findings
Kouba, et al. (2007) (6)	Retrospective	545	43	67	Diagnosis of RM	3	/	13	1.01	/	/	/	Watchful waiting for RMs is a valid option for selected patients, and an eventual delayed intervention does not have a negative impact on pathological outcomes
Crispen, et al. (2008) et al. (7)	Retrospective	82	82	64	RM ≤ 4 cm	1.8	25	82	0.30	No	/	/	Small renal tumors have a slow interval growth, and their management can be delayed without limiting available treatment options or incurring high disease progression
Rais-Bahrami, et al. (2009) (5)	Retrospective	32	32	59	Incidentally discovered RMs who underwent laparoscopic partial nephrectomy	1.3	/	32	0.56	/	/	/	A delay in surgery of SRMs of > 1 year does not preclude patients from undergoing definitive surgery via a minimally invasive approach with an equal oncolgical outcome
Zini, et al. (2009) (29)	Retrospective	10 292	433	61.9	RCC ≤ 4 cm treated with either nephrectomy or non-surgical management	4.2	/	/	/	/	/	/	Non-surgical management of RMs has higher RCC specific mortality rates than nephrectomy
Lane, et al. (2010) (27)	Retrospective	537	105	75	cT1 renal tumors	3.9	/	/	/	Yes (n=26)	76	/	In patients > 75 years, surgical management of clinically localised renal cortical tumors is not associated with increased survival
Brunocilla, et al. (2014) (10)	Retrospective	42	42	75	Contrast-enhancing SRMs suspicious for RCC	5.8	15	12	0.8	Yes (n=2)	/	/	Faster growth rates in SRMs could be an expression of malignant disease, suggesting delayed surgical intervention. AS is an option for the management of SRMs in low life expectancy patients
Patel, et al. (2012) (30)	Retrospective	234	71	71.9	T1a SRMs managed with AS, RN, or PN	2.8	7	14	0.21	Yes (n=1)	83	98.6	AS of SRMs offers oncological efficacy equivalent to surgery in the short/intermediate term
Brunocilla, et al. (2013) (14)	Retrospective	62	62	75	Contrast enhancing SRMs suspicious of RCC.	7.6	25	20	0.4	Yes (n=2)	/	/	Most SRMs have an indolent course, and AS is an option for selected patients

First Author (Year)	Study Type	N (Patients with RM)	N (AS Group)	Mean Age	Inclusion Criteria	Follow-up (Years)	N of patients who underwent renal mass biopsy	N of AS patients who underwent delayed intervention	Growth Rate (cm/year)	Development of Metastatic Disease	5-Year OS (%) in AS	5-Year CSS (%) in AS	Key Findings
Sugimoto, et al. (2013) (24)	Retrospective	292	32	63.7	cT1aN0M0 SRMs managed by immediate or delayed intervention	2.2	/	32	/	/	72.6	87.5	Delayed surgery for SRMs is a treatment option, and has non inferior overall survival rate compared to immediate surgery
Pierorazio, et al. (2015) (8)	Prospective	497	223	70.6	cT1a SRM on axial imaging	2.1	32	21	0.11	No	75	100	AS is not inferior to primary intervention
Danzig, et al. (2015) (26)	Prospective	162	68	71.7	SRMs managed with either AS or PI, with respectively preoperative/ postoperative or 2 consecutive serum creatinine values	1.5	/	/	/	/	/	/	Patients in AS have superior eGFR rate preservation than those who undergo RN, but no significant difference than those who undergo PN
Bazan, et al. (2018) (12)	Retrospective	82	82	77	Contrast-enhancing (> 20 HU) RMs ≤ 4 cm (cT1aN0M0) or renal cysts (BosniakIIF-IV)	4.6	0	5	/	No	/	/	AS is a safe option for the management of SRMs
Gupta, et al (2018) (11)	Prospective	371	371	71.3	RMs ≤ 4 cm undergoing AS or primary intervention	2	52	46	0.18	No	/	/	AS is a safe management option, but counseling is essential to determine suitability of patients
Petros, et al. (2019) (21)	Prospective	272	272	68.5	SRMs ≤ 4 cm	4.8	105	64	0.24	Yes (n=4)	73	98	Survival of patients with SRMs < 3 cm on AS improves after the initial 2 years, suggestinf role for re-counselling those who survuve the 2 year landmark
Alam, et al. (2019) (18)	Prospective	638	339	70.6	SRMs ≤ 4 cm managed with AS, ablative therapy, PN, or RN.	3.0	11	46	/	Yes (n=2)	66.1	100	AS is a reasonable option for selected patients (old patients with multiple comorbidities)

First Author (Year)	Study Type	N (Patients with RM)	N (AS Group)	Mean Age	Inclusion Criteria	Follow-up (Years)	N of patients who underwent renal mass biopsy	N of AS patients who underwent delayed intervention	Growth Rate (cm/year)	Development of Metastatic Disease	5-Year OS (%) in AS	5-Year CSS (%) in AS	Key Findings
Tan, et al. (2020) (16)	Retrospective	14 677	627	55	Patients < 70 years with cT1aN0M0 RCC and Charlson Comorbidity Index 0	6.9	/	627	/	/	89.9	/	No significant difference in OS between immediate nephrectomy vs. delayed nephrectomy, suggesting that a period of observation is safe to allow identification of RMs that will benefit from surgery.
Marchioni, et al. (2021) (9)	Retrospective	483	121	80	Patients ≥ 75 years with SRMs ≤ 4 cm managed with AS or PI	2.3	/		/	/	70	/	AS is an appealing treatment for very elderly patients with SRMs, and it does not compromise survival outcomes
Jakubowicz, et al. (2022) (22)	Prospective	106	41	80.5	Patients ≥ 75 years with clinically localized RMs	3.4	7	8	/	Yes (n=2)	68.3	95.1	AS is superior to watchful waiting, and should be preferred to active intervention at the beginning of the management.
Metcalf, et al. (2021) (19)	Prospective	224	82	54.6	Patients ≤ 60 years undergoing AS or primary intervention	4.9	/	13	0.09	No	90.8	100	AS is a safe initial strategy in younger patients
Umari, et al. (2022) (23)	Prospective	134	75	69.8	Single cT1a renal tumor managed with AS or percutaneous cryoablation (PCA)	3	50	12	/	Yes (n=1)	82.4	98.2	AS and PCA provide similiar outcomes and are safe and valid management options for elderly and comorbid patients with SRM2
Su, et al. (2022) (28)	Cost-effectiveness	/	/	/	Patients with SRMs undergoing either RN, PN, TA or AS	/	/	/	/	/	/	/	AS has the lowest total cost per patient among the different management options for SRMs
Cheung, et al. (2023) (25)	Retrospective	377	205	64	Patients aged 55-75 years with SRM ≤ 4 cm	4.6	100	20	/	/	95	/	AS is safe in routine clinical practice
Bertolo, et al. (2024) (15)	Prospective	356	49	66	cT1a RMs	1.5	/	49	/	/	/	/	Deferred partial nephrectomy is a safe approach in patients with SRMs

First Author (Year)	Study Type	N (Patients with RM)	N (AS Group)	Mean Age	Inclusion Criteria	Follow-up (Years)	N of patients who underwent renal mass biopsy	N of AS patients who underwent delayed intervention	Growth Rate (cm/year)	Development of Metastatic Disease	5-Year OS (%) in AS	5-Year CSS (%) in AS	Key Findings
Foret, et al. (2024) (17)	Retrospective	104	/	72.2	Patients who underwent concomitant RTB and microwave ablation of SRM	1.9	104	/	/	/	/	/	Microwave ablation has shown clinical safety and efficacy in the management of RMs
Gao, et al. (2023) (31)	Retrospective	159	50	63.4	RMs ≤ 4 cm which underwent CNBs	3.4	159	/	/	/	/	/	Employment of CNB in SRMs may reveal benign diagnosis, avoiding overtreatment for benign lesions.
Finelli, et al. (2020) (33)	Prospective	134	49	70	Patients with T1aN0M0 RM, who elected not to have immediate treatment, and underwent renal mass biopsy	5.8	134	85	0.28	Yes (n=6)	/	/	Initial follow-up of histologically characterized SRMs can inform personalized treatment for patients on AS
Mazin, et al. (2024) (32)	Retrospective	195	79	70	Patients with SRMs who underwent RTB	3.5	195	/	/	/	/	/	RTB is a safe diagnostic method that provides accurate histopathological information, reducing overtreatment of benign SRMs

AS = Active Surveillance; PI = Primary Intervention; RM = Renal Mass; SRM = Small Renal Mass; RCC = Renal Cell Carcinoma; PN = Partial Nephrectomy; RN = Radical Nephrectomy; OS = Overall Survival; CSS = Cancer-Specific Survival; CNB = Core Needle Biopsy; RTB = Renal Tumor Biopsy; eGFR = estimated Glomerular Filtration Rate; TA = Thermal Ablation.

/ = indicates data not reported or not applicable

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Antonio Silvestri, MD
Department of Urology, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS
Largo Agostino Gemelli, 8, 00136 Roma RM
Lazio 00168, Italy
E-mail: a.antosilvestri@gmail.com

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One-stage Closure of the Small Non-growing Bladder Plate: New Insight into the Anatomy of Exstrophy - Trapezoid Interpubic Ligament (TIPL)

Vasily V. Nikolaev [1, 2], **Nikita V. Demin** [2]

[1] Pirogov Russian National Research Medical University, Moscow, Russia, [2] Clinical and Research Institute of Emergency Pediatric Surgery and Trauma, Moscow, Russia

ABSTRACT

Purpose: The purpose of this study is to examine whether retrovesical fibromuscular structures—specifically the trapezoid interpubic ligament (TIPL)—mechanically restrict the inversion of small, non-growing bladder plates (SNGBP) in bladder exstrophy, and to evaluate bladder growth after one-stage closure with TIPL dissection, including the effect of anticholinergic therapy.

Materials and Methods: Between 2004 and 2023, 15 patients with SNGBP underwent one-stage bladder closure using a modified surgical approach with TIPL dissection. The TIPL, identified as a fibromuscular structure impeding bladder plate (BP) inversion, was targeted. Postoperative bladder capacity was evaluated based on age at surgery and the use of anticholinergic therapy.

Results: The TIPL was identified as the primary mechanical impediment to BP inversion. Its dissection restored tissue compliance, facilitating successful one-stage closure in all patients. In children under three years of age at the time of surgery, the mean annual bladder capacity increased by 17.76 mL. Anticholinergic therapy further enhanced bladder growth.

Conclusion: TIPL dissection enables one-stage closure in SNGBP patients who were previously considered unsuitable for this method. Early intervention supports bladder development and favorable functional outcomes. These findings provide novel anatomical insights, warranting further morphological and embryological research to validate the universality of this structure and technique.

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Vasily Nikolaev
https://orcid.org/0000-0001-7815-4825

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INTRODUCTION

Bladder exstrophy, a rare and complex congenital anomaly, severely alters the lower urinary tract, anterior abdominal wall, and pelvic ring anatomy. Despite notable progress in surgical reconstruction in recent decades, various anatomical and biomechanical factors, especially those affecting primary bladder closure feasibility, remain inadequately elucidated (1–5). Patients with small BPs, typically characterized by a width under 3 cm and inadequate tissue for tension-free closure, pose a significant challenge (6). Primary closure is often deemed unfeasible due to suboptimal tissue quality, heightened stiffness, and limited growth capacity. Closure feasibility is assessed under anesthesia via the BP inversion test, applying gentle pressure to evaluate compliance. Failure to invert the plate is generally regarded as a contraindication to primary closure (7, 8). In such cases, a common approach is watchful waiting to permit spontaneous growth and improved compliance (6). If growth does not occur, cystectomy with enterocystoplasty is typically conducted (9). Alternatively, a two-stage method entails suturing the BP to the anterior abdominal wall in the neonatal period, creating a hernia-like sac to promote expansion via intra-abdominal pressure, though its advantage over natural growth lacks confirmation (10).

Among patients with small BP, a distinct subgroup exhibits no growth despite prolonged observation. These patients often wait years for BP expansion that, for reasons yet unclear, fails to materialize. Termed SNGBP, this subgroup constitutes roughly 10% of classical bladder exstrophy cases. While resistance to BP inversion critically affects surgical decisions, its anatomical and histological underpinnings remain elusive. Fibrotic remodeling is frequently presumed to be the chief constraint on tissue pliability. We hypothesize that, beyond intravesical fibrosis, the biomechanical attributes of retrovesical fibromuscular structures in the interpubic region may serve as an additional mechanical impediment, limiting BP inversion and decreasing the probability of successful primary closure. To test this hypothesis, we defined two objectives:

- To investigate whether retrovesical fibromuscular structures mechanically restrict bladder plate inversion, thus impeding primary closure in patients with SNGBP.
- If mitigating their mechanical effect facilitates closure, to analyze bladder growth dynamics and their reliance on anticholinergic therapy.

MATERIALS AND METHODS

Patient Selection

This cohort study, conducted from 2004 to 2023, encompassed all patients referred to our institutions with a diagnosis of bladder exstrophy accompanied by a SNGBP. Initially, patients were admitted to various neonatal surgical departments shortly after birth. These individuals were deemed unsuitable candidates for bladder closure due to inadequate bladder elasticity, diminished bladder size, multiple hamartomatous polyps, and unfavorable findings during examination under anesthesia (which assessed the feasibility of BP inversion into the pelvic cavity). The inclusion criteria comprised absence of prior surgical correction of bladder exstrophy, age exceeding six months, and a non-invertible BP measuring less than 3 cm.

Ethics

This study was approved by the research ethics committees of both participating institutions (No. 05/1602 and No. 180226).

Preoperative Examination

Pelvic MRI was conducted in recent cases before surgery to identify anatomical structures potentially limiting BP inversion and to correlate MRI findings with intraoperative observations. This method assessed MRI's diagnostic utility in preoperative planning and explored the visibility of the interpubic ligamentous complex.

Surgical Procedure

All patients underwent uniform BP closure, adapting a previously reported technique (11) for this study. Modifications included microdissection of retrovesical structures obstructing SNGBP inversion. Large BP polyps hindering closure were excised in 4 of 15 patients. The bladder was inverted, sutured longitudinally, and shaped with a funnel-like neck over a No. 8Ch pigtail catheter, then placed in the pelvic cavity. Ureteral re-

implantation was not performed during primary closure. Paravesical fat from the Retzius space was mobilized from the pelvic walls and sutured anteriorly to the bladder neck. Microdissection utilized surgical loupes (×3.5 to ×6.5 magnification), a monopolar microdissection needle electrode (fine tip), and microsurgical scissors. Among the 15 patients, pubic bone approximation was performed in 7 more recently treated cases.

A bone-holding clamp reduced interpubic diastasis, and fixation was achieved with two opposing U-shaped interrupted No. 2 Vicryl sutures. This was indicated when the interpubic gap surpassed 4 cm or pelvic instability persisted post-bladder plate positioning.

Postoperative Management

All patients received intravenous broad-spectrum antibiotics from surgery until discharge, followed by oral prophylaxis. Oxybutynin anticholinergic therapy (0.4 mg/kg/day) began on the first postoperative day and continued until bladder catheter removal. Patients rested in bed or their mother's arms without immobilization and were discharged between postoperative days 8 and 17 (median: 11.6 days). Per protocol, boys underwent epispadias repair 6–12 months later (12).

Outcomes Assessment

Successful bladder closure was defined as an intact repair showing no bladder prolapse, dehiscence, vesicocutaneous fistula, or outlet obstruction (13). For patients over 1 year, bladder capacity monitoring involved parental measurement of morning urine volume, routine ultrasound, and voiding video documentation. Per protocol, evaluations occurred at 1, 3, and 5 years, and prior to bladder neck reconstruction. In delayed primary closure cases, study timing was tailored to clinical status. In-hospital capacity was assessed via gravitational cystometry during cystography under anesthesia, maintaining physiological pressure at 15 cm H2O. Patients over five years with bladder capacity above 60 mL underwent subsequent bladder neck reconstruction. Continence was assessed in children at least six years old, typically one-year post-bladder neck reconstruction (BNR). Urinary continence was defined as a dry interval of 3+ hours without nocturnal enuresis (14). Follow-up spanned 12 months to 9 years (median: 4.6 years). No patients were lost to follow-up, with ongoing communication sustained via online contact with one author (VVN). Families regularly reported voiding patterns, outpatient ultrasound findings, and urinalysis results.

Statistical Methods

We statistically analyzed bladder capacity increases with and without anticholinergic agents using the R programming language. The difference between therapy initiation and volume measurements was determined, dividing patients into "before" and "after" administration groups. The ggplot2 library facilitated visualization of bladder capacity changes and range diagrams. To evaluate differences in capacity increase rates pre- and post-anticholinergic therapy, we computed the rate of increase between measurements. A matched-pairs Wilcoxon test was used to compare the groups. Medians and quartiles were calculated as descriptive statistics (15).

RESULTS

Management before referral

Seven patients in the cohort received botulinum toxin injections into the detrusor muscle at their neonatal centers to enhance BP compliance, yet subsequent anesthesia-based assessments revealed no measurable improvement. These non-invertible cases were referred to our center for further evaluation and surgical intervention.

Primary Bladder Closure

Fifteen patients, aged 6 to 85 months (including three girls), underwent a modified primary bladder closure procedure. Enterocystoplasty was performed in one 5-year-old female with an extremely small (<2 cm), polyposis SNGBP, where primary closure was considered unfeasible.

TIPL Dissection and Bladder Plate Inversion

Intraoperative exploration identified a previously unreported fibromuscular structure, tightly linked to

the BP and impeding its inversion in all SNGBP patients. Named the Trapezoid Interpubic Ligament (TIPL) (Figure-1), this ligament consistently restricted BP inversion. It was securely anchored to the detrusor in the supratrigonal region and to the diverging aponeurotic fibers of the linea alba, forming the medial boundaries of the rectus abdominis muscle (RAM) sheaths. Cranio-lateral traction from the RAM through these fibers shaped the ligament's distinctive trapezoidal form. Intraoperative findings revealed that transecting the TIPL near the pubic bones alone did not enable BP inversion. When the ligament remained attached to the detrusor, inversion was unachievable despite partial release. Inversion occurred only after complete detachment of the TIPL from the detrusor (Figure-2). To clarify the TIPL's relationship with adjacent pelvic ligaments, targeted anatomical dissection was performed in six patients. The ligament was separated from the detrusor and rectus abdominis sheaths while preserving its pubic bone attachment. Detaching the TIPL from the rectus sheath relaxed the ligament and consistently widened the interpubic gap, mirroring effects seen post-transection. Bladder plate inversion required full detachment from the detrusor. Near its attachment to the superior pubic rami, the pubovesical (PVL) and pubourethral (PUL) ligaments were inserted into the TIPL at a 70–90° angle and were transected there to facilitate deep pelvic descent of the vesicourethral segment. The PVL ran nearly horizontally under the trigone, while the PUL extended more caudally beneath the proximal urethral plate. After deeper descent of the bladder plate, the TIPL, remaining in its original position, came to lie anterior to it (Figures 1B and C). Figure-3 illustrates the spatial relationships among the TIPL, PVL, PUL, and BP relative to the anterior abdominal wall defect.

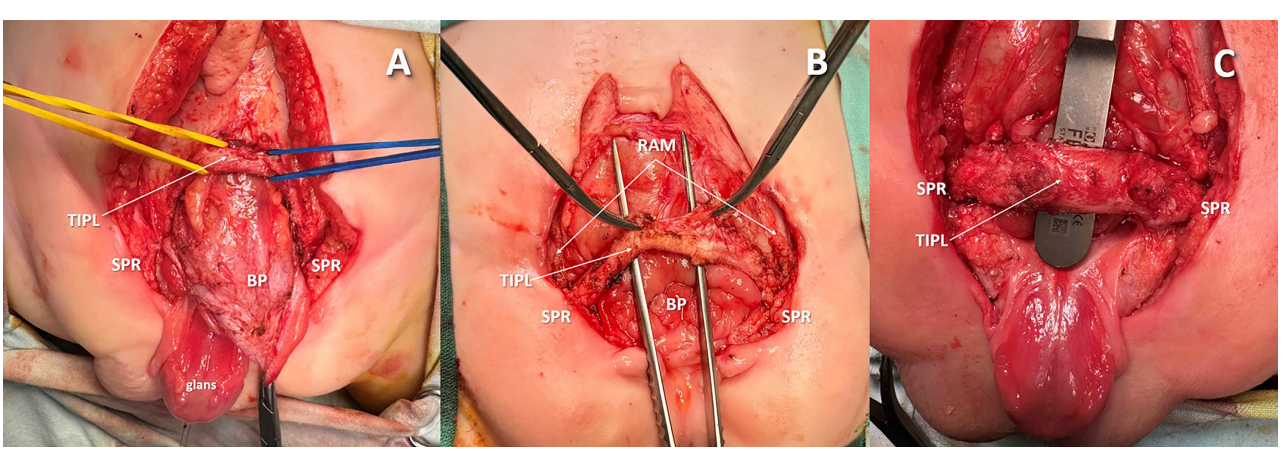
MRI study

Pelvic MRI, conducted in five patients from the cohort's latest subset, revealed a trapezoid-shaped structure spanning from the supratrigonal region to the medial edges of the rectus abdominis muscles in all cases. Its oblique alignment and partial overlap with adjacent tissues prevented MRI from fully defining its continuity or attachments. These observations were correlated with intraoperative findings to evaluate MRI's diagnostic utility in preoperative planning (Figure-4).

Biopsy

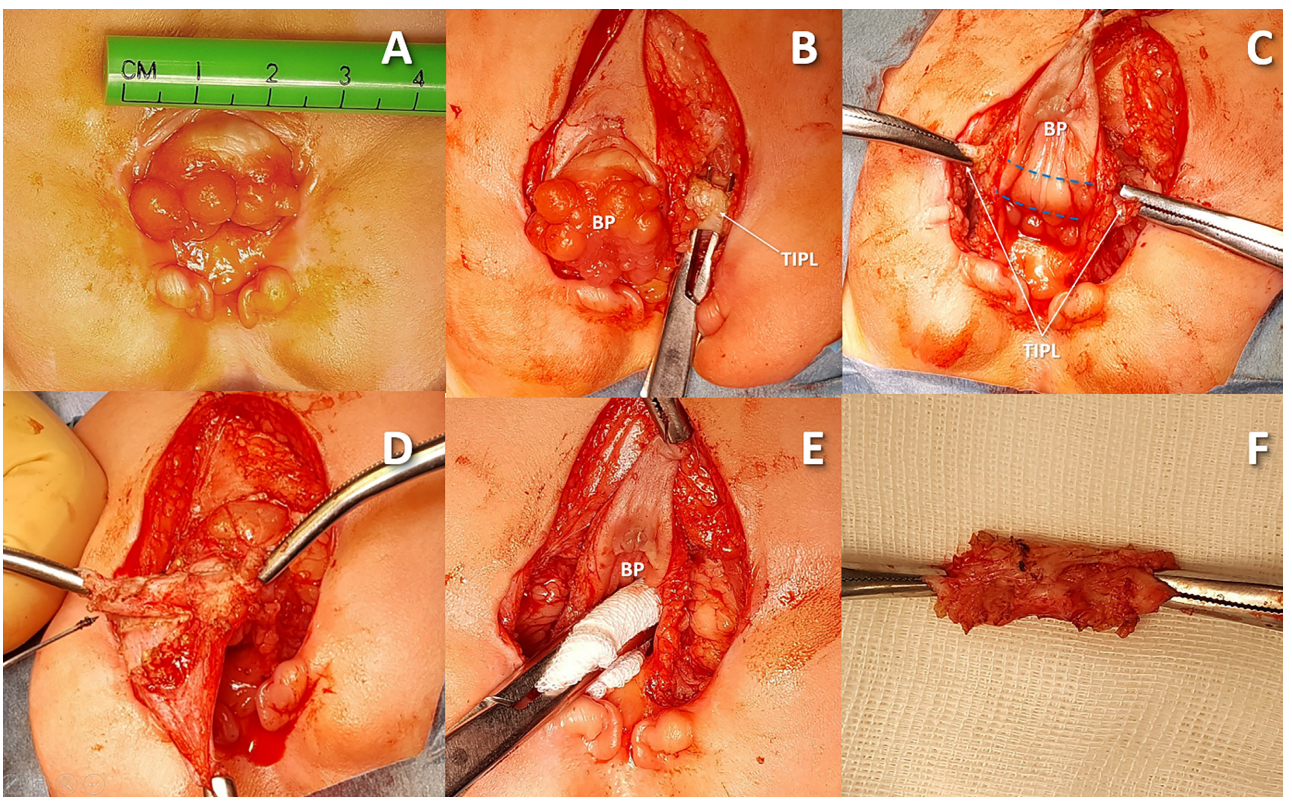
Gross examination of the TIPL revealed a round or elliptical 5–9 mm cross-section in most patients, with greater thickness in those with a narrow-

Figure 1 - Separation of the TIPL from the detrusor.



A) from RAM and bladder plate **B, C.**
A) A horizontal part of TIPL at the RAM diastasis (between the holders) following the separation of the ligament from the detrusor, but without the dissection from the RAM sheath (BP turned caudally). **B, C)** TIPL is isolated from the RAM sheath and the bladder plate with preserved attachment to the SPR.

Figure 2 - Stages of dissection and small bladder plate compliance restoration through complete dissection of the TIPL.



A) Small bladder plate in a 30-month-old girl. **B)** Initial stages of ligament separation. Clamp is placed underneath the TIPL between the pubic bone and the bladder plate. **C)** TIPL is dissected from the pubic bones, but remains attached to the detrusor. At this stage, the bladder plate remains non-invertible, highlighting the importance of detrusor separation and division of pubic ligamentous attachments. **D)** Technique of TIPL separation from the detrusor muscle. **E)** Free inversion of the urinary bladder with a gauze ball following the dissection of the retrovesical ligament from the detrusor**. F)** Gross TIPL preparation following separation from the pubic bones, detrusor and the RAM sheath.

er interpubic space. In one case, the TIPL formed a 20 mm wide, 12 mm long, 5 mm thick plate, anchored to the pubic bones by paired short filaments. Biopsies from the midportion of the TIPL in 10 patients showed a fibromuscular composition with plentiful smooth muscle bundles, consistent with a ligament (Figure-5).

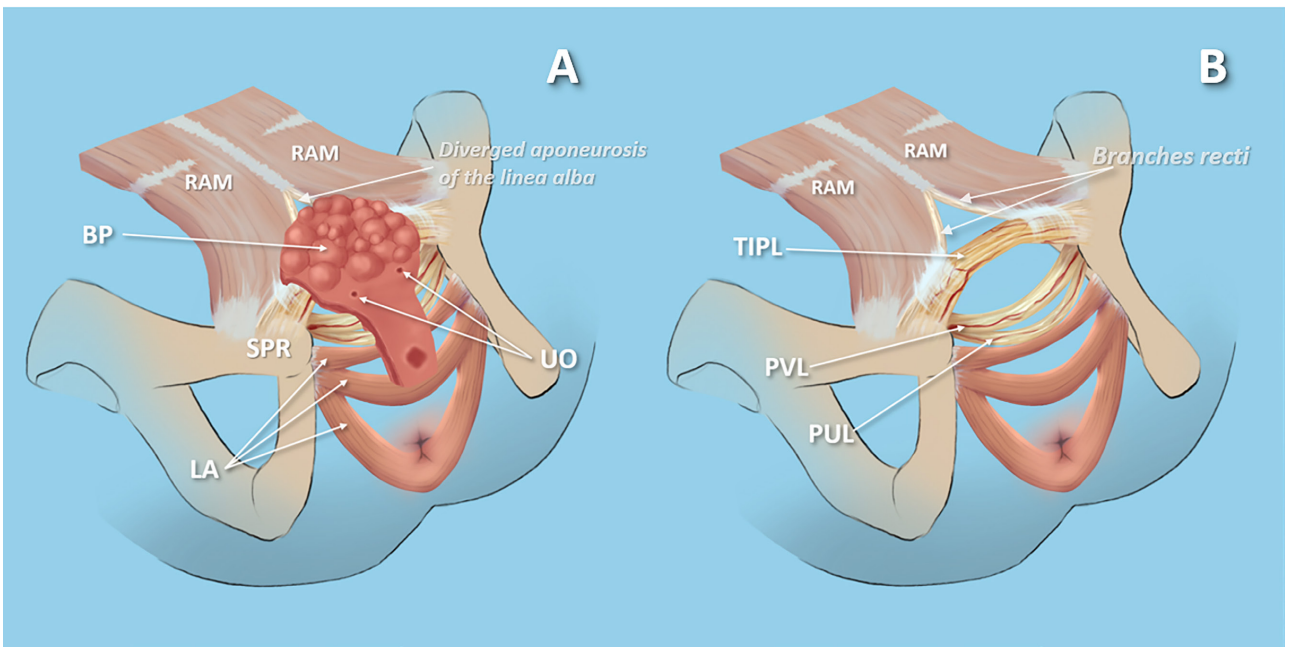
Clinical Outcomes and Bladder Growth

Bladder closure was successfully completed in all 15 cases. Three patients had minor skin dehiscence (Clavien-Dindo I) anterior to the neomeatus. One developed a urethrocutaneous fistula (Clavien-Dindo II) that healed spontaneously. Two experienced febrile urinary tract infections from transient bladder neck obstruction post-catheter removal, effectively treated with urethral stenting and antibiotics.

Bladder Capacity and Continence Outcomes

Patients undergoing bladder closure before age three exhibited notable bladder capacity gains, with a mean annual increase of 17.76 mL/year. Anticholinergic agents further enhanced growth. Pre-therapy, the median monthly bladder capacity increase was 1.48 mL/month

Figure 3 - Anatomical disposition of the trapezoid interpubic ligament (TIPL).



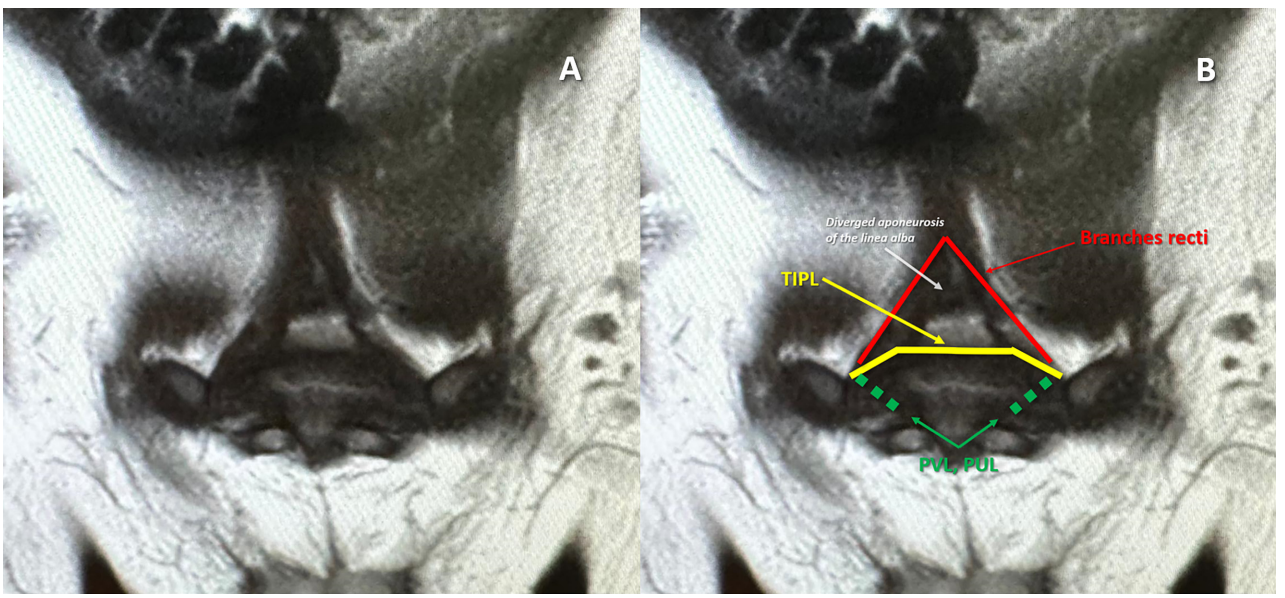
A) Diagram illustrating the SNGBP and anatomical structures surrounding the bladder plate and the infraumbilical anterior abdominal wall defect. **B)** Position of the TIPL, pubovesical, and pubourethral ligaments in the absence of the bladder plate. Attachments of the TIPL to the diverging aponeurosis of the linea alba and the rectus abdominis sheaths deform the ligament, pulling it cranially and giving it a trapezoid shape.

(1st quartile: 0.89; mean: 1.90; 3rd quartile: 2.50), rising to 2.63 mL/month post-therapy (1st quartile: 1.75; mean: 2.64; 3rd quartile: 3.52). A matched-pairs Wilcoxon test showed no significant difference in growth rates pre- and post-therapy ($p = 0.4469$), though visual trends indicated increased growth post-therapy. Bladder neck reconstruction (BNR) occurred in 8 of 9 patients over five with capacities above 60 mL, yielding positive continence results, with most achieving daytime continence and some full continence without nocturnal enuresis (Table-1).

DISCUSSION

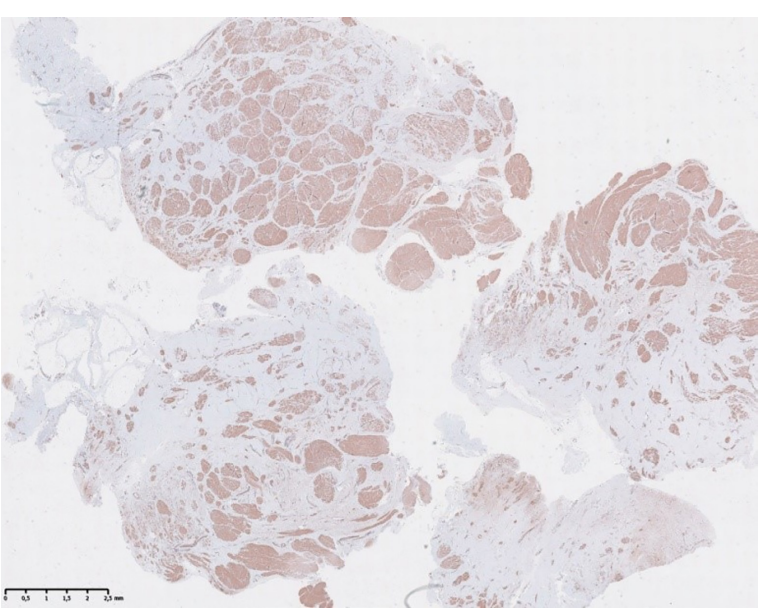
Reconstructive surgery for exstrophy fundamentally aims to preserve all normal lower urinary tract anatomical structures (16, 17). However, reconstruction is only feasible after transection of the ligaments that anchor the bladder plate to the pelvic sidewalls. Historically, exstrophy was thought to lack normal pubic ligaments (anterior, posterior, superior, and inferior) (18, 19). Wood (1869) described a robust fascial membrane connecting the PB behind the urethra, supporting the bladder base and penis, yet noted no interpubic structures above or anterior to the urethra (20). Shattock (1994), examining St. Thomas' Hospital Museum specimens, confirmed the bladder muscle wall's attachment to the PB's posterior surface, identifying the suburethral filamentous triangular urethral ligament (urogenital diaphragm) as the sole fibrous PB connection in exstrophy (21). Mid-20th-century surgeons developing systematic reconstruction also found no anterior pubic ligaments (16), reinforcing the view that pubic ligaments are absent in exstrophy, with lateral bladder attachments tied to urogenital diaphragm structures (22). The surgical community maintained this view largely unquestioned until the modern era.

Figure 4 - MRI image of SNGBP.



A, B) The image clearly demonstrates divergence of the linea alba aponeurosis (red) and its fusion with the Trapezoid Interpubic Ligament (TIPL, yellow). The directions of the pubourethral (PUL) and pubovesical (PVL) ligaments are marked in green but are less distinct due to the mismatch in imaging planes.

Figure 5 - Microscopic TIPL preparation.



Reaction with SMA (smooth muscle actin) - smooth muscle bundles. Collagenic fibrous tissue with few cells and incorporated smooth muscle bundles.

Before microdissection, we, like other surgeons, assumed the short segment between the BP and superior pubic ramus was the pubovesical ligament (23, 24). Microdissection, however, clarified that this is merely a component of the TIPL, affiliated not with the urogenital diaphragm but with the anterior abdominal wall. The TIPL's lateral portions merge with the inner aponeurotic edges of the rectus abdominis sheaths, resembling a divided linea alba aponeurosis—characteristic of the anterior pubic ligament. This supports the view that the TIPL originates from and integrates with anterior abdominal wall structures, aligning with the anterior pubic ligament's configuration, not the urogenital diaphragm as previously thought, potentially explaining its absence from earlier anatomical descriptions (19, 25, 26).

This explains why the TIPL remained unidentified. Standard BP mobilization begins with detachment from the rectus abdominis sheaths for access, followed by severing all connective structures between the BP and pubic bones, typically through an incision along the superior pubic ramus. Alternatively, surgery starts at the pubic tubercles, promptly transecting ligaments to

Table 1 - Patients who underwent bladder closure, the surgery performed and the increase in bladder capacity.

№ of patients/sex/age (month) of BC	1 y/o	3 y/o	5 y/o	7 y/o	12 y/o	Results of BNR (3-8y/o outcome	Pubic bones approximation
1/m/8m	11	17	44>	>	162BNR	Continence	-
2/f/30m	0	12>	75/BNR			Continence	-
3/m/10m	10	38	47>	110/BNR		Day continence	-
4/f/85m	0	0	0	BC>	30BA+ECP		-
5/m/7m	22>	70 X	95/BNR			Day continence	-
6/m/13m	0	34>	52>	83/BNR		Day continence	-
7/m/6m	18>	86 X	113/BNR			Partial continence 0.5-1h	-
8/m/8m	15	29>	65/BNR			Partial continence 0,5-1,0-1h	-
9/f/13m>	0	92 X	130/BNR			Day continence	+
10/m/6m>	38>	141 X					+
11/m/36m>	0	>	51>				+
12/m/11m>	6>	33>					+
13/m/14m>	0	80 X					+
14/m/7m	17>						+
15/m/6m>	20>						+

f = female; m - male
> start or continuation of longstanding cholinolytic use X -discontinuation of cholinolytics BC - Bladder Closure
BA = Bladder augmentation
BNR = Bladder Neck Reconstruction

the pubic bones, then accessing the paravesical space via Retzius fat, and separating the BP from fascial layers and peritoneum. These techniques prioritize surgical efficiency and safe mobilization over preserving ligamentous anatomy, obscuring original insertions and interpubic connections before identification. Moreover, fixed formalin specimens apt for detailed dissection are scarce, and post-fixation dissection of fused fibromuscular structures is markedly challenging. Thus, prior studies' failure to note the TIPL likely stems from its routine transection, not its absence.

Though the BP in SNGBP cases is often labeled inelastic or fibrotic, our findings suggest its limited pliability largely results from extrinsic mechanical traction by the TIPL. Full dissection from the detrusor considerably enhanced compliance in all cases, enabling inversion. This implies that reduced elasticity is partly mechanically induced and reversible, not solely due to intrinsic fibrosis.

Near its pubic attachment, the pubovesical (PVL) ligaments join the TIPL at a 70–90-degree angle, while the pubourethral (PUL) ligaments merge slightly more caudally and laterally. Typically, PVL and PUL insert into the posterior pubic ligament (PPL), as supported by studies of the normal pubic symphysis (19, 25, 26). Pieroh et al. (2021) identified the PPL as a distinct ligament reinforcing the pubic periosteum, linking to lateral PVL fibers and receiving PUL terminal insertions. These findings reveal the TIPL, by integrating PVL and PUL, mirrors the PPL's topographical and morphological traits (19), suggesting it may be a persistent or unregressed element of this ligamentous complex in the exstrophic pelvis. Collectively, these observations suggest that the TIPL is a fibromuscular complex that topographically and structurally combines traits of all known pubic ligaments—both anterior and posterior—into a single, previously unrecognized interpubic entity in exstrophy cases.

The widened interpubic space following ligament mobilization and transection highlight its role in maintaining pelvic anatomical stability. Though seemingly paradoxical, this aligns with the 'posterior' designation of the posterior pubic ligament, which pertains to its position relative to the pubic bones, not the bladder. In exstrophy's everted anatomy, this ligamentous structure shifts behind the BP, whereas in normal anatomy, it would reside anterior to the bladder and posterior to the pubic symphysis.

Though fibromuscular like the urogenital diaphragm or pelvic floor, we propose the TIPL as a unique anatomical structure. Pre-inversion, it lies posterior to the BP within the interpubic space, arising from the pubic bone periosteum and extending cranio-medially into the rectus abdominis sheath—unlike the caudal, dorsal orientation of pelvic diaphragm muscles. Histologically, the predominance of smooth muscle bundles indicates a visceral rather than skeletal origin, distinguishing the TIPL from pelvic floor structures such as the voluntary urethral sphincter and the levator ani. We posit that the TIPL is a persistent midline mesenchymal remnant of the anterior abdominal wall, unregressed from embryogenesis, mechanically impeding BP inversion in exstrophy. This sets it apart from the dynamic muscular supports tied to continence in prior studies (27).

Clinical data revealed a mean bladder capacity increase of 17.76 mL/year without anticholinergic therapy, exceeding prior reports (6–14 mL/year) (28, 29). Anticholinergic use further boosted growth. We attribute this to enhanced detrusor compliance post-TIPL dissection and the lack of PB approximation in long-term cohort cases, as bone approximation reduces pelvic volume and may restrict bladder expansion. Closure before age three correlated with normal bladder growth. Eight of ten patients showed rising capacity, facilitating later bladder neck reconstruction with positive outcomes. These findings are promising, given SNGBP patients' complexity within the exstrophy spectrum. Despite low initial capacity, their growth neared normal rates (~18 mL/year vs. ~30 mL/year in healthy children), with minimal surgical complications. One patient underwent delayed bladder closure at age 7, followed by enterocystoplasty at 12 due to insufficient growth, highlighting the limitations of extended observation in SNGBP and the risk of missing optimal functional development windows. This supports early primary closure once mechanical barriers like the TIPL are resolved.

To the best of our knowledge, this is the first documented successful one-stage closure in an SNGBP cohort, a subgroup historically deemed unfit for this ap-

proach. Though small, this rare cohort reflects years of observation of an underexplored population. We identified a novel fibromuscular structure, likely a persistent pubic ligament bundle, previously thought absent in exstrophy. Its smooth muscle fibers suggest an immature phenotype tied to failed pubic fusion and persistent diastasis. The structure's anatomy and location imply incomplete regression of ventral mesenchymal elements during embryogenesis. These insights may extend beyond SNGBP, enhancing understanding of ventral body wall defects and informing surgical and developmental models of lower abdominal wall formation, aligning with recent embryological research on midline fusion complexities (30).

Despite the importance of identifying the TIPL, this study faces limitations. The small sample size limits the findings' generalizability. The extended study duration introduces variability in patient care and compromises data uniformity. Furthermore, incomplete data on TIPL variations across BP sizes hinder confirmation of result universality. MRI visualization of TIPL awaits further validation. While no surgical complications arose from TIPL dissection, its proximity to the detrusor demands precision to avoid impairing BP vascularity. Currently, no publications detail technique modifications for one-stage SNGBP closure, precluding comparisons with our approach.

CONCLUSION

In conclusion, identifying and defining the TIPL as a fibromuscular complex obstructing SNGBP inversion enhance our understanding of exstrophy anatomy. This enables one-stage closure of small bladder plates, fosters bladder growth, and enhances functional outcomes. Further research integrating embryological, morphological, and clinical data is essential to validate this technique's universality and optimize surgical methods. Though small, this cohort represents a rare, clinically significant bladder exstrophy subgroup—patients with small, SNGBP. The condition's scarcity has impeded anatomical study and surgical progress, rendering even modest data impactful. Our findings offer novel anatomical insights that could shape future surgical approaches for this challenging population.

ABBREVIATIONS

BP = Bladder plate
SNGBP = Small non-growing bladder plate
TIPL = Trapezoid Interpubic Ligament
PVL = Pubovesical ligament
PUL = Pubourethral ligament
RAM = Recti abdominis muscles
PB = Pubic bones
SPR = Superior pubic ramus
BC = Bladder Closure
BNR = Bladder Neck Reconstruction

ETHICS APPROVAL

The study protocol was approved by the institutional Research Ethics Board (No. 05/1602). The research was performed in compliance with the research ethics board requirement.

The patients in this manuscript have given written informed consent to publication of their case details.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Nikita V. Demin, PhD
Clinical and Research Institute of
Emergency Pediatric Surgery and Trauma
Bolshaya Polyanka St, 22, Moscow, Russia, 119180
Telephone: +7 903 183-0141
E-mail: urodemin@gmail.com

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Redo Laparoscopic Pyeloplasty in Children: Results from a Multicentric Series

Pedro-Jose Lopez [1,2,3], Alejandro Calvillo-Ramirez [1], Ahmet Sancaktutar [1], Francisca Yankovic [4], Juan Manuel Moldes [1, 2, 5], Juan Pablo Corbetta [6], Luis Garcia-Aparicio [7], Luis H. Braga [8], Francisco Reed [3, 4]

[1] Division of Urology, University Hospitals Rainbow Babies and Children's, Cleveland, OH, USA; [2] Case Western Reserve University, Cleveland, OH, USA; [3] Universidad de Chile, Santiago de Chile, Chile; [4] Hospital Exequiel González Cortes, Santiago de Chile, Chile; [5] Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [6] Hospital de Niños JP Garrahan, Buenos Aires, Argentina; [7] Sant Joan de Deu Hospital, Barcelona, Spain; [8] McMaster Children's Hospital, Hamilton, ON, Canada

ABSTRACT

Purpose: To describe the experience of five training centers with redo laparoscopic pyeloplasty (RLP) in children with restenosis of the uteropelvic junction (UPJ), assessing whether this approach increased or not postoperative complications or surgery failure.

Materials and Methods: A retrospective, descriptive study was conducted, including 19 patients who underwent transperitoneal RLP at five independent training centers across 4 different countries between January 2009 and December 2017. All patients had previously undergone Anderson-Hynes dismembered pyeloplasty. Primary outcomes included postoperative complication rates and redo surgery failure.

Results: There were 19 RLP out of 744 primary laparoscopic pyeloplasties. Median operative time was 150 minutes (interquartile range [IQR] 126.2-180), extended by 19 minutes when colon mobilization was performed. No cases required conversion to open surgery. A median postoperative analgesic requirement and length of stay of 5 and 4 days, respectively, were recorded. No major complications were reported except a single instance of temporary UPJ stenosis, which was managed with a nephrostomy tube and did not require further surgery. After a median follow-up of 17 months, we achieved a 100% success rate. A significant reduction in renal pelvis dilation was noted, with the median anteroposterior diameter (APD) decreasing from 43 mm preoperatively to 17 mm postoperatively (IQR 10–22).

Conclusions: Our findings suggest that RLP remains a feasible approach in the management of restenosis of the UPJ even in such different healthcare settings, providing success rates as high as those described in primary pyeloplasty while maintaining a safety profile.

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Alejandro Calvillo-Ramirez
https://orcid.org/0009-0005-6983-9116

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INTRODUCTION

Ureteropelvic junction obstruction (UPJO) is the most common anatomical cause of hydronephrosis in children (1). Since its first description, laparoscopic pyeloplasty (LP) has become the standard of care for managing ureteropelvic junction obstruction (UPJO) in pediatric patients. Its widespread adoption is driven by significant benefits, including reduced postoperative pain, shorter hospital stays, and improved cosmetic outcomes. Nevertheless, the unique technical challenges in pediatric populations make LP particularly demanding for pediatric urologists (2–7).

LP is reported to have a success rate exceeding 90% (2, 4), however, adverse outcomes such as restenosis can still occur, posing additional management challenges due to potential altered anatomy and scarring at the re-stenosed UPJ. Emerging evidence suggests that redo laparoscopic pyeloplasty (RLP) remains the preferred approach in most cases of restenosis (8, 9), demonstrating a superior efficacy compared to endourological procedures such as endopyelotomy (10). Nevertheless, multicenter studies remain limited and lack detailed data, especially those involving diverse institutional settings and operative techniques.

In this study, we aimed to describe the results obtained across five teaching centers in four countries with RLP for UPJ restenosis, focusing on surgical outcomes. Additionally, we provide insights drawn from the collective expertise of the contributing authors. We hypothesized that the safety and efficacy of RLP in these teaching institutions are as high as what has been reported for primary LP, even when performed in varied healthcare settings (2).

MATERIAL AND METHODS

Patients and Data Collection

In our previous endeavor involving 744 LP in children across 11 participating centers over a 9-year period, 30 patients presented UPJ restenosis, requiring re-operative pyeloplasty (2); 12 were excluded from this study due to incomplete data/inadequate follow-up. Building on that work, this retrospective study focuses on children who underwent RLP. Of these, 18 cases were derived from the original cohort after meeting inclusion criteria, and one additional case involved a child who had undergone open primary pyeloplasty at one of the participating centers, yielding a total of 19 patients for inclusion. Data for this study were provided by five of the initial 11 centers. The protocol (IRB N193/2023) was approved by the ethics committees of all participating centers and data sharing was obtained.

Inclusion criteria were limited to pediatric patients who underwent transperitoneal RLP and had both baseline and postoperative ultrasonography, preoperative dynamic renal scintigraphy (DRS), and a minimum follow-up period of one year. Exclusion criteria included children with incomplete data or follow-up, or a follow-up duration of <1 year.

Recurrent UPJO was diagnosed using ultrasound criteria according to the Society for Fetal Urology (increased APD of the renal pelvis), scintigraphy findings (obstructed drainage curve on DRS), and/or symptomatology presence, primarily colicky pain. These same criteria were used to define redo surgery failure and determine the need for reoperation. Surgical success was defined as a reduction in APD on postoperative ultrasound and throughout the follow-up period, along with resolution of symptoms when present. Additionally, in seven patients where a reduction in hydronephrosis was not initially evident, success was further supported by the improvement in drainage curve on DRS.

Data collected included patients' baseline characteristics, intraoperative parameters, and follow-up information. Baseline characteristics comprised age, sex, weight, preoperative presentation, and ultrasound parameters. For RLP-specific variables, data on primary surgery, the time interval between primary and redo surgeries, and temporizing interventions were recorded. Perioperative data included operative time (OT), operative side, surgeon, drainage, length of stay (LOS), postoperative complications, and surgery failure. Ultrasound

parameters included APD, and differential renal function (DRF) assessed via DRS were also recorded when available. Postoperative complications were classified according to the Clavien-Dindo grading system, with major complications defined as grade ≥3. The primary outcomes were the rate of postoperative complications and redo surgery failure, defined as the requirement for additional redo pyeloplasty based on postoperative obstruction and persistent/worsening hydronephrosis, along with persistent symptoms. The surgical technique employed in RLP has been previously described (11).

Statistical analysis was performed with R V4.4.1 and SPSS V26 software. Descriptive statistics were used to summarize the data. The Kolmogorov-Smirnov test was employed for testing data normality. Due to nonparametric distribution, continuous variables are presented as medians and interquartile ranges (IQR), and between-group comparisons were performed with the Mann-Whitney U test. Categorical variables were expressed as frequencies with percentages, and comparisons between groups were analyzed with the Chi-square test or Fisher's exact test. Additionally, we performed a subgroup analysis incorporating a group of primary pyeloplasty from our previous series. Propensity score-matching (PSM) using the nearest neighborhood method was implemented to account for potential confounders. Therefore, the groups were balanced according to patient's characteristics, namely, age at surgery, preoperative pain and urinary tract infection (UTI), and preoperative APD and DRS. All tests were two-sided, with $p < 0.05$ used to define significance.

RESULTS

Over the 9-year study period, 19 RLPs were performed in 19 renal units, all through a transperitoneal approach. Of these, 18 patients initially underwent LP as primary treatment, while 1 patient was managed with open surgery. The cohort consisted of 14 males (73%) and 5 females (27%), with a median age at RLP of 56 months (32-131), and a median weight of 19.5 kg (12-31). Preoperative imaging showed progressive renal pelvis dilation, with a median APD of 43 mm (27.5-55). DRS revealed obstructed drainage curve patterns in 63% of cases, with a median renal function of 42% (30.5-45.75). The median time interval between PP and RLP was 20 months. Table-1 depicts the baseline characteristics of the studied population.

Fourteen RLP were performed on the left side and 5 on the right. In 8 left-sided cases, the UPJ was accessed through a transmesocolic window (Supplementary Figure-1A), while in the remaining 11 (6 left-sided, 5 right-sided), the colon was mobilized. Anderson-Hynes dismembered pyeloplasty was performed in 18 cases, while one patient required a ureterocalyceal anastomosis, due to excessive scar tissue at UPJ. A percutaneous Hitch stitch was used in 9 cases to stabilize and expose the renal pelvis (Supplementary Figure- 1B). A crossing vessel was identified in 3 patients (16%).

The median OT was 150 minutes (126.2-180), with an additional 19 minutes when colon mobilization was performed. No conversions to open surgery were necessary. Median LOS was 4 days (2-5). All patients received chemoprophylaxis for a median of 4 days (2-30) and analgesics for a median of 5 days (2.5-6).

One complication (Clavien-Dindo IIIb) was observed: temporary stenosis of the UPJ in a single patient, identified by an increased APD of the renal pelvis. This case was managed with a nephrostomy tube (NT), which remained in place for 7 days. No DJ stent was placed in this patient. Kidney function was preserved, and renal pelvis dilation stabilized by the study's conclusion. The patient also developed a postoperative UTI (Clavien-Dindo II), which was successfully managed with antibiotic therapy. No additional complications were reported, and no redo surgery failures occurred in this series.

An external drain was placed in 11 patients (57.8%) to evacuate peri-anastomotic fluid collections, kept in place for a median of 6 days (5-7). Double-J stents were inserted in 17 patients (89.4%) for a median of 8 weeks (6.5-9). Transurethral catheters were used in 18 patients (94.7%) for a median of 4 days (2-5.5).

Table 1. Baseline and perioperative characteristics of the studied population.

Number of patients	19 (100%)
Gender	Male: 14 (73%)
	Female: 5 (27%)
Age (months)	56 (32-131)
Operative side (L/R)	14/5
Preoperative APD (mm)	43 (27.5-55)
Preoperative DRF	42 (30.5-45.7)
Follow-up (months)	19 (12-78)
Operative time (min)	150 (126.2-180)
Length of stay (days)	4 (2-5)
Length of analgesic requirement (days)	5 (2.5-6)
Duration of chemoprophylaxis (days)	4 (2-30)
External drainage (%)	11 (57.8%)
Double-J stent (%)	17 (89.4%)
Major complications (%)	1 (5.2%)
Success (%)	19 (100%)
Postoperative DRS (%)	7 (36.8%)
Postoperative DRF[a]	40 (17-48)
Postoperative APD (mm)	17 (10-22.2)

Categorical data expressed as number of events (%)
Continuous data expressed as median with interquartile range (IQR)
APD = anteroposterior diameter; DRF = differential renal function; DRS = dynamic renal scintigraphy.
[a]Abstracted from seven patients.

With a median follow-up post-RLP of 17 months (12-86), 94.7% of patients had uneventful outcomes (1 case needed a NT). A significant reduction in renal pelvis dilation was noted, with the median APD decreasing from 43 mm preoperatively to 17 mm postoperatively (10-22). Postoperative DRS was performed in 7 patients, demonstrating improved drainage curves. Relative kidney function remained stable, with a postoperative median renal function of 40% (17-48%). Patient-level APD and DRF changes are displayed in Figure-1.

Subgroup analysis comparing primary LP vs. RLP

Before PSM, the primary LP (PLP) group included 393 patients, while the RLP group comprised 19 patients (Table-2). Patients in the PLP group had an older median age compared to those in the RLP group (73 months vs. 56 months; p=0.005). Preoperative pain and UTI significantly differed between groups, both more common in the RLP group. RLP patients demonstrated a greater increase in preoperative APD (p=0.001) and a slightly lower DRF based on DRS results (p=0.004).

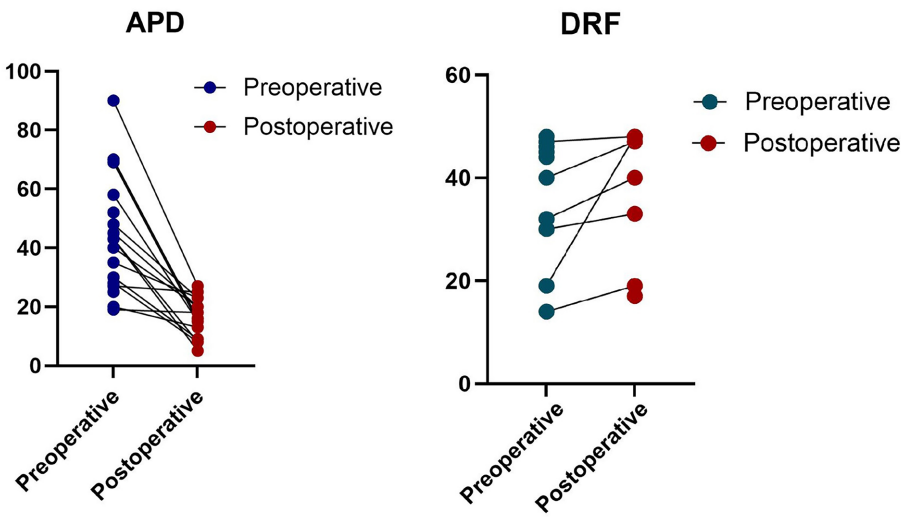
Among patients who received a DJ stent, the median time to stent removal was significantly longer in the RLP group (8 weeks vs. 4 weeks; p=0.0001). Major complications were also more frequently observed in the RLP group (p=0.001).

Following PSM, both groups were balanced with 19 individuals each. Preoperative DRF remained slightly lower in the RLP group (p=0.02), as did the longer median time to stent removal (0.03). However, no significant differences were observed in age, pre- and postoperative APD, or major complications between the two groups.

DISCUSSION

In the present study, 19 patients with UPJ restenosis were managed with RLP. After a median follow-up of 17 months, only one postoperative complication was observed, and no cases of redo surgery failure were reported, yielding a 100% success rate. Previous studies on RLP in children similarly reported high success rates and low complication rates. For instance, a 22-patient series documented a 91% success rate with minimal complications (12), while Li et al. reported no surgical failures in their 10-case series, despite three postoperative complications (13). These findings align with the current study, which demonstrated no instances of redo surgery failure and fewer postoperative complications. Furthermore, we observed similar

Figure 1 - Patient-level APD and DRF changes.



results to those reported for conventional pyeloplasty, whether performed using minimally invasive surgery (MIS) or open techniques (2-8, 14, 15).

MIS has gained significant traction in pediatric urology, facilitated by advancements in instrumentation and growing expertise across training centers. For instance, the da Vinci Single Port platform has been increasingly adopted recently, with emerging evidence supporting its use in the management of UPJO (16). Despite these advances, up to 10% of patients undergoing primary pyeloplasty experience anastomotic restenosis, representing an ongoing clinical challenge (17). Both laparoscopic and robotic approaches have shown promising outcomes in the redo setting, with reported success rates exceeding 80% (12,18-20). In contrast, primary balloon endopyelotomy has shown approximately a 65% success rate, which is lower than that of RLP, particularly in patients with complete failure of the initial anastomosis (21).

As laparoscopic technology becomes more affordable and accessible, the adoption of this technique has become feasible even in resource-limited settings, unlike robotic surgery, which remains cost-prohibitive in many regions (2). Laparoscopy thus represents a viable option for managing failed primary pyeloplasties, offering the advantages of MIS at a lower overall cost.

Achieving success in both primary and redo pyeloplasty requires attention to several key technical considerations. We highlight the importance of adequate tissue irrigation and meticulous dissection down to healthy tissue. In cases where this is not feasible, ureterocalyceal anastomosis serves as a viable alternative (19), as in one case of this series. It should be noted that no matter how thin the renal parenchyma is, bleeding from this technique can complicate the anastomosis, necessitating aspiration via a fourth trocar/trocar-less approach. Watertight suture and tension-free anastomosis are other crucial aspects for a successful RLP, even though these may be more challenging to achieve in a redo setting (13, 22). One advantage of performing this suture laparoscopically is the enhanced visualization provided, ensuring tight closure and improved anchoring.

Colon mobilization plays a crucial role in identifying possible aberrant vessels that may have been missed during previous surgery, as observed in 16% of our population. In redo pyeloplasty, significant fibrosis is often encountered at the UPJ. We stress that colon mobilization improves the surgical field

Table 1. Baseline and perioperative characteristics of the studied population.

	Before PSM			After PSM		
	PLP (n = 393)	RLP (n = 19)	P value	PLP (n = 19)	RLP (n = 19)	P value
Gender (M/F)	265/128	14/5	0.75	13/6	14/5	0.72
Age (months)	73 (23-130)	56 (32-131)	0.005	99 (39-144)	56 (32-131)	0.57
Weight (kg)	19.5 (10.5-36.4)	19.5 (12-31)	0.98	22 (18-45.4)	19.5 (12-31)	0.20
Preoperative pain (Y/N)	168/225	10/3	0.0001	14/5	10/3	0.83
Preoperative UTI (Y/N)	79/314	3/13	0.0001	4/15	3/13	0.86
Preoperative APD (mm)	27 (21-36)	43 (27.5-55)	0.001	34 (26.7-37.7)	43 (27.5-55)	0.10
Preoperative DRF (%)	48 (40-51.4)	42 (30.5-45.7)	0.004	48.5 (38.5-51)	42 (30.5-45.7)	0.02
Side (L/R)	255/138	14/5	0.59	11/8	14/5	0.30
Crossing vessel (Y/N)	106/287	3/15	0.33	8/11	3/15	0.09
Operative time (min)	180 (135-210)	150 (126.2-180)	0.22	165 (120-210)	150 (126.2-180)	0.53
Double-J stent (Y/N)	354/39	17/2	0.93	18/1	17/2	0.54
Duration of stent (weeks)	4 (4-6)	8 (6.5-9)	0.0001	5.5 (4-8)	8 (6.5-9)	0.03
Analgesic duration (days)	3 (2-4)	5 (2.5-6)	0.008	3 (2-4)	5 (2.5-6)	0.11
LOS (days)	2 (2-3)	4 (2-5)	0.25	3 (2-4)	4 (2-5)	0.53
Postoperative APD (mm)	13 (6-21)	17 (10-22.2)	0.20	13 (7.7-34.5)	17 (10-22.2)	0.69
Postoperative pain (Y/N)	8/308	3/12	0.0001	0/14	3/12	0.07
Postoperative UTI (Y/N)	4/386	1/16	0.07	1/16	1/16	1.00
Overall complications (Y/N)	4/161	1/15	0.49	1/11	1/15	0.78
Minor complications (Y/N)	4/161	0/16	0.52	1/11	0/16	0.21
Major complications (Y/N)	0/165	1/15	0.001	0/11	1/15	0.39

APD: anteroposterior diameter; DRS: dynamic renal scintigraphy; LOS: length of stay; PLP: primary laparoscopic pyeloplasty; PSM: propensity score-matching; RLP: redo laparoscopic pyeloplasty; UTI: urinary tract infection.

and facilitates the procedure by allowing dissection to begin from healthy ureteral tissue, facilitating the procedure, even though almost half of the left-sided RLP in this series (n=8) could be performed transmesocolically.

One recognized limitation of laparoscopy is the longer OT. However, it has been shown that OT decreases with experience as surgeons move beyond the learning curve (19,22,23). All centers included in this study are teaching institutions with considerable expertise in MIS, where LP is a standard practice. This might explain our median OT of 150 minutes. Interestingly, the OT observed in this study is shorter than that reported in our initial multicenter series, contrary to initial expectations (2). This could be due to less centers, concentrated cases and better learning curve.

On the other hand, a recent meta-analysis evaluating RLP in children suggested that shorter LOS was influenced by studies conducted in countries where surgeons may be inclined to shorter stays due to cost constraints (20). The 84% of the studied population in the current study was provided by South American institutions, where longer hospital stays may not present the same financial burden as in US or European countries. This cultural and healthcare context may partially explain the longer LOS, rather than patient condition.

The absence of significant bleeding and postoperative UTI in uneventful patients are other aspects that increase the likelihood of a successful RLP. Both factors are known to exacerbate tissue inflammation and increase the risk of secondary fibrosis (15, 21). Indeed, the only patient requiring subsequent management with NT experienced a UTI during the early postoperative period.

The use of DJ stents in urological procedures remains a subject of debate with pyeloplasty not being the exception, though their benefits in providing anastomotic support and preventing edema have been described in the latter (24, 25). In our current work, a DJ stent was placed in 89.4% of cases, a rate similar to the 87% observed in our initial series (2). Despite the widespread use of DJ stents, we observed low rates of UTI and major complications in both our initial and current series.

Our study reinforces previously reported findings on RLP, demonstrating its feasibility and safety in managing UPJO recurrence, with high success rates. However, several limitations must be acknowledged. First, the retrospective and observational nature of the study introduces potential observer bias and confounding. Additionally, a substantial number of patients were excluded due to incomplete data and/or a follow-up duration of <1 year at the time of study inception, which reduced the final sample size, representing a major drawback to our study—though it is important to note that these excluded patients had successful surgical outcomes. This may be further accentuated by the uncommon nature of UPJO recurrence requiring RLP. Although a subgroup analysis comparing PLP and RLP was performed, not all variables were uniformly recorded across patients, limiting statistical power and potentially affecting the robustness of comparisons. Furthermore, the short follow-up period restricted our ability to assess long-term outcomes, thereby limiting the generalizability of our findings to prolonged recovery timelines. Despite these limitations, our study provides valuable insights and further supports the feasibility and effectiveness of RLP, particularly when performed in experienced centers with established expertise in PLP.

CONCLUSIONS

The findings in the current study demonstrate that RLP remains a feasible approach in the management of restenosis of the UPJ, with success rates similar to those reported in PLP, without increasing the risk of complications. Surgeons with enough expertise performing PLP may not be discouraged to pursue this approach whenever UPJ restenosis requires redo surgery. Future research should implement longer follow-ups across larger sample sizes to draw more robust conclusions, especially to consult parents.

ABBREVIATIONS

APD = Anteroposterior diameter
DRF = Differential renal function
DRS = Dynamic renal scintigraphy

LOS = Length of stay
LP = Laparoscopic pyeloplasty
MIS = Minimally invasive surgery
NT = Nephrostomy tube
OT = Operative time
PLP = Primary laparoscopic pyeloplasty
PSM = Propensity score-matching
RLP = Redo laparoscopic pyeloplasty
UPJ = Ureteropelvic junction
UPJO = Ureteropelvic junction obstruction
UTI = Urinary tract infection

CONFLICT OF INTEREST

None declared.

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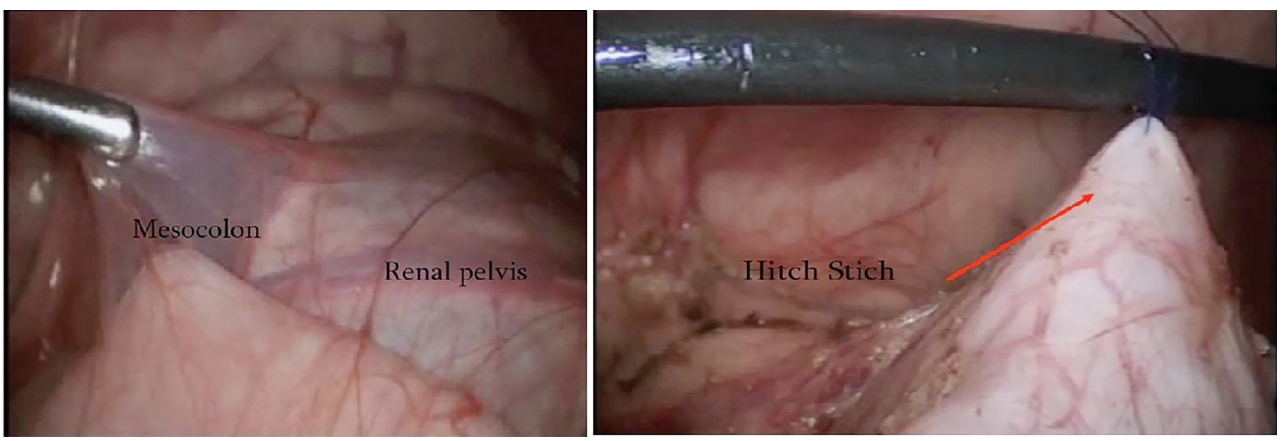
Correspondence address:
Alejandro Calvillo-Ramirez, MD
Division of Urology,
University Hospitals Rainbow Babies and Children's
Euclid Avenue 11100
Cleveland, OH 44106, USA
E-mail: alejandro.calvilloramirez@uhhospitals.org

APPENDIX

Supplementary Figure 1A - Transmesocolic access. **Supplementary Figure 1B - Percutaneous hitch stitch.**



ORIGINAL ARTICLE

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Parasacral Transcutaneous Electrical Nerve Stimulation with Desmopressin Acetate for Treating Primary Monosymptomatic Enuresis: A Randomized Controlled Clinical Trial

Melissa Faria Dutra [1], Eleonora Moreira Lima [1], José Murillo Bastos Netto [2, 3], Lidyanne Ilídia da Silva de Paula [2], José de Bessa Júnior [4], Amanda Lima Alves Pereira [1], Glaúcia Cristina Medeiros Dias [1], Mônica Maria de Almeida Vasconcelos [1], Flávia Cristina de Carvalho Mrad [1]

[1] Departamento de Pediatria Unidade de Nefrologia Pediátrica, Faculdade de Medicina, Hospital das Clínicas, Universidade Federal de Minas Gerais - UFMG, Belo Horizonte, MG, Brasil; [2] Divisão de Urologia, Departamento de Cirurgia, Universidade Federal de Juiz de Fora - UFJF, Juiz de Fora, MG, Brasil; [3] Hospital e Maternidade Therezinha de Jesus da Faculdade de Ciências Médicas e Saúde de Juiz de Fora - HMTJ-SUPREMA, Juiz de Fora, MG, Brasil; [4] Departamento de Urologia, Universidade Estadual de Feira de Santana -UEFS, Feira de Santana, BA, Brasil

ABSTRACT

Purpose: Approximately one-third of the children with primary monosymptomatic enuresis (PMNE) do not respond to first-line treatment. We aimed to investigate the short-term and six-month effectiveness of combining desmopressin acetate with parasacral transcutaneous electrical nerve stimulation (PTENS) in these children and adolescents.

Materials and Methods: Participants aged six–17 years with PMNE were randomly assigned to receive desmopressin acetate with active or sham PTENS. Both groups participated in weekly 30-minute electrotherapy sessions for 15 weeks. The intervention group (IG) received electrotherapy at a frequency of 10 Hz and pulse width of 700 µs. A dry and wet nights calendar assessed the frequency of wet nights in the short term and six months after the intervention ended.

Results: Of 66 participants, 34 were randomized to the IG. The median age was 10.3 years (8.8 – 12), and 53% were male. Intention-to-treat analysis showed a significant reduction in the frequency of wet nights after the interventions ($p < 0.001$) in both groups, with the IG demonstrating significant improvement, immediately after the interventions ($p=0.005$) and after six months ($p<0.001$) compared to the placebo group (PG). The Kaplan-Meier survival analysis showed improvement in the IG that became more pronounced from the 15th week onwards (log-rank test, $p < 0.01$).

Conclusions: A 15-week treatment with desmopressin acetate and PTENS significantly reduced wet nights in children and adolescents with PMNE, and this improvement was maintained six months after the interventions.

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Flavia Cristina de Carvalho Mrad
https://orcid.org/0000-0001-5484-2252

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INTRODUCTION

Primary monosymptomatic enuresis (PMNE) is defined as intermittent urinary incontinence that occurs during sleep in children five years or older. This condition is characterized by at least one episode per month lasting at least three months, with no other lower urinary tract symptoms and no more than six consecutive months of dry periods (1-3). Recent studies have identified 12 protein-coding genes, including PRDM13, S1M1, and EDNRB (4), that play a significant role in the three main mechanisms underlying PMNE: nocturnal polyuria, decreased bladder storage capacity, and an increased excitation threshold in the bladder (1-3).

Children and adolescents with PMNE may experience embarrassment, anxiety, social isolation, and a high risk of bullying as well as physical and emotional abuse. These factors can negatively impact self-esteem and quality of life (5, 6). Effective treatment is crucial. First-line treatment includes enuresis alarms and desmopressin acetate (1-3). Roughly one-third of patients may not respond to these treatments (7). Enuresis alarms have a cure rate of 40% to 70%, but many patients discontinue therapy (8). Desmopressin acetate achieves complete response in one-third of cases but has a 70% relapse rate after discontinuation (9). This highlights the need for more effective and lasting alternatives (10-12), such as parasacral transcutaneous electrical nerve stimulation (PTENS), which shows promise in treating urinary incontinence in children and adolescents (13).

PTENS is a non-invasive technique stimulating the S2 and S3 sensory nerves, potentially activating cortical areas involved in bladder control and promoting neural reconditioning via neuroplasticity (14, 15). A systematic review by Dutra et al. (11) found that PTENS, in three RCTs (16-19), reduced wet nights' frequency in participants with PMNE. However, one RCT reported no significant benefit over controls (19). More high-quality studies are needed to confirm PTENS effectiveness for this condition.

We hypothesize that incorporating PTENS into the treatment of patients with PMNE, who are already using desmopressin acetate, could improve therapeutic outcomes and offer potential short- and long-term benefits. In this context, this study aimed to assess the short-term efficacy and six-month effectiveness of combining PTENS with desmopressin acetate for the treatment of children and adolescents with PMNE.

MATERIALS AND METHODS

Ethical approval

The study was registered in the Brazilian Registry of Clinical Trials (RBR—4dcjfr7) (20) and approved by the Institutional Review Board (IRB) under protocols CAAE 35990620200005149 (position statement number 4,453,428) and CAAE 35990620230015133 (position statement number 5,553,832), respectively. Legal guardians and participants aged 10 and 17 signed the Informed Consent Term and the Assent Term, respectively.

Study Participants

One hundred eight children and adolescents aged six–17 who were diagnosed with PMNE based on the International Children's Continence Society (ICCS) criteria (1-2) were recruited. The participants were from the Multidisciplinary Outpatient Clinic for Children and Adolescents with Enuresis at the university hospitals of the two participating institutions. To be eligible, participants had to attend the clinic once a week, had a final Vancouver Symptom Score < 11 points and have not undergone treatment for enuresis for at least six months before the start of the study (21). Participants who were not included in this study or whose intervention protocols were discontinued were referred for appropriate treatment and evaluation. For socioeconomic status, participants were categorized according to the Brazilian Economic Classification Criteria (22).

Participants on medications affecting the detrusor muscle or external urethral sphincter, those with a pacemaker, polydipsia, untreated attention deficit hyperactivity disorder, severe intellectual disability, central nervous system or spinal cord injuries, and urological malformations were excluded.

Study Design

This randomized, blinded, placebo-controlled clinical trial was conducted from June 2022 to July 2024. The study followed the Consolidated Standards of Reporting Trials (CONSORT) (23) reporting guidelines (Supplement-1).

The randomization process was conducted using Microsoft Excel's RAND function to assign participants to either the placebo group (PG) or intervention group (IG). The results were placed in sealed numbered envelopes to ensure allocation concealment and were distributed to participants during their first appointment. Participants, their families, and study researchers who assessed the interventions outcomes were blinded to participant allocation. Emergency disclosure of allocations was permitted in cases of adverse events, to ensure appropriate therapy.

A detailed medical history and physical examination were performed during the first appointment. All participants underwent renal and bladder ultrasonography, urinalysis, and urine culture.

Participants were instructed to fill out a wet and dry night calendar for 14 days to assess the frequency of enuresis. To determine nocturnal urinary output, participants wore diapers overnight for seven days. The nocturnal urine output was calculated by summing the weight of the diaper (in kg), the volume of the first urination, and the volume of any nocturia episodes. Nocturnal polyuria was defined as a nocturnal urine output that exceeds 130% of the estimated bladder capacity (EBC) (1-3), determined by averaging the largest volumes recorded over seven days (24). The EBC for children aged four–12 years was calculated as 30 × (age in years + 1), whereas it was set at 390 mL for older participants (25). Maximum voided volume was classified as small if it was less than 65% of the EBC and as large if it exceeded 150% of EBC (1).

Participants returned with the requested data completed at least 14 days after the initial appointment. Both eligible groups started the protocol by receiving desmopressin acetate with guidance on its proper use and PTENS therapy (Dualpex 961*Quark@ device). A pulsed, biphasic, and symmetrical current was used in transcutaneous application mode with the following parameters: frequency of 10 Hz, pulse duration of 700μs, maximum but comfortable current amplitude (sensory level) applied for 30 min (26), once a week (27) at the outpatient clinic for 15 weeks. In both groups, a pair of self-adhesive surface electrodes measuring 5 × 5 cm were fixed in the sacral region of S2-S3 and another in the scapular region. In the IG, only the channel positioned in the sacral region was activated, and in the PG only the scapular electrodes. These were turned on briefly for 30 s, after which the current was reduced to zero. In the IG, the pulse amplitude was adjusted if the current sensation decreased.

Participants in the PG and IG received desmopressin acetate at no cost, starting with a daily dose of 0.2 mg. Doses were adjusted according to the ICCS criteria: if participants experienced a reduction of less than 50% on wet nights, they were classified as non-responders. In such cases, the dose was increased by 0.1 mg, up to a maximum of 0.4 mg daily (1, 2). The intervention protocol was discontinued for participants who did not show improvement while receiving the maximum dosage of desmopressin acetate, which was achieved in the 7th session. It is important to highlight that desmopressin acetate should not be administered for longer than four weeks without demonstrating observable efficacy. This approach is crucial to meet our ethical responsibility to discontinue ineffective treatments and prioritize patient safety.

Compliance to desmopressin acetate was assessed by monitoring participants' attendance at scheduled appointments related to other interventions specified in the protocol, as well as analyzing the completion of their diaries. During the reassessments, participants not only provided responses on the answer sheets but were also asked questions about any challenges they encountered regarding the use, dosage, and replacement of desmopressin acetate tablets, as well as any side effects they experienced.

Participants who showed a reduction of 50% or more in the frequency of wet nights continued in

the study protocol, undergoing weekly sessions of PTENS combined with desmopressin acetate until they had completed 15 weeks.

Desmopressin acetate was gradually discontinued from the 12th session, and in the 15th session, all participants completely stopped receiving medication.

The study intervention protocol is presented in Figure-1.

Assessments

The frequency of wet nights was assessed using wet and dry night calendars over 14 days. Participants completed the questionnaire daily, beginning 14 days before treatment, throughout the 16-week interventions, and six months post-interventions.

Treatment outcomes were evaluated according to ICCS criteria (1,2), classifying improvement as no-response (<50% reduction in the frequency of wet nights), partial response (50–99% reduction in the frequency of wet nights), or complete response (100% absence of wet nights). Continued success was defined as the absence of relapse within six months after treatment completion.

Final assessments were conducted at the 16th session and again six months post-intervention. Therefore, the study protocol included a follow-up assessment six months following the completion of treatment. Throughout this period, our team closely monitored the participants, who did not receive any additional treatment.

Participants classified as no-responders after the 7th session were referred to alternative treatment options. Those still considered non-responders by the 16th session remained in the study protocol and underwent a reassessment after six months. If they continued to be categorized as non-responders after this reassessment, they were referred to other treatment options according to the ICCS-based protocol (1) of the multidisciplinary outpatient clinic.

Sample detection power analysis

The sample detection power was calculated by comparing the outcomes of the two groups, PG and IG. In the evaluations conducted during the 16th session and six months after the interventions, we analyzed the reduction in the frequency of wet nights as a continuous variable. The percentage of improvement after the interventions was treated as a categorical variable for our calculations. As a result, the sample detection power ranged from 82.3% for the continuous variable to 78.8% for the categorical variable during the 16th session. Six months after the interventions, the sample detection power increased to 96.3% for the continuous variable and 91.3% for the categorical variable.

Statistical Analysis

The primary analysis was performed on an intention-to-treat basis, including all participants who were randomly assigned. Data from those who discontinued treatment at the 7th week were imputed for the 16th-week and six-month post-intervention analysis.

When comparing the PG and IG, the Mann-Whitney test was used for numerical variables, and the student's t-test was used for age analysis.

Pearson's chi-square test or Fisher's exact test were used to compare categorical variables. The non-parametric Wilcoxon test was used to compare the frequency of wet nights before and after the interventions and during the six-month follow-up.

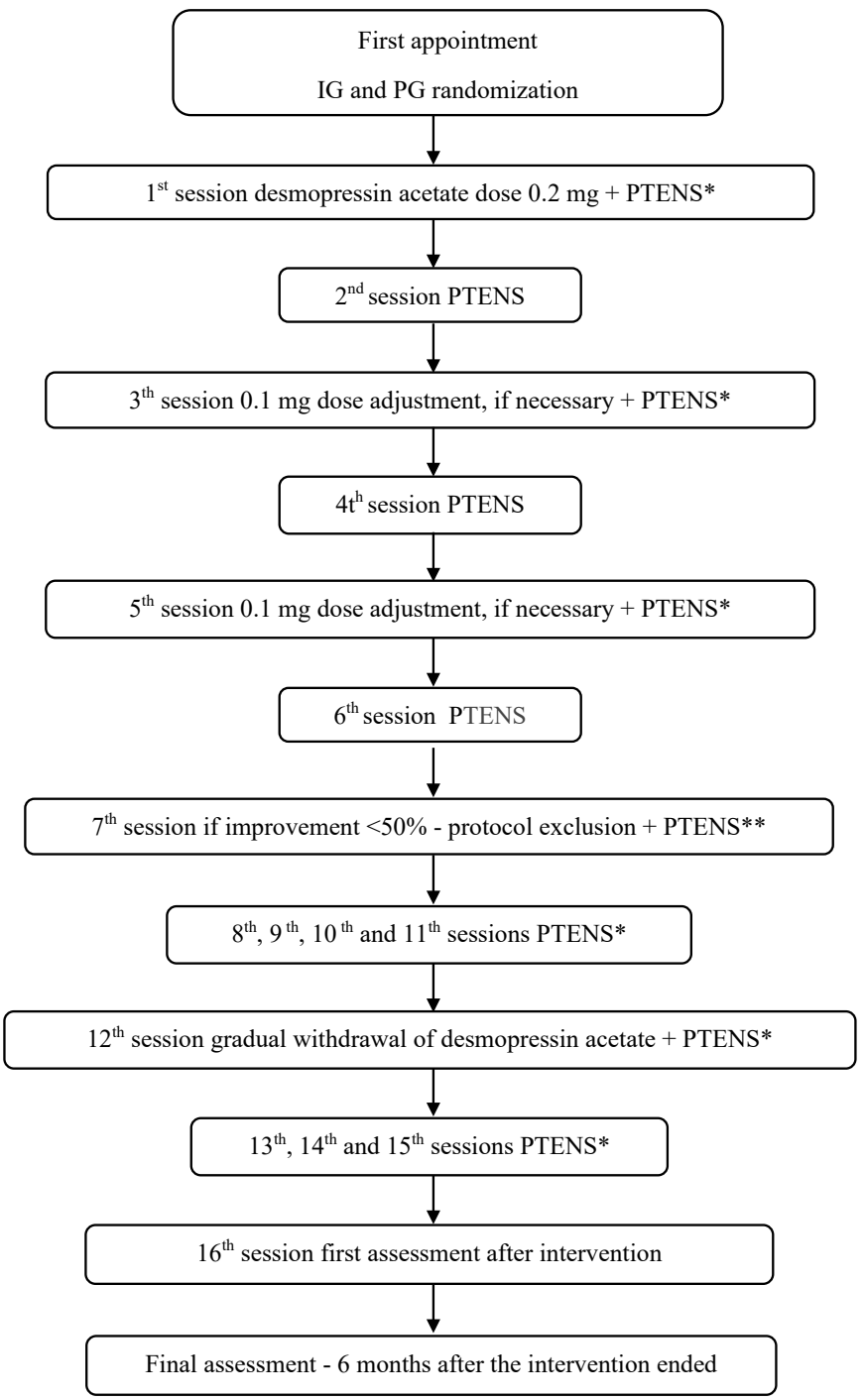
Kaplan-Meier survival analysis was used to evaluate the time until improvement occurred. The 3rd, 5th, 7th,15th was considered time units for analysis. The participants were assessed at the 16th week and at the six-month follow-up. A log-rank test was used to compare PG and IG.

For all analyses, a p-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics (version 21.0; IBM Corp, Armonk, NY, USA). G*Power version 3.1 was utilized to perform power calculations.

RESULTS

Of the 108 participants, 66 were eligible for the study and randomly assigned to 32 in the PG and 34 in the IG. Among the 42 excluded, six had second-

Figure 1 - Flowchart of the intervention protocol.



PG Placebo group, IG Intervention group
*PTENS parasacral transcutaneous electrical nerve stimulation: active PTENS (IG) and placebo PTENS (PG).
**PTENS for participants who continued in the protocol study.

ary enuresis, 12 had non-monosymptomatic enuresis, five had spina bifida, four had severe intellectual disabilities, one had cerebral palsy, and 14 declined to participate.

The baseline characteristics of participants are shown in Table 1. There were no significant differences in socioeconomic status between the groups. Among the participants who started the protocol, 53.1% (17/32) in the PG completed all 15 sessions, compared to 82.4% (28/34) in the IG. All participants who discontinued the protocol did so because they experienced a reduction of less than 50% in the frequency of wet nights by the seventh session; 46.9% (15/ 32) were from the PG. This demonstrated a significant difference compared to 17.6% (6/ 34) from the IG ($p = 0.01$).

Regarding the nocturnal polyuria analysis, there was no significant difference in the reduction of 50% or more in the frequency of wet nights within the groups ($p = 0.23$ for the PG and $p = 0.11$ for the IG) after the interventions. However, there was a significant difference in the proportion of participants who showed improvement between the groups. The PG showed an improvement of 41.1% (7/17), while the IG showed an improvement of 75% (18/24) ($p = 0.02$).

In the comparison between the beginning and after the interventions (16th week), there was a more significant reduction in the frequency of wet nights in IG (= 0.005). (Table 1) The IG showed a 52.7% reduction in the frequency of wet nights, while PG recorded a 27.6 % reduction ($p = 0.006$). (Table 2)

At the six-month follow-up, the IG showed a significant reduction in the frequency of wet nights compared to the PG ($p=0.001$). (Table 1). The IG experienced a decrease in the frequency of wet nights to 61.6%, while the PG demonstrated a reduction of 26.4% ($p=0.001$) (Table-2).

Kaplan-Meier analysis indicated that the frequency of wet nights improved earlier in the IG than in the PG, with a significant difference observed after the 15th week (log-rank test $p< 0.01$) (Figure-2).

In this randomized controlled trial, no adverse side effects were observed.

DISCUSSION

Approximately one-third of patients with PMNE do not respond to first-line treatment (7). Therefore, this study aimed to investigate combination therapy and its potential benefits in managing a common condition in the pediatric population. To our knowledge, this is the first study to combine desmopressin acetate and PTENS under these conditions. After 15 weeks of combined treatment, participants in the IG exhibited a significant decrease in the frequency of wet nights, with an even more significant improvement observed six months after the intervention ended.

In our study, both PG and IG significantly reduced the frequency of wet nights ($p < 0.001$) after the intervention. Similar to our research, two RCTs used PTENS to treat children and adolescents with PMNE. These trials combined PTENS with standard urotherapy and demonstrated a reduction in the frequency of wet nights after interventions, with a statistically significant difference between PG and IG (16, 18). In one of these studies, the IG underwent ten sessions of PTENS treatment, resulting in a reduction of 61.8% compared to 37.3% in the PG (16). The other study using PTENS with 20 sessions, three times a week, showed a progressive decrease in the frequency of wet nights for the IG over 90 days of follow-up (18).

Nonetheless, at the six-month follow-up after the intervention ended, our study found that the IG experienced a 65.5% reduction in the frequency of wet nights. In comparison, the PG showed a 20.6% reduction. This difference was statistically significant ($p= 0.001$). Kaplan-Meier survival analysis revealed that the IG experienced improvement sooner than the PG. This difference was more significant between the 15th week and the six-month follow-up, with a statistically significant variance observed (log-rank test, $p < 0.01$). In a study by Abdelhalim and Ibrahim (17), PTENS and transcutaneous interferential electrical stimulation were compared in participants with PMNE. Both treatments significantly reduced the frequency of wet nights, but transcutaneous interfer-

Table 1 - Baseline characteristics of participants and frequency of wet nights before, after interventions and at six-months follow-up.

	Total sample (n=66)	Placebo (n=32)	Intervention (n=34)	*p*- value
Gender n (%)				
Male	35 (53)	16 (50)	19 (55.9)	**0.63***
Female	31 (47)	16 (50)	15 (44.1)	
Age				
Mean ± SD	10.3 ± 1.9	10.4 ± 1.9	10.2 ± 1.8	**0.87****
Median (P25-P75)	10.3 (8.8 – 12)	10.3 (8.8 – 11.9)	10.3 (8.7 – 11.9)	
Nocturnal Polyuria (NP) n (%)				
No	25 (37.9)	15 (46.9)	10 (29.4)	**0.20*****
Yes	41 (62.1)	17 (53.1)	24 (70.6)	
Percentage of nights with NP				
Mean ± SD	44.4 ± 40.7	43.7 ± 44.4	45.1 ± 37.5	**0.90****
Median (P25-P75)	42.9 (0 – 77.7)	42.9 (0 – 100)	42.9 (0 – 72.3)	
Frequency of wet nights baseline				
Mean ± SD	11.3 ± 2.8	11.1 ± 3.2	11.4 ± 2.4	0.98**
Median (P25 - P75)	12 (10 – 13)	12 (10– 13)	12 (10 – 13)	
Frequency of wet nights after interventions				
Mean ± SD	6.6 ± 4.1	8.1 ± 4.3	5.3 ± 3.5	**0.005****
Median (P25 - P75)	7 (3 – 10)	9 (5 – 11)	4.5 (2 – 8)	
p-value frequency comparison baseline versus after interventions	<0.001****	<0.001****	<0.001****	
Frequency of wet nights at six-months follow-up				
Mean ± SD	6.0 ± 4.4	8.0 ± 4.3	4.1 ± 3.7	**<0.001****
Median (P25-P75)	6 (2 – 10)	9.5 (4.5 – 11)	3.5 (0.7 – 6.5)	
p-value frequency comparison after interventions versus at six-months follow-up	**0.003******	0.824*****	**0.008******	

P25 = Percentile 25; P75 = Percentile 75; SD = Standard Deviation; NP = nocturnal polyuri

* Chi-square test; ** Mann-Whitney test; ***Fisher's exact test; ****Wilcoxon test; p-value < 0.05.

Table 2 - Percentage improvement in the frequency of wet nights after interventions and at six-months of follow-up.

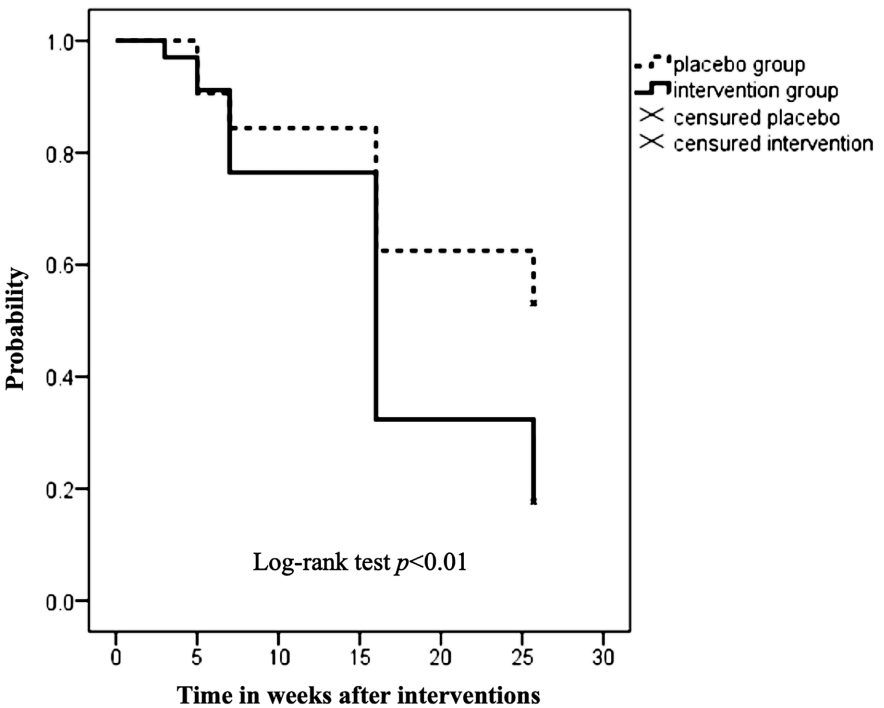
	Total sample (n=66)	Placebo (n=32)	Intervention (n=34)	*p*-value
Reduction of the frequency of wet nights after interventions (%)				
Mean ± SD	40.5 ± 36.7	27.6 ± 36.9	52.7 ± 32.5	**0.006****
Median (P25 - P75)	42.9 (0 – 71.7)	21.5 (0 – 50)	59.4 (24.5 – 78.3)	
Response after interventions n (%)				
No-response	34 (51.5)	22 (68.8)	12 (35.3)	
Partial + complete response	32 (48.5)	10 (31.3)	22 (64.7)	**0.007*****
Partial response	26 (39.4)	7 (21.9)	19 (55.9)	
Complete response	6 (9.1)	3 (9.4)	3 (8.8)	
Reduction of the frequency of wet nights at six-months of follow-up (%)				
Mean ± SD	44.6 ± 41.2	26.4 ± 39.2	61.6 ± 35.8	0.001**
Median (P25 - P75)	45.5 (0 – 83.3)	20.6 (0 – 55.4)	65.5 (25 – 64.6)	
Response at six-months of follow-up n (%)				
No-response	34 (51.5)	23 (71.9)	11 (32.4)	**0.001*****
Partial + complete response	32 (48.5)	9 (28.1)	23 (67.6)	
Partial response	21 (31.8)	6 (18.8)	15 (44.1)	
Complete response	11 (16.7)	3 (9.4)	8 (23.5)	
p-value comparison after intervention versus at six-months of follow-up	0.08*	0.999*	**0.019***	

P 25 = Percentile 25; P75 = Percentile 75; SD = Standard Deviation
*Wilcoxon test; **Mann-Whitney test; ***Fisher's exact test; *p*-value <0.05

ential electrical stimulation provided longer-lasting short-term results than PTENS. Lordelo et al. (26) and Veiga et al. (28) demonstrated the effectiveness of PTENS in long-term follow-up in children with overactive bladder and with non-monosymptomatic enuresis respectively. Borch et al. (29) found no immediate effect on urodynamic parameters during the use of PTENS. However, after four weeks of treatment with PTENS at home, 61% of the participants showed a significant improvement in urinary incontinence. These results suggest that PTENS can affect urinary control by neuromodulation of brain areas. A study by Netto et al. indicated that PTENS significantly impacts the central nervous system. Magnetic resonance imaging confirmed increased connectivity between the anterior cingulate and dorsolateral prefrontal cortex, possibly influencing autonomic balance for bladder control. Thus, when combined with desmopressin, the modalities would have a complementary effect (30).

The frequency of PTENS sessions was a critical factor in our study. Currently, we are in the

Figure 2- Kaplan-Meier survival analysis estimates the weeks until the frequency of wet nights decreases in the six months following the interventions



process of defining the most effective treatment protocol. Our study used a once-a-week session frequency based on the study's findings by De Paula et al. (27). In this randomized controlled trial, children with overactive bladder and enuresis showed significant improvement in urinary urgency and enuresis in the evaluation conducted 60 days after the end of treatment (p=0.03). These data suggest that weekly sessions of PTENS may be sufficient to achieve the desired results (27). This is an important point given the difficulty of finding time for physiotherapy sessions in parents' busy routines. Similarly, Veiga et al. (28) conducted a study in children with overactive bladder, comparing the effects of PTENS treatment administered twice a week in one group and three times a week in another group. The results showed no significant differences in symptom improvement between the two groups (28).

Individualizing PMNE treatment may improve overall efficacy and outcomes, considering its multifaceted characteristics (31). This study demonstrated a new therapeutic option for those who do not respond to desmopressin acetate alone. Results show that combining desmopressin with weekly sessions PTENS significantly reduced wet nights both in the short term and six months after the end of interventions, showing a sustained therapeutic response compared to the PG.

Despite promising results, this study has limitations. Future research should use neuroimaging and neuropsychological assessments to clarify PTENS-related neural changes. Optimizing PTENS parameters (frequency, duration, intensity) and evaluating long-term effects, including maintenance sessions, could further refine treatment strategies.

CONCLUSIONS

After 15 weeks of treatment, a combination of desmopressin and weekly PTENS reduced the frequency of wet nights in children and adolescents with PMNE. This improvement was sustained for six months following the completion of the interventions.

ABBREVIATIONS

CONSORT= Consolidated Standards of Reporting Trials
ICCS = International Children's Continence Society
IG = Intervention group
PG= Placebo group
PMNE = Primary monosymptomatic enuresis
PTENS = Parasacral transcutaneous electrical nerve stimulation
RCTs-Randomized and controlled clinical trials

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DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author. Data will be made available upon request.

COMPLIANCE WITH ETICAL STANDARDS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Legal guardians signed the Informed Consent Form, while participants aged 10–17 years signed the informed consent form.

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CONFLICT OF INTEREST

None declared.

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Correspondence address:
Flávia Cristina de Carvalho Mrad, MD
Faculdade de Medicina - Departamento de Pediatria
Unidade de Nefrologia Pediátrica - Hospital das Clínicas,
Universidade Federal de Minas Gerais – UFMG
Avenida Alfredo Balena 190. sala 267, Santa Efigênia,
Belo Horizonte, MG, 30130-100, Brasil.
E-mail: flaviacarvalhomrad@gmail. com

APPENDIX

Supplement 1. Consolidated Standards of Reporting Trials (CONSORT) checklist (23)

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2
	2b	Specific objectives or hypotheses	2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	2,3
	4b	Settings and locations where the data were collected	2,3
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	3,4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	5
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	3
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	3
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	3
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	3
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	3
	11b	If relevant, description of the similarity of interventions	3,4

Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	5
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	5
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	6
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 1,2 Figures 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	6
Harms	19	All important harms or unintended effects in each group	6
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	8
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	7,8
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	7,8
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	Not applicable
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	13

ORIGINAL ARTICLE

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Arterial Embolization versus Robotic Partial Nephrectomy for the Treatment of Renal Angiomyolipomas

Idir Ouzaid [1], Pierre-Etienne Gabriel [1], Byron Lee [2], Gauthier Delporte [3], Philippe Puech [4], Laurent Lemaitre [4], Evanguelos Xylinas [1], Arnauld Villers [3], Georges-Pascal Haber [2]

[1] Department of Urology, Bichat Claude Bernard Hospital, Paris University, Paris, France; [2] Glickman Urological and Kidney Institute, Cleveland Clinic, Ohio; [3] Department of Urology, CHU de Lille, Lille, France; [4] Department of Radiology, CHU de Lille, Lille, France

ABSTRACT

Objective: To compare the outcomes of robotic-assisted partial nephrectomy (RALPN) and selective arterial embolization (SAE) for the treatment of sporadic renal angiomyolipoma (AML).

Patients and methods: The outcomes of patients who were managed by RALPN (n = 191) or SAE (n = 51) for sporadic renal AML were matched (2:1) using a propensity score for analyses. The primary endpoint was therapeutic success defined as the absence of secondary treatment. Secondary endpoints were post-operative complications and renal function preservation (loss of eGFR at 6 months). Univariate and multivariate logistic regression analyses were used to predict factors associated with re-intervention.

Results: Patients baseline characteristics in the matched population (RALP, n=96 vs. SAE, n=48) were balanced. LOS was shorter (mean: 4.2 vs. 3.1 days; p = 0.004) and EBL was lower (327 mL vs. 0 mL, p < 0.0001) in the SAE group. Overall (PN: 15.2% vs. AES: 11.7% p = 0.09) and Clavien-Dindo stratified (p = 0.62) complications were similar in both groups. After a comparable mean follow-up time (33 vs. 40 months, p = 0.63), there was an overall mean loss of eGFR of 7.7±26 mL/min/1.73m2 (p = 0.001). This loss was similar between the two groups (PN: 6.87±26 vs. AES: 11.56±23, p = 0.36). After adjusting for identified confounding factors including tumor size, type of primary intervention (RALPN vs SAE) was the only predictive factor for secondary intervention.

Conclusion: RALPN was associated with decreased need for secondary treatment with no increase in morbidity compared with SAE.

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Pierre-Etienne Gabriel
https://orcid.org/0009-0000-5263-1398

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INTRODUCTION

Renal angiomyolipomas (AML) are benign tumors of the kidney that account for approximately 3% of all renal tumors (1, 2). Smooth muscle, aneurismal vessels, and adipose tissue are three pathological components that define AML (3). Eighty percent of AML are sporadic and 20% are associated with a genetic syndrome such as tuberous sclerosis complex (4). Although most AML are detected incidentally, patients can present with flank pain, recurrent gross hematuria, and life-threatening retroperitoneal hemorrhage (5).

Active surveillance (AS) is the management choice for most asymptomatic patients with AML, but over half of patients will ultimately undergo active treatment (6, 7). For most patients, nephron sparing approaches such as partial nephrectomy (PN) and selective arterial embolization (SAE) are the most used options (8, 9).

Historically, SAE was associated with fewer post-procedural complications and improved preservation of renal function compared with PN. However, SAE also required more secondary procedures compared with PN (10). Recent advances in robot-assisted PN (RALPN) technique have resulted in improved peri-operative outcomes compared with historical series (11, 12).

Thus, our study aimed to examine the outcomes of SAE and RALPN in the management of a contemporary cohort of patients with sporadic renal AML.

PATIENTS AND METHODS

Patients and study design

A multi-institutional (n=3), institutional review board (IRB-20-836)-approved database was queried to identify patients who were diagnosed with a sporadic renal AML and primarily treated with RALPN (n = 191) or SAE (n = 51). Diagnosis of AML required a clearly identifiable fat component on CT (13). Patients diagnosed with Tuberous Sclerosis Complex (TSC) syndrome and concomitant or past contralateral kidney disease (cyst, RCC) were excluded from the analyses. AML presented with life-threatening and/or active hemorrhage were excluded from the analysis. Given the retrospective aspect of the study design, individual informed consent was waived.

Baseline characteristics including age, gender, tumor size, and chronic kidney disease (CKD) stage were retrieved. Operative complications, estimated blood loss, length of stay, 90-d postoperative complications according to the Clavien-Dindo classification were also recorded. During follow-up, secondary procedures were triggered upon physician opinion according to patient's symptoms and tumor evolution.

Hypotheses and endpoints

We hypothesize that RALPN is associated with a decreased need for secondary treatment, without an increase in morbidity compared to SAE.

The primary endpoint was therapeutic success defined as the absence of secondary procedures for the same AML. Secondary endpoints were postoperative complications and estimated glomerular filtration rate (eGFR) 6 months after the intervention.

Statistical analysis

Differences between patients undergoing RALPN and those undergoing SAE were compared using the Chi-square or Fisher exact tests for categorical variables (presented as proportions) and student t-test or Wilcoxon rank sum test for continuous variables (presented as mean ± standard deviation, SD). Univariate and a multivariate cox regression model were used to predict risk factors for re-intervention.

Since patients were not randomly assigned to either surgical approach, treatment effect estimates are biased if selection biases were left unadjusted. Propensity score and matching techniques have been used to remove bias of measured variables and optimize unbiased estimate of treatment effects. Maximum balance between multivariate covariates were achieved at baseline where a genetic search algorithm was used to determine the optimal weight of each covariate (14). A 2:1 matching method was used with no replacement. Using this algorithm, we were able to match 48 patients who underwent SAE to 96 unique control patients (RALPN group). Statistical analysis was performed using R 3.0.0

(www.r-project.org) and p-values were two-sided and statistical significance was defined as a p<0.05.

RESULTS

Baseline characteristics of the patients included in the study

Baseline characteristics of the treatment groups are summarized in Table-1. Patients who underwent SAE were younger (40 vs 52 years, p < 0.0001) and were more likely to have multiple (37% vs 15%, p < 0.001), larger (6.4 vs 4.6 cm, p < 0.0001), and more symptomatic (flank pain: 41% vs. 14%, p < 0.001) tumors.

The propensity score matching resulted in 48 (SAE) and 96 (RALPN) patients' groups with similar baseline characteristics allowing the comparison of their respective outcomes (Table-1).

Perioperative outcomes according to the type of treatment in the matched population

Patients who underwent SAE had shorter hospital stay (3.1 days vs 4.2 days, p = 0.006) compared with patients who underwent RALPN (Table-2). SAE was also associated with lower blood loss than RALPN. However, overall complications rates were not significantly different between RALPN and SAE

Table 1 - Baseline characteristics of the study population before and after matching.

	Before propensity score			After propensity score		
	RALPN	SAE	p	RALPN	SAE	p
	n = 191	n = 52		n = 96	n = 48	
Age, years, mean±SD	52±14	40±14	<0.0001	42±5	41±6	0.28
Gender, n (%)						
Female	148 (78%)	45 (88%)	0.09	78 (81%)	43 (89%)	0.19
Male	43 (22%)	6 (12%)		18 (19%)	5 (11%)	
BMI, kg/m^2, mean±SD	28 ± 8	25 ± 6	0.515	27 ± 6	25 ± 4	0.38
Side, n (%)						
Right	90 (47%)	20 (38%)		44 (46%)	20 (42%)	0.2
Left	97 (51%)	24 (46%)	0.7354	50 (52%)	24 (50%)	
Bilateral	4 (2%)	8 (16%)		2 (2%)	4 (8%)	
Tumor size, cm, mean±SD	4.6 ± 4.1	6.4 ± 3.2	<0.006	5.3 ± 3.1	5.9 ± 2.9	0.26
Symptoms, n (%)						
Incidentalomas	114 (59%)	14 (27%)		42 (51%)	15 (31%)	
Flank pain	36 (19%)	25 (49%)		36 (37%)	24 (50%)	
Hematuria	26 (14%)	6 (12%)	<0.01	10 (10%)	5 (10%)	0.48
Retroperitoneal hematoma	15 (8%)	6 (12%)		8 (10%)	4 (9%)	
Number of tumors, n (%)						
1	131 (68%)	24 (46%)	<0.001	49 (68%)	22 (46%)	
2	21 (11%)	9 (17%)		18 (11%)	9 (17%)	0.79
Multiples	29 (15%)	19 (37%)		29 (15%)	17 (37%)	
eGFR, mL/min/1.73m^2, mean ± SD	92 ± 27	100 ± 37	0.098	92 ± 24	96 ± 2.9	0.032

RALPN = Robot-assisted laparoscopic partial nephrectomy; SAE = Selective arterial embolization; eGFR = estimated glomerular filtration rate

Table 2 - Perioperative outcomes of RALPN and SAE in the treatment of renal AML.

	RALPN	SAE	p
	n = 96	n = 48	
Hospital stays, days, mean± SD	4.19 ± 1.65	3.14 ± 3.49	**0.006**
Blood loss, mL, mean± SD	327 ± 436	-	**<0.0001**
Overall complications, n (%)	14 (14.5%)	6 (12.5%)	0.09
Postoperative complications, n (%)			
Minor (1-2)	10 (10.4%)	4 (8.3%)	0.62
Major (3-5)	4 (4.1%)	2 (4.1%)	
Postoperative eGFR, mL/min/1,73m^2, mean±SD	84 ± 30	87 ± 30	0.06

RALPN = Robot-assisted laparoscopic partial nephrectomy; SAE = Selective arterial embolization; eGFR = estimated glomerular filtration rate

(15.2% vs. 11.7%, p = 0.09). Clavien-Dindo minor (Grade 1-2) and major (Grade 3-4) complication rates in the two groups and did not find any statistically significant difference as well (p = 0.62).

Reintervention outcomes in the matched population

After median follow-up of 33 months (IQR: 6-229) and 40 months (IQR: 6-173) (p=0.63), 4 (4.1%) and 14 (29.1%) patients underwent a secondary treatment in the RALPN and SAE group, respectively. Secondary treatments in the RALPN group included repeat PN (n=2) radical nephrectomy (n=1), and cryoablation (n=1) for tumor recurrence. Mean tumor size in the failed RALPN group was 6.5 cm (range: 4,5-7.7 cm). In the SAE group, secondary treatments included repeat SAE in (n=12) and RALPN (n=2). Mean tumor size in the failed SAE group was 6 cm (range: 4-8).

Renal function preservation in the matched population

During follow-up, overall mean loss of eGFR was 7.7±26 mL/min/1.73m^2 after any intervention. This loss was similar between the two groups (RALPN: 6.87±26 vs. SAE: 11.56±23, p = 0.36).

Predictors of reintervention in the matched population

In the univariable analysis, patient age, tumor size, tumor number, and treatment type were associated with secondary treatment. However, after adjusting for confounding factors, the multivariable logistic regression model showed that the primary treatment type (RALPN versus SAE) was the only significant factor associated with secondary treatment (Table-3). Patients primarily treated with SAE were more likely to undergo a secondary procedure during follow-up (RALPN versus SAE: HR :0.16; 95%CI: 0.05-0.55; p = 0.003).

DISCUSSION

Given the benign nature of this disease, AS is the management of choice for AML. However, symptomatic AML may necessitate active treatment, especially in the case of life-threatening retroperitoneal hemorrhage (15, 16). Surgery and SAE are used in respectively in 31% and 17% of the cases (16). Contemporary studies comparing peri-procedural, tumor control, and functional outcomes between surgery and SAE in AML management are lacking, with all studies published more than a decade ago (17-19). Since then, there have been significant advances in both interventional radiology and surgical techniques. Herein, we report a retrospective study comparing RALPN and SAE. To the best of our knowledge, this is the first and largest series to be specifically designed for this purpose in the modern era of robotic assisted surgery.

Table 3 - Univariate and multivariate analyses exploring predictive factors of reintervention.

Variables	Univariate analyses		Multivariate analyses	
	HR (CI 95%)	p	HR (CI 95%)	p
Age	0.98 (0.93-0.98)	0.005	0.98 (0.95-1.02)	0.405
Tumor size	1.10 (1.01-1.19)	0.02	1.04 (0.93-1.16)	0.404
Symptoms (Yes vs. No)	1.09 (0.87-4.45)	0.13	1.76 (0.61-5.05)	0.550
Number of tumors (multiple vs. unique)	4.04 (1.70-9.63)	0.002	1.70 (0.62-4.63)	0.291
Treatment type (RALPN vs. SAE)	0.11 (0.04-0.29)	<0.0001	0.16 (0.05-0.55)	0.003

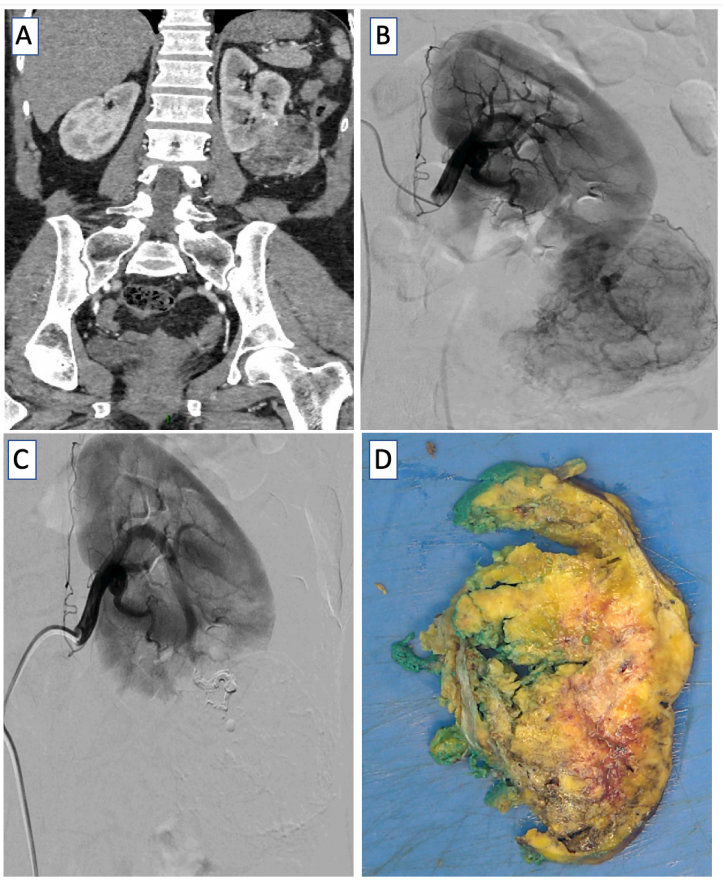
RALPN = Robot-assisted laparoscopic partial nephrectomy; SAE = Selective arterial embolization

Our findings suggest the superiority of the surgical approach with respect to tumor control. Over a comparable follow-up period, SAE was associated with a failure rate of 29.1% while less than 5% of patients undergoing RALPN required repeat intervention. These findings are consistent with historical comparative studies examining effectiveness of SAE and RALPN in tumor control (17-19) . Peri-procedural complications were rare in both modalities; and when they did occur, most were minor (Clavien-Dindo 1-2). Importantly, renal function was well-preserved, and there was no significant difference in post-procedural eGFR between SAE and RALPN (10).

The management of sporadic renal AML depends on clinical presentation, and there is a role for both SAE and RALPN. The main criteria that drive decision making are the presence of major or life-threatening symptoms and radiologic characteristics (size, location, number). For example, SAE is often used in cases with retroperitoneal hemorrhage, multiple, or large tumors. In these cases, SAE offers a relatively rapid and safe approach for temporization in an urgent setting, but it is important to note that even after an ablative procedure, RALPN should be considered a viable definitive treatment (20). In fact, secondary bleeding or tumor growth occurred more frequently in the follow up period, which necessitated definitive treatment either with repeat SAE or surgery. On the other hand, our data suggest that RALPN would be preferred in situations where lack of immediacy does not lead to adverse clinical outcomes. We showed that modern RALPN technique is safe, effective, and resulted in good preservation of renal function (21).

The diagnosis of renal AML is based on axial imaging and uncomplicated in most cases. Sometimes, fat-poor AMLs are encountered, which may warrant further investigation (e.g. renal mass biopsy) to rule out renal cell carcinoma or epithelioid AML that may require extirpation (22). Nonetheless, most AML can be managed with active surveillance, and the traditional 4-cm cut-off alone should not trigger active treatment (16, 23). During active surveillance, changes in tumor growth kinetics, symptoms, and patient preference can serve as triggers for intervention. For those who require treatment, the presence of life-threatening hemorrhage should be managed with SAE before definitive treatment with excision. In the absence of the active bleeding, and given the failure rate up to 30% of the cases, we recommend upfront nephron sparing surgery (NSS) (15). During surgical planning, if unacceptable blood loss and/or prolonged warm ischemia time (>25-30 min) are anticipated, one option would be to employ a combined approach with pre-operative SAE followed by RALPN. This approach minimizes warm ischemia time, allows maximum parenchymal preservation, and decreases need for repeat intervention (Figure-1) (24).

Figure 1 - Combined approach for a 8 cm symptomatic AML.



The CT scan (A) shows a distinct fat component (-63 HU). Pre-embolization (B) and post-embolization angiography (C) before off-clamp robotic assisted laparoscopic partial nephrectomy with an estimated blood loss <100mL. Pathology revealed a typical renal AML staining positive for HMB45 (Human Antibody 45), Melan A (Melanoma A), and MSA (Muscle Specific Actin).

Our study is limited by its retrospective design and resulting selection bias. Specifically, SAE was more frequently used than RALPN in symptomatic patients and those with larger tumors. To minimize this bias, we adjusted our analyses for all available and measured confounding factors, and differences using a propensity score strategies. Secondly, the study period in the SAE group spanned longer than the RALPN group, and earlier SAE procedures may have benefited from advances in embolization agents and stenting materials with potential better outcomes (25).

In summary, our findings suggest, based on a large propensity score study, the superiority of RALPN in achieving tumor control and renal preservation with acceptable perioperative morbidity. RALPN is preferred in scenarios where immediate treatment (ie : active bleeding) is not needed to avoid an adverse clinical outcome.

CONCLUSIONS

This study compares modern robotic-assisted partial nephrectomy to selective arterial embolization in the management of sporadic renal angiomyolipoma. Robotic-assisted partial nephrectomy was associated with less treatment failure than selective arterial embolization with similar preservation in renal function. Moreover, advances in robotic surgery have decreased peri-operative morbidity and com-

plication rates. Unless the patient has a life-threatening hemorrhage, they should be advised to consider robotic-assisted partial nephrectomy as a definitive treatment for sporadic renal angiomyolipoma.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Idir Ouzaid, MD, PhD
Department of Urology,
Bichat Claude Bernard Hospital
46, rue Henri Huchard
75018 Paris, France
E-mail : idir.ouzaid@free.fr

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Cadaveric Penile Microdissection and its Impact on Live Donor Penile Transplantation: an Experimental Case Series Study

Miroslav L. Djordjevic [1, 2], Marta Bizic [1, 2], Borko Stojanovic [1, 2], Bojana Radnic [2], Milenko Bogdanovic [2], Sinisa Ducic [2] Vesna Popovic [2], Tatjana Atanasijevic [2]

[1] Belgrade Centre for Genitourinary Reconstructive Surgery, Belgrade 11000, Serbia; [2] Faculty of Medicine, University of Belgrade, Belgrade 11000, Serbia

ABSTRACT

Purpose: We evaluated the possibility of using remaining penile tissue such as preserved corpora cavernosa, the remaining glans tissue with neurovascular components and the anterior urethra, after femininizing gender affirmation surgery for live donor penile transplantation.

Materials and Methods: Between January 2022 and January 2024, penile dissection was performed in 31 male cadavers, aged 20-59 years (mean 42 years). The dissection with tissue preservation was based on penile disassembly principles: penile skin, part of the glans with neurovascular elements, and proximal urethra were prepared for feminizing genitoplasty while remaining penile tissue such as full corpora cavernosa, glans and anterior urethra were micro dissected and properly measured.

Results: Mean penile length was 10.24 cm in the flaccid and 14.6 cm in the stretched state. The mean diameters of the deep dorsal vein and the right and left arteries were measured at 2.8 mm, 1.9 mm and 1.8 mm, respectively. Penile nerves with an anatomical distribution were found in all cases. The mean length and girth of cavernosum bodies were 19.24 cm, and 7.29 cm, respectively. The mean length of the distal urethra was 15.73 cm (range 11-21 cm), without registered anomalies. The mean volume of the glans after neoclitoris creation was 89% of total. All dissections were completed successfully, and all entities were joined again in all cadavers.

Conclusions: The cadaveric study has confirmed the technical feasibility and possibilities of using all remaining penile tissue for possible live donor penile transplantation.

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Miroslav L Djordjevic
https://orcid.org/0000-0003-2298-3450

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INTRODUCTION

Gender affirming vaginoplasty is the last step in transfemale surgical transition. Surgery includes several procedures such as bilateral orchiectomy, penectomy, clitoroplasty, labioplasty and vaginoplasty. Dissection of the penile entities represents a basis for the construction of the new female genitalia: penile and scrotal skin are used for vaginoplasty and labioplasty, a small part of the glans with neurovascular bundle for clitoroplasty and proximal part of the urethra for neovaginal vestibulum and female urethral orifice. All other parts, completely preserved corpora cavernosa, most of the volume of the remaining glans and distal penile urethra, are not necessary and are usually removed (1).

Penile transplantation represents an ideal substitute in cases with aphallia, penile trauma or penile cancer as well as for gender affirming phalloplasty. Recently, five allogenic human penile transplantations were performed in cis-men from deceased donors (2-6). The main goal of this cadaveric study was to demonstrate anatomical dissection of penile entities as a standard part for penile inversion vaginoplasty, and complete preservation of all available penile tissue as a possible material for live donor penile transplantation. We hypothesized that these remaining penile tissue with associated blood vessels and nerves, could be successfully transferred to a recipient. This could be the largest cadaveric study on genital organ dissection in the literature (7-9).

MATERIALS AND METHODS

Between January 2022 and January 2024, we performed anatomical dissection of the genitalia of 31 male human fresh-frozen cadavers, aged 20-59 years (mean 42 years). The study protocol was provided by the University Forensic Institute as a part of 2020 Project. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee (1322/X-16, 2020). Informed consent was not required because the study did not include live human subjects. Exclusion criteria were cadavers older than 62 years, malignancy or trauma to the genitalia and medical comorbidities that may result in dissection difficulties. The identification of cadavers was confidential and protected according to the ethical principles.

The approach is based on vast experience in penile disassembly, which was introduced for the treatment of congenital and acquired penile anomalies (10, 11). Cadaveric dissection was separated in two stages: dissection of the penile entities that would be used for standard penile inversion vaginoplasty, and microdissection of the remaining tissue of the penis with preservation of all blood vessels and nerves. Clinically, penile inversion vaginoplasty includes several sub-procedures and the technique has already been described (12). Usually, the penis is separated into its anatomical components, i.e. the corpora cavernosa, the glans cap with neurovascular bundle, urethra and the vascularized penile skin. Distal part of the glans is dissected with the neurovascular bundle and used to create the clitoris. Urethra is mobilized at the prebulbar level and divided. The distal part remains attached to the corpora cavernosa, whereas the proximal part is spatulated up to the bulbus for creation of female-type urethra. The corpora cavernosa with remaining glans tissue at the top and part of anterior urethra are removed up to their attachments to the pubic bones, preventing postoperative erections (Figures 1A and B). Finally, penile skin is inverted and joined with scrotal skin grafts, forming the neovagina. Vulvoplasty involves the creation of the labia minora and majora. The remaining part of the base of the penile skin is used to form the labia minora, whereas the scrotal skin is dissected and used for labia majora.

Cadaveric dissection

Cadaver is placed in proper supine position with good exposure of genitalia. Dissection is started with a circumcision incision, 2.5 cm under the glans corona, followed by proper degloving of the penile skin. A midline incision of the scrotum is used for penile body transposition and possible removal of both

Figure-1A. Feminizing gender affirming surgery. Penile disassembly includes separation of all penile entities, corpora cavernosa and glans with dissected neurovascular bundle (dorsally) and urethra (ventrally). Corpora cavernosa are completely detached from the glans.

Figure-1B. New clitoris is created, with preserved vascularization and innervation. Urethra is divided at prebulbar level and prepared for creation of vulvo-vestibular complex. Penile skin is prepared for inversion and creation of the new vagina. All penile remnants are prepared for removal: corpora cavernosa with both crura, distal urethra and glans remnant.

Figure -1C. Cadaveric dissection of the penis. Penile entities are separated and parts for feminizing genital reconstruction are properly prepared: neoclitoris with neurovascular bundle, penile skin and proximal part of the urethra. Complete dissection of the remaining entities (cavernosal bodies, crura, distal urethra and glans remnant) is done for potential graft preparation.

Figure-1D. Dissection of the neurovascular bundle. Dorsal nerve and penile artery with the deep dorsal vein are micro dissected along with the neoclitoris, leaving the other penile artery and nerve preserved and attached to the tunica albuginea with cavernosal bodies. In this way, arterial and nerve supply to the glans remnant is preserved without compromising vascularization and innervation of the neoclitoris.

testes. The penis is invaginated through the incision to provide an excellent access to the entire length of the penis. Ventrally, the urethra is mobilized at prebulbar level and divided. This way, the proximal part of the urethra is prepared for reconstruction of the vestibulo-vaginal complex and the new female orifice. Neurovascular bundle is evaluated, and all neurovascular structures, deep dorsal vein, two penile arteries and two penile nerves, are confirmed. The dissection includes mobilization of one penile nerve, one penile artery, and deep dorsal vein. Neurovascular elements are very precisely lifted from the tunica albuginea and all perforant and communicant branches are divided, leaving the other artery and nerve attached to the corpora cavernosa. Distally, the dissection is continued to the dorsal surface of the glans. The glans is lifted to a level determined by the appropriate size of the new clitoris. Further dissection includes removal of the glans tissue. Approximately 1-1.5 cm on either side of midline on the coronal ridge are divided from the glans and coned to shape the new clitoris. The remaining part of the glans is left in place and attached to the tips of the corpora cavernosa. Based on the experience in epispadias repair, the dorsal defect is closed directly giving a good shape of the glans (13).

This meticulous microdissection results in preservation of the remaining nerve and penile artery that remain attached to the cavernosal body. This way, all small branches are preserved and in contact with nerve and artery, as well as with ipsilateral cavernosum body. Finally, our primary dissection defined two groups of the tissues. The first group included completely preserved penile skin, coronal ridge of the glans with the deep dorsal vein, penile artery and nerve and proximal urethra, which could be used to create the neovagina, clitoris and vestibulo-vaginal complex (Figure-1C).

All the remaining parts are micro-dissected, offering good tissue for possible donation. Their dissection is continued toward the pubic bones. The crura are separated ventrally from bulbar urethra. The fundiform and suspensory ligaments are divided at the level of their attachment to the pubic bone. Both crura of the corpora cavernosa are mobilized together with ischio-cavernosal muscles. Partial neurovascular bundle (one-side penile artery and nerve) is left attached to the tunica albuginea during dissection. Both cavernosum arteries are precisely identified and dissected (Figure-1D).

Cadaveric dissection includes precise measurement of penile entities: length of the penis in flaccid and stretched position; length and girth of the corpora cavernosa, length of the penile and bulbar urethra and its remaining part after division, as well as glans volume, total and after the removal of the part that is to be used for creation of the new clitoris. Cadavers are classified in 3 groups according to age, and comparison of all parameters between groups is performed using Kruskal-Wallis test, with $p<0.05$ presenting statistical significance. In addition, we verified the presence of the neurovascular elements, deep dorsal vein, penile arteries, penile nerves, crural arteries and veins as well all other elements such as perforant and circumflex branches and nerve endings. All dissection stages were photographed in situ and documented.

RESULTS

Macro-dissection was straightforward and revealed the usual penile anatomy without penile deformities in all cadavers. The penises consisted of non-deformed corpora cavernosa, well developed skin, good volume of the glans and urethra without any deformities, either congenital (hypospadias) or acquired (stricture). All penile structures were separated without complications and prepared for creation of the female genitalia according to standard feminizing gender affirming surgery.

Penile entities were measured, as shown in Table 1. The mean penile length was 10.24 cm (ranging 6-14 cm) in the flaccid and 14.6 cm (11.5-18 cm) in the stretched state, while the penile circumference in the middle part ranged from 7 to 9 cm (mean 8 cm). Next, the distribution of the neurovascular bundle was determined, and regular anatomy was found in all cases: two penile nerves, two penile arteries

Table 1 - Measurement of penile entities during cadaveric micro-dissection.

No.	Age	Penile length(cm): flaccid/stretched	Corpora (cm): Length/girth	Urethral length (cm): Total/distal	Glans volume (mL) (total)	Glans volume (mL) (resected)	Glans volume (mL) (remnant)
1	38	10.5/14	22/7	23/16	3.5	0.5	3
2	32	13/16	24/8	25/21	5.3	0.56	4.74
3	48	8.5/14	20.5/8.5	21/16	4.1	0.4	3.7
4	29	6/12	19/7.5	20/14	3	0.28	2.72
5	38	12/18	19/8	20/16	4.7	0.45	4.25
6	47	11/16	18/7	23/19	4.2	0.4	3.8
7	51	11/14	17.5/6.5	19/16	3.5	0.5	3
8	41	11/16	18/7.5	18.5/13.5	3.5	0.4	3.1
9	43	11/15	18/6.5	19/15.5	4	0.45	3.55
10	34	9.5/13.5	17.5/6	18.5/15	3.8	0.42	3.38
11	43	14/17	20/11	23/19.5	4.1	0.34	3.76
12	58	13/15	22/7	23/16	4	0.4	3.6
13	20	10/13	23/7.5	23/15	3.5	0.5	3
14	41	12/15	19/5.5	22/16	4.2	0.3	3.9
15	59	7/12	20/6	22/15	3.4	0.32	3.08
16	45	8/15	19.5/6.5	19/15	3	0.43	2.57
17	48	9/14	20/9	22/15	3.2	0.35	2.85
18	53	9/15	15/7	18.5/14	4	0.36	3.64
19	26	8.5/11.5	15.5/6.5	13/11	3.1	0.44	2.66
20	33	11/14.5	20.5/8	20/16	3.5	0.5	3
21	50	10.5/14.5	19/7	19/15	3.4	0.32	3.08
22	42	12/17	21/9	22/16.5	4.4	0.4	4
23	49	9/14.5	17/6.6	20/15	3.8	0.42	3.38
24	38	9.5/15	17.5/6	20/16	3.4	0.34	3.06
25	56	8/14	17/6	19/15	3.2	0.36	2.84
26	58	11/15	19/7.5	22/16	4	0.4	3.6
27	40	10/14	20/7.5	22/16.5	3.5	0.4	3.1
28	27	10/14	19.5/7	21/15	3.5	0.4	3.1
29	30	12.5/16	21.5/9	23/17	4.2	0.3	3.9
30	37	11.5/15	19/7	22/16	4	0.44	3.56
31	46	8.5/13	18/7	19/15	3.8	0.4	3.4
Mean	42	10.24/14.60	19.24/7.29	20.69/15.73	3.77	0.40	3.37
SD	-	2.12/1.70	2.35/1.26	2.72/2.22	0.59	0.07	0.59

[a] SD - standard deviation

and deep dorsal vein. As lumen of the blood vessels could not be precisely measured, external diameter was measured at two points, distally and proximally. Average diameters of deep dorsal vein, right and left artery were 2.8 mm, 1.9 mm and 1.8 mm, respectively. Penile nerves with the usual anatomical distribution were found in all cases. Maximal volume of the glans was 5.30 mL and decreased down to 3 mL (mean 3.77 mL, SD – 0.593) Finally, the volume of the neoclitoris (resected part of the glans) was quantified and ranged from 0.28 mL to 0.56 mL (mean – 0.40 mL, SD – 0.074). Penile and scrotal skin were preserved in all cases and being sufficient for neovaginal reconstruction. The penile urethra length was sufficient in all cases and adequate for joining with female urethra of the potential recipient.

Remaining penile tissue were then precisely measured. The average volume of the remaining glans tissue after creation of the neoclitoris was 3.37 mL (89% of total volume) (ranged from 2.57 to 4.74 mL, SD – 0.591). Mean length and girth of cavernosum bodies were 19.24 cm (from 15 to 24cm) and 7.29cm (from 5.5 to 11cm), respectively. Both crural arteries were identified in all cases. The length of the distal urethra ranged from 11 to 21 cm (mean 15.73 cm), without registered anomalies or signs of spongiofibrosis or stricture. Circumflex branches and perforators of the blood vessels were detected in all cases. Mean values of all anatomical entities in three age groups are presented in Table 2. There is no statistically significant difference between groups in any parameter (p>0.05). (Table-2) All dissections were completed successfully, and all entities were assembled again in all cadavers.

DISCUSSION

In recent decades, there has been an intensive search for ideal phallic reconstruction. Neophalloplasty still represents the most used penile replacement method and includes the use of pedicled or free flaps. The success of these procedures is limited and associated with poor cosmetic result, complications (strictures and urethral fistulas) and poor erectile function (14, 15). Moreover, in severe trauma, genital injury is usually associated with limb injuries, making the use of reconstructive flaps problematic. Recently, the vascularized composite allotransplantation has become an option for the treatment of complex hand and face defects, offering the same idea as a viable alternative for genital reconstruction (16, 17). The first penile transplantation was reported in 2006, and four more have been performed since (2-6). The allograft was procured from a suitable deceased donor, with a cold ischemia time of 16 hours. The team had practiced the transplantation technique, including the microsurgical reconstruction, on cadaver-to-cadaver transplantation extensively before undertaking the operation in their landmark case. Despite the improvements in surgical techniques, many questions

Table 2 - Comparison of parameters between age groups.

Group No.	Age (years)	Penile length (mean, cm): flaccid/ stretched	Corpora (mean, cm): Length/girth	Urethral length (mean, cm): Total/distal	Glans volume (mL) (total, mean)	Glans volume (mL) (resected, mean)	Glans volume (mL) (remnant, mean)
1	<40	10.3/14.4	19.8/7.3	20.7/15.6	3.8	0.43	3.36
2	40-49	10.3/15	19/7,6	20.9/16	3.8	0.4	3.4
3	>50	10/14.2	18.5/6.7	20.4/15.3	3.6.	0.38	3.26
P values*		0.859/0.441	0.465/0.281	0.686/0.632	0.525	0.198	0.619

* Kruskal-Wallis Test

remain (18, 19). Procurement of the penis from a deceased donor is prolonged owing to additional multi-organ donor, highly complex procedure. Long cold ischemia, which is one of the main limitations, could be avoided by live donor transplantation. As the number of transgender surgeries continues to increase globally, in candidates who have elected feminizing gender affirmation procedures, the removed penile tissue (corpora cavernosa, remaining volume of the glans and anterior urethra) could be potentially suitable for live donor transplantation (12).

A clear understanding of normal penile anatomy represents the foundation of our research. Our experience with penile reconstructive surgery for different congenital and acquired anomalies, allowed us to be confident that we could dissect all penile elements in an anatomical fashion, and preserve all penile tissues. Penile disassembly has been previously defined as an option in the treatment of very severe penile deformities, preserving all penile structures with their functional assembly after correcting the anomaly (10, 11). Based on our anatomical dissections, we propose that the corpora cavernosa with tunica albuginea could be completely separated during the feminizing gender affirming surgery. The standard technique involves dissection of a small piece of the glans for reconstruction of the clitoris, leaving the rest of the glans tissue attached to the tips of corpora cavernosa. Since the new clitoris is supported by dorsal penile artery, deep dorsal vein, and penile nerve, we left the other penile artery and nerve attached to the tunica albuginea together with all perforant and circumflex branches. The main question remaining open is venous drainage of the glans after harvesting and dissection of deep dorsal vein. We hypothesized that the distal part of the urethra, which is connected to the glans and anterior part of the corpora cavernosa, enables additional venous drainage from the glans. This is one of the main points in urethral dissection. The male urethra is very long, and only a short segment of anterior urethra is usually necessary for the creation of the new female orifice. Almost the entire anterior urethra, which is very rich in blood vessels due to its connection to the tunica albuginea, could be preserved and used for joining with the original urethra in the recipient.

We precisely measured all penile structures to estimate the quality and quantity of the tissue after using the parts necessary for the reconstruction of the female genitalia. The main ethical request was to enable a completely normal reconstruction of female genitalia according to more recent techniques in feminizing gender affirming surgery. Our results showed an excellent potential of the penile tissue remnants, encouraging us to continue with our project and improve ideas on how to transplant tissue after dissection. In all cases we found good anatomical relations for safe dissection of all corpora cavernosa, including crura and joints with the pubic bones. The length of the corpora cavernosa with associated crural arteries was sufficient for microvascular transfer to a potential recipient. Also, we found no evidence of potential hypotrophy of penile structures with aging, since all measurements do not show significant variations according to age. In contrast to reported cases of penile transplantation, there would be a lack of penile skin for transplantation since all penile skin is usually used for standard gender affirming vaginoplasty (18). Lack of penile skin for transplantation could be resolved with recipient's genital skin.

The possibility of living and healthy donors of organs represents a great improvement in transplant surgery with the best post transplantation results. We are certain that penile transplantation will be accepted by all surgeons and health professionals who believe that it will be an ideal option for organ replacement. One of the limitations – the lack of available donors will be resolved by the possibility to use tissues from live donors, i.e., transwomen, where the penis is planned to be removed. We confirmed in our research with 41 transwomen that completely preserved corporal bodies with a good volume of remaining glans tissue and anterior urethra present viable tissue for potential live donor penile transplantation (20).

Recently, the incidence of transgender population has changed, ever growing, with a pre-

dominance of transwomen candidates. It could be the biggest bank for male organs, mostly penises, in the world. The development of immunosuppressive therapy could improve our goals for live donor penile transplantation as an ideal solution for all candidates (e.g., transwomen, trauma, malignancy, absence, etc.).

CONCLUSIONS

The anatomical principles of penile disassembly in feminizing gender affirmation surgery have been precisely described. Cadaveric dissection of the penis was defined as a similar procedure with detailed recovery of the remaining penile tissues after creation of new female genitalia. This preserved tissues such as corpora cavernosa with anterior urethra, ventrally, and glans with nerves and blood supply, dorsally, could be used for safe and successful live donor penile transplantation. Preliminary results of our cadaveric study have confirmed the technical feasibility, but further research could improve technical possibilities and offer standardization of operative techniques that will lead to the final goal of achieving a male genital organ ideal in all aspects.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee (1322/X-16, 2020). Informed consent was not required because the study did not include live human subjects.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Miroslav L. Djordjevic, MD, PhD
Faculty of Medicine, University of Belgrade
Department of Urology, Tirsova 10, Belgrade
11000 Belgrade, Serbia
Telephone: + 38 163 380-282
E-mail: djordjevic@uromiros.com

EDITORIAL COMMENT

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Importance of Penile Vascularization in Live Donor Penile Transplantation

Luciano A. Favorito [1, 2]

[1] Unidade de Pesquisa Urogenital - Universidade do Estado do Rio de Janeiro - Uerj, Rio de Janeiro, RJ, Brasil; [2] Serviço de Urologia, Hospital Federal da Lagoa, Rio de Janeiro, RJ, Brasil

COMMENT

The paper by Djordjevic and colleagues (1) is very interesting and shows the possibility of using remaining penile tissue, such as preserved corpora cavernosa, the remaining glans tissue with neurovascular components, and the anterior urethra, after feminizing gender affirmation surgery, for live donor penile transplantation. It confirms the technical feasibility and the possibilities of using all remaining penile tissue for possible live donor penile transplantation.

Knowledge of penile anatomy is a crucial step in this procedure. The penis is irrigated by two internal pudendal arteries, branches of the internal iliac (hypogastric) artery. After its various perineal branches, the pudendal arteries combine to form the so-called common penile artery, which divides into three branches: the bulbourethral artery, the dorsal penile artery, and the cavernosal artery. The cavernosal artery is located inside the corpus cavernosum, the bulbourethral artery is responsible for irrigating the corpus spongiosum and urethra, and the dorsal penile artery is located between the tunica albuginea and Buck's fascia (2). The collateral communications between the bulbourethral artery and the dorsal artery are fundamental for dissection during the procedure described in this paper. This is an example of the importance of anatomy in urological surgery.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Luciano A. Favorito, MD, PhD
Unidade de Pesquisa Urogenital
da Universidade do Estado de Rio de Janeiro - UERJ,
Rio de Janeiro, RJ, Brasil
E-mail: lufavorito@yahoo.com.br

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Luciano A. Favorito
https://orcid.org/0000-0003-1562-6068

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EXPERT OPINION

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Male Infertility: Diagnostic Approach – A Committee Opinion

Sandro C. Esteves [1, 2], Marina C. Viana [1], Augusto B. Reis [3, 4], Filipe Tenório Lira Neto [5, 6], Thiago Afonso Teixeira [7, 8, 9], João Paulo Camarço [10, 11], Matheus Gröner [12, 13], Antônio José T. Paula [14, 15], Alberto C. Stein [16], Maria Gabriela F. Mulato [1], Jorge Hallak [8, 9, 17, 18, 19], Renato Fraietta [12, 13]

***on behalf of the Andrology Committee, Brazilian Society of Human Reproduction (SBRH), 2023-2025 term**

[1] ANDROFERT, Clínica de Andrologia e Reprodução Humana, Campinas, SP, Brasil; [2] Departamento de Cirurgia (Disciplina de Urologia), Faculdade de Ciências Médicas, Universidade Estadual de Campinas - UNICAMP, Campinas, SP, Brasil; [3] Departamento de Cirurgia e Programa de Pós-graduação em Ciências Aplicadas à Cirurgia e Oftalmologia, Faculdade de Medicina da Universidade Federal de Minas Gerais - UFMG, Belo Horizonte, MG, Brasil; [4] Serviço de Urologia, Laboratório de Reprodução Prof. Aroldo Fernando Camargos, Belo Horizonte, MG, Brasil; [5] Departamento de Cirurgia, Universidade Federal de Pernambuco - UFPE, Recife, PE, Brasil; [6] Instituto de Medicina Integral Prof. Fernando Figueira & Clínica Andros Recife, Recife, PE, Brasil; [7] Disciplina de Urologia, Departamento de Cirurgia, Faculdade de Medicina, Universidade Federal do Amapá - UNIFAP, Macapá, AP, Brasil; [8] Grupo de Estudos em Saúde Masculina, Instituto de Estudos Avançados, Universidade de São Paulo - IEA-USP, São Paulo, SP, Brasil; [9] ANDROSCIENCE, Centro de Ciência e Inovação em Andrologia & Laboratório Clínico e de Pesquisa de Alta Complexidade, São Paulo, SP, Brasil; [10] Departamento de Urologia, Hospital Estadual Alberto Rassi, Goiânia, GO, Brasil; [11] Humana Medicina Reprodutiva & Urocenter, Goiânia, GO, Brasil; [12] Disciplina de Urologia, Departamento de Cirurgia, Universidade Federal de São Paulo - UNIFESP-EPM, São Paulo, SP, Brasil; [13] Setor Integrado de Reprodução Humana, Universidade Federal de São Paulo -UNIFESP-EPM, São Paulo, SP, Brasil; [14] ANDROLIFE, Centro Integrado de Saúde do Homem, Rio de Janeiro, RJ, Brasil; [15] Vida Medicina Reprodutiva, Rio de Janeiro, RJ, Brasil; [16] Divisão de Oncofertilidade, Cellmed - Terapia Celular e Medicina Regenerativa, Porto Alegre, RS, Brasil; [17] Departamento de Patologia, Unidade de Toxicologia Reprodutiva, Faculdade de Medicina da Universidade de São Paulo - FMUSP, São Paulo, SP, Brasil; [18] Disciplina de Urologia, Departamento de Cirurgia, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - FMUSP, São Paulo, SP, Brasil; [19] Instituto ANDROSCIENCE, de Ciência, Educação e Projetos Avançados em Saúde Masculina, São Paulo, SP, Brasil

INTRODUCTION

Male infertility is a disorder of the male reproductive system recognized as a global health issue (1, 2). Its most common causes include congenital, genetic, anatomical, endocrine, functional and immunological factors, infections of the genital tract, cancer and its treatments, and sexual dysfunctions that prevent natural intercourse (1-5). Critical contributors include poor lifestyle habits, exposure to toxic substances, environmental influences, and advanced

paternal age, which may act independently or exacerbate known causal factors (1-5).

Approximately 17% of couples of reproductive age experience difficulty conceiving. In about 20% of cases, infertility is exclusively male-related, and when combined with female factors, this percentage exceeds 50% (1, 2, 6).

WHEN SHOULD EVALUATION BE INITIATED?

Male infertility should be investigated concurrently with female assessment in couples attempting conception for 12 months or more (1-5). In women aged 35 years or older, this evaluation should begin after six months of unprotected intercourse.

The goals of the evaluation are to identify (Figure-1):

(i) reversible causes;

(ii) irreversible conditions amenable to assisted reproductive technology (ART) using the partner's sperm;

(iii) irreversible conditions where heterologous gametes/embryos or adoption are the only options;

(iv) underlying medical conditions that may impact overall male health;

(v) genetic abnormalities that could affect the offspring.

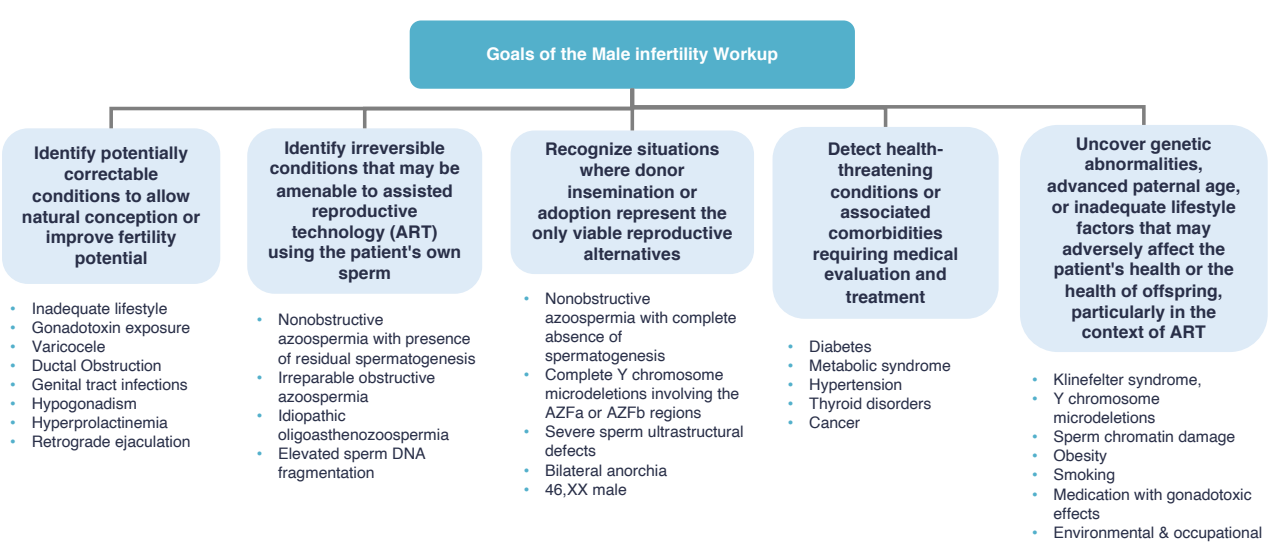
HOW SHOULD EVALUATION BE CONDUCTED?

As a disease of the male reproductive system, male infertility warrants a diagnostic work-up that goes beyond basic semen analysis. A comprehensive and standardized approach should include the following components (1-5, 7; Figure-2):

Detailed Medical History

- Infertility history, sexual habits, childhood, and pubertal development (e.g., delayed puberty, cryptorchidism, hypospadias, epispadias, hernia, mumps orchitis, testicular trauma, or torsion).

Figure 1 - Goals of the male infertility diagnostic approach, including identifying correctable and irreversible conditions, recognizing when donor insemination or adoption are necessary, detecting health-threatening comorbidities, and uncovering genetic or lifestyle factors that may impact patient or offspring health, especially in the context of assisted reproductive technology (ART).



- Prior systemic illnesses and history of sexually transmitted infections.
- Surgical history (e.g., orchidopexy, herniorrhaphy, pelvic, scrotal, or pituitary surgery).
- Exposure to gonadotoxins (e.g., pesticides, marijuana, anabolic steroids, medications including alpha/beta blockers, calcium channel blockers, anti-depressants, opioids, chemotherapy, and radiotherapy).
- Family history (infertility, endocrine disorders, cystic fibrosis, Kartagener syndrome).
- Current lifestyle (diet, alcohol intake, tobacco use, recreational and prescription drugs, physical activity, occupation).

Physical Examination

- Evaluation of secondary sexual characteristics.
- General and focused genital exam assessing for gynecomastia, surgical scars, testicular size and consistency, epididymal and vas deferens palpation, and spermatic cord assessment.
- Clinical diagnosis of varicocele while standing in a temperature-controlled room:
  - Grade I: veins palpable with Valsalva maneuver
  - Grade II: veins palpable at rest
  - Grade III: veins visible at rest

Semen Analysis

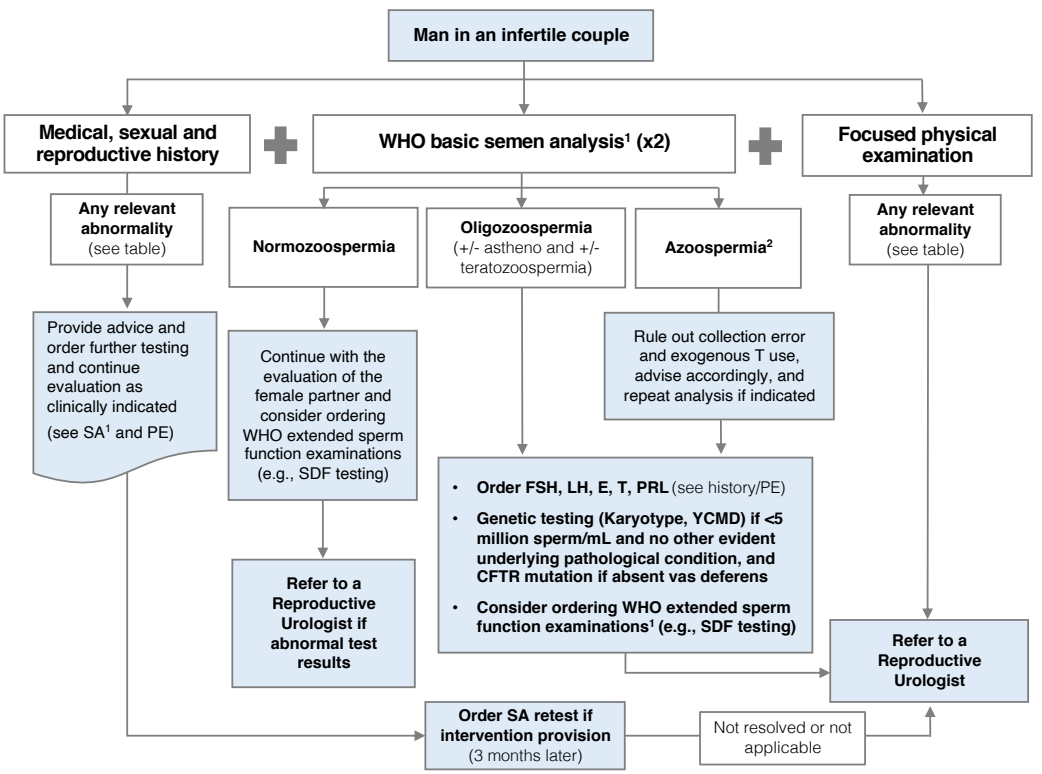
Conducted per the World Health Organization (WHO) 6th edition guidelines, after 2–7 days of ejaculatory abstinence (preferably 2–3 days) (8, 9) (Table-1). At least two analyses are recommended, especially when the first is abnormal. No consensus exists on the ideal interval between collections, but a two-week gap is suggested.

Advanced sperm function tests such as sperm DNA fragmentation (SDF) analysis should be considered in couples with recurrent pregnancy loss (natural or ART conception), unexplained male infertility, or before the use of assisted conception, including intrauter-

Table 1 - World Health Organization reference limits for basic semen analysis parameters (6th edition, 2021). Data were derived from approximately 3,500 men whose partners achieved a natural pregnancy resulting in a live birth within one year of unprotected intercourse. The values represent the pooled distribution of semen analysis results, with the fifth percentile considered the lower reference limit to assist clinical decision-making.

	Centiles		
	5th	50th	90th
Semen volume (mL)	1.4	3.0	5.5
Sperm concentration (x10^6/mL)	16	66	166
Total sperm number (x10^6 per ejaculate)	39	210	561
Total Motility (%)	42	64	83
Progressive motility (%)	30	55	71
Normal forms (%)	4	14	32
Vitality (%)	54	78	95

Figure 2 - Algorithm for the initial evaluation of the male partner in an infertile couple. The process begins with a thorough medical, sexual, and reproductive history, followed by a focused physical examination. At least two semen analyses should be obtained according to WHO guidelines. Subsequent steps include laboratory testing (e.g., hormonal profile, genetic testing), imaging, and extended sperm function testing, including sperm DNA fragmentation analysis, as clinically indicated. The goal is to guide diagnosis and management tailored to the identified abnormalities.



History	Components
1) Infertility History	• Age of partners, length of time attempting to conceive • Contraceptive methods/duration • Previous pregnancy/miscarriage (current partner/partner/another partner) • Previous treatments • Treatments/evaluations of female partner
2) Sexual History	• Potency, libido, lubricant use • Ejaculation, timed intercourse, frequency of masturbation
3) Childhood and Development	• Cryptorchidism, hernia, testicular trauma, testicular torsion, infection (e.g., mumps) • Sexual development, puberty onset
4) Personal History	• Systemic diseases (e.g., diabetes, cirrhosis, hypertension) • Sexually transmitted diseases, tuberculosis, viral infections, genital and systemic bacterial infections, history of fever
5) Previous Surgery and/or Treatment	• Orchidopexy, herniorrhaphy, orchiectomy (e.g., testicular cancer, torsion) • Retroperitoneal and pelvic surgery (e.g., prostatectomy) • Other inguinal, scrotal, or perineal surgery • Bariatric surgery, bladder neck surgery, transurethral resection of the prostate
6) Gonadotoxin Exposure	• Pesticides, alcohol, illicit drugs • Medication (e.g., chemotherapy agents, cimetidine, sulfasalazine, nitrofurantoin, allopurinol, colchicine, thiazide, α- and ß-blockers, calcium blockers, finasteride, serotonin reuptake inhibitors) • Organic solvents, heavy metals • Anabolic steroids, tobacco smoking, vaping • High temperatures, electromagnetic energy • Radiation (e.g., therapeutic, nuclear power plant workers)
7) Family History	• Cystic fibrosis, endocrine diseases • Family history of infertility
8) Current Health Status/Lifestyle	• Respiratory infection, anosmia • Galactorrhea, visual disturbances • Obesity, metabolic syndrome

Physical Exam	Components
1) Overall body characteristics	• Virilization • Gynecomastia • Obesity
2) Inguinal and genital areas	• Scar
3) Penis	• Hypospadia, epispadias • Phimosis, curvature
2) Testes	• Location • Size • Consistency • Pain/nodules/tenderness
3) Ductal structures (vas, epididymis)	• Present/absent • Normal/signs of obstruction or inflammation
4) Spermatic cord/scrotum	• Varicocele • Hydrocele • Cysts

[1]WHO semen analysis manual (6th ed.)

[2]Consider post ejaculate urinalysis to rule out retrograde ejaculation if low semen volume & normal pH & normal hormones and no signs of obstruction or testicular dysfunction; if retrograde ejaculation, refer to a specialist

CFTR: Cystic fibrosis transmembrane conductance regulator
E: Estradiol
FSH: Follicle-stimulating hormone
LH: Luteinizing hormone
PE: Physical examination
PRL: Prolactin
SA: Semen analysis
SDF: Sperm DNA Fragmentation
T: Testosterone
WHO: World Health Organization
YCMD: Y chromosome microdeletion

ine insemination (IUI), conventional in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI) (10).

Hormonal Evaluation

- Indicated for men with abnormal semen parameters (especially sperm concentrations <10 million/mL), clinical signs of hypogonadism, gynecomastia, sexual dysfunction, or suspected endocrine disorders.
- The minimum hormonal panel includes serum follicle-stimulating hormone (FSH) and total testosterone. It should ideally be supplemented with luteinizing hormone (LH), estradiol, prolactin, sex hormone-binding globulin (SHBG), thyroid-stimulating hormone (TSH), free thyroxine (T4L), and calculated free testosterone.

Genetic Evaluation

- Mandatory in cases of non-obstructive azoospermia or severe oligozoospermia (sperm concentration <5 million/mL), given that genetic abnormalities are present in up to 15% of infertile men.
- The basic genetic work-up includes G-banded karyotype analysis and Y-chromosome microdeletion testing.
- Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutation testing should be performed in patients with congenital absence of the vas deferens, as mutations are present in up to 80% of such cases.

Imaging Studies

- Scrotal ultrasound is indicated for unclear physical examination findings, palpable testicular masses, a history of cryptorchidism, and non-obstructive azoospermia due to elevated testicular cancer risk.
- Transrectal ultrasound or pelvic magnetic resonance imaging (MRI) may be required when ejaculatory duct obstruction is suspected.
- A pituitary MRI or computerized tomography scan is advised for cases with hyperprolactinemia.

Testicular Biopsy

- Reserved for selected azoospermic patients to differentiate between obstructive and non-obstructive causes (11).
- It may be performed via percutaneous or open techniques; specimens should be preserved in Bouin or Zenker solution.
- Preferably conducted in facilities equipped for sperm cryopreservation.

CONCLUSIONS

Infertility affects a significant proportion of men of reproductive age. Understanding the nuances of its diagnosis is essential for guiding effective treatment. A thorough and structured evaluation enables the identification of underlying causes and facilitates tailored therapeutic strategies, ultimately improving the likelihood of conception—either naturally or via ART.

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CONFLICT OF INTEREST

None declared.

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Esteves, SC
https://orcid.org/0000-0002-1313-9680

Correspondence address:
Sandro C. Esteves, MD, PhD
Av. Dr. Heitor Penteado, 1464
13075-460, Campinas, SP, Brasil
E-mail: s.esteves@androfert.com.br

EXPERT OPINION

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Reframing Anesthetic Principles: Telesurgery as the Natural Evolution of Robotic Surgery

Giovana Barani [1], Marcio Covas Moschovas [1, 2], Belmira Luís [3], Bruno Gallo [1], Vipul Patel [1, 2]

[1] AdventHealth Global Robotics Institute, Kissimmee, FL, USA; [2] University of Central Florida - UCF, FL, USA; [3] Complexo Hospitalar Cardeal Dom Alexandre do Nascimento, Luanda, Angola

COMMENT

We read with great interest the article by Wang and colleagues describing the anesthesia perspective in telesurgery procedures (1). The expansion of telesurgery through the integration of high-speed 5G networks has enabled the remote delivery of surgical care using robotic systems (2, 3). This development has been highlighted for its potential to democratize access to high-quality surgical expertise, particularly in regions with limited local resources (4, 5). However, the anesthetic management of these procedures is often portrayed as novel or fundamentally different. We argue that telesurgery is an extension of robotic surgery; thus, the anesthetic principles applied to robotic procedures should also govern telesurgical practice (6-8).

In this context, considering that telesurgery is a form of robotic surgery, the foundational anesthetic principles—general anesthesia with deep muscle relaxation, appropriate monitoring, and multimodal analgesia—apply equally to telesurgery (6). The patient's physiology and the type of procedure are not affected by the geographic location of the surgeon. Consequently, from the anesthesiologist's perspective, anesthetic goals remain unchanged: to ensure immobility, hemodynamic stability, adequate ventilation, and rapid recovery. Specific considerations such as patient positioning, pneumoperitoneum effects, neuromuscular blockade, and temperature regulation are identical to traditional robotic cases and should be managed accordingly. Furthermore, robotic surgery technology has been established for several years, and even the most recent platforms have demonstrated safety in clinical settings before market release (9, 10). Therefore, the robotic platform—whether operated locally or remotely—offers the same performance and safety for patients, and communication between anesthesia providers and local surgeons remains unchanged.

On-site surgical expertise is imperative to ensure patient safety and optimal outcomes (11, 12). Despite the advanced capabilities of remote control in telesurgical procedures, the physical presence of an experienced surgeon in the operating room is non-negotiable (8). This individual plays a critical role in managing potential intraoperative complications, such as unexpected bleeding, conversion to open surgery, or system failure due to signal loss. Their immediate availability ensures procedural continuity and safeguards patient safety during high-stakes or time-sensitive events.

From the anesthetic standpoint, coordination with the local surgeon is equally essential, especially when sudden changes in the surgical plan require prompt anesthetic adjustments. However, it is important to empha-

size that anesthetic management in telesurgery remains fundamentally the same as in conventional robotic surgery. Regardless of the scenario, the anesthesiologist prepares and monitors the patient as they would for any standard robotic procedure. This consistency is made possible by the presence of the local surgical team, who can intervene directly and promptly if needed. As a result, the anesthesia team can rely on established protocols, ensuring safety and stability throughout the case while maintaining seamless communication with both local and remote surgical teams.

Another important aspect discussed in the article is the potential impact of remote surgeon performance on anesthesia management and patient recovery. It is essential to highlight that when an expert telesurgeon is in control, the benefits extend well beyond surgical precision (8). Highly experienced telesurgeons can simplify complex operations by minimizing unnecessary instrument movements, avoiding indecision, and executing each step efficiently. This results in shorter operative times, directly reducing anesthetic exposure.

From an anesthetic perspective, this reduction is highly beneficial. Shorter anesthesia durations are associated with decreased risks of intraoperative hypothermia, lower incidence of postoperative delirium—particularly in elderly or vulnerable patients—and faster recovery, all contributing to a smoother and more predictable postoperative course. Additionally, shorter procedures reduce the need for prolonged intraoperative support measures such as fluid resuscitation or vasopressor use, improving overall patient stability. These clinical benefits also carry important economic implications. Reduced operative time leads to more efficient use of operating room resources, decreased staffing demands, and lower overall procedural costs (13). Patients benefit not only from a safer anesthetic experience but also from reduced hospital stays, earlier mobilization, and a quicker return to daily activities. In this context, the involvement of a highly skilled telesurgeon generates a cascade of anesthetic and systemic advantages, improving patient outcomes while reducing the healthcare burden.

The authors also emphasize the importance of communication between the remote surgeon and the anesthesia team. While this is a valid point, it is important to clarify that such communication is already an inherent and well-established component of any telesurgical setup. As with conventional robotic procedures, there is continuous and structured communication between the console surgeon, the bedside assistant, and the anesthesia providers. The local surgeon, physically present with the patient, remains fully informed of the intraoperative course and serves as a key intermediary, relaying any necessary updates to the remote surgeon in real time. Modern telesurgical systems utilize stable, secure communication channels that function seamlessly throughout the procedure, typically through encrypted platforms or direct audio connections via smartphone technology. In this regard, communication in telesurgery closely mirrors current practices in many operating rooms, where surgical teams use headsets, video monitors, and team-based communication protocols.

Thus, the notion that communication presents a significant barrier in telesurgery is largely overstated. The setup is intuitive and comparable to established workflows for both the anesthesia team and the remote surgeon. Even in high-pressure situations such as trauma or intraoperative emergencies, the presence of a local surgeon mitigates delays in decision-making or intervention, ensuring that patient safety is not compromised. Effective communication in telesurgery is not a limitation but a built-in feature that enables fluid collaboration across distances with the same reliability as traditional robotic procedures.

Moreover, when establishing a telesurgery program, simulation and training for integrated teams are essential. Given the unique configuration of telesurgical teams, we recommend incorporating simulation training that includes anesthesiologists, local surgical staff, and remote surgeons. Scenarios should address network latency, device failure, and intraoperative emergencies to ensure that all team members can respond efficiently and cohesively. These simulations should also evaluate nontechnical skills such as communication clarity, teamwork, and leadership in distributed environments.

Another point raised by the authors concerns the potential health risks of "5G radiation exposure" dur-

ing telesurgery—a claim that lacks scientific foundation and may be misleading. Although isolated studies have explored the biological effects of 5G, there is currently no conclusive evidence linking standard 5G exposure to harmful health outcomes. Importantly, 5G technology is already integrated into daily life through smartphones, wireless devices, and urban infrastructure, often for extended periods (2). In the context of telesurgery, 5G is used exclusively for data transmission between surgical sites and does not involve direct or prolonged exposure to the patient or surgical team. The intensity and duration of 5G exposure in these procedures are minimal and comparable to everyday mobile technology use. While continued research into the long-term effects of emerging technologies is appropriate, highlighting 5G in telesurgery as a unique health risk is not scientifically justified and detracts from the broader benefits and established safety of these communication systems.

Finally, ethical considerations for anesthesiologists in telesurgery should include aspects of informed consent. Patients must be appropriately informed about the nature of telesurgical procedures, including the potential risks associated with remote operation and network dependency (8). Although surgeons typically lead these discussions, anesthesia providers are responsible for clearly communicating perioperative anesthetic risks within this novel context. Anesthesiologists participating in 5G-enabled robotic surgery face distinct challenges, including patient immobility, real-time monitoring, remote coordination, network reliability, emergency management, pain control, and the need for specialized training. By following current recommendations—such as employing general anesthesia with deep muscle relaxation, enhancing monitoring, ensuring robust communication, preparing for network disruptions, planning for emergencies, implementing multimodal analgesia, and participating in simulation training—anesthesiologists can provide safe and effective care.

As telesurgery becomes more widespread, the role of the anesthesiologist will grow in both complexity and importance. However, we must resist the urge to reinvent foundational principles. Telesurgery is a natural evolution of robotic surgery, in which procedures are performed remotely. By applying established anesthetic protocols, ensuring the presence of on-site surgical support, and investing in structured communication strategies, we can safely incorporate telesurgery into routine clinical practice. Prioritizing these principles will enhance procedural safety, improve patient outcomes, and support the expansion of surgical access across geographic boundaries.

CONFLICT OF INTEREST

None declared.

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ARTICLE INFO

Marcio Covas Moschovas
https://orcid.org/0000-0002-3290-7323

Correspondence address:
Marcio Covas Moschovas, MD, PhD
AdventHealth Global Robotics Institute, USA
380 Celebration Pl Suite 401,
Celebration, FL 34747, USA
E-mail: marcio.doc@hotmail.com

VIDEO SECTION

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Single-Port Robot-Assisted Post-Chemotherapy Unilateral Retroperitoneal Lymph Node Dissection: Feasibility and Surgical Considerations

Sisto Perdonà [1], Alessandro Izzo [1], Roberto Contieri [1], Francesco Passaro [1], Savio Domenico Pandolfo [2], Roberto Corrado [3], Giovanna Canfora [3], Rocco Damiano [4], Riccardo Autorino [5], Gianluca Spena [1]

[1] Department of Urology, Istituto Nazionale Tumori di Napoli, IRCCS, Fondazione "G. Pascale", Napoli, Italy; [2] Department of Neurosciences and Reproductive Sciences and Odontostomatology, Federico II University of Naples, Naples, Italy; [3] Department of Anesthesiology, Istituto Nazionale Tumori di Napoli, IRCCS, Fondazione "G. Pascale" Napoli, Italy; [4] Department of Urology, Magna Graecia University of Catanzaro, Catanzaro, Italy; [5] Department of Urology, Rush University Medical Center, Chicago, IL, USA

ABSTRACT

Introduction: Retroperitoneal lymph node dissection (RPLND) is indicated for testicular cancer patients with residual masses post-chemotherapy or stage I-II non-seminomatous germ cell tumors (NSGCT) (1, 2). Open RPLND remains the standard but carries significant morbidity. The laparoscopic approach, while minimally invasive, presents notable technical challenges (3). Robotic-assisted RPLND (rRPLND) offers a minimally invasive alternative with comparable oncological outcomes (4, 5). The Da Vinci Single Port (SP) system presents new possibilities for reducing surgical morbidity (6, 7).

Methods: We report a case of SP-rRPLND using a unilateral modified template and a lower anterior access (LAA) in a 41-year-old man with NSGCT (pT2, UICC Stage IB) who underwent left orchiectomy, followed by adjuvant chemotherapy. A CT scan revealed a 3.5 cm residual retroperitoneal mass in the left hilar region.

The surgical procedure, performed with the Da Vinci SP system, involved a 2.5 cm McBurney incision for retroperitoneal access. Instrument configuration followed a "Camera below" setting. The unilateral left-sided modified template guided dissection from the aortic bifurcation to the renal hilum, preserving vascular structures. A 3,5 cm residual mass and para-aortic nodes were excised with the help of flexible Greena® applicator for clips.

Results: Anesthetic management prioritized opioid-sparing techniques to enhance recovery. The patient received regional anesthesia, multimodal analgesia, and had an NRS pain score of 0 at discharge.

The console time was 79 minutes, with minimal blood loss and no complications. The patient resumed oral intake on postoperative day 1 and was discharged on day 2. Postoperative recovery was uneventful, with no complications or need for conversion to open or laparoscopic surgery.

Final histopathological examination revealed a germ cell tumor with features suggestive of immature teratoma, along with over 10 lymph nodes showing sinus histiocytosis. At six months post-RPLND, the patient remains disease-free, with a good general condition and no new symptoms. Tumor markers (AFP, β-hCG, LDH) are within normal limits, and CT imaging shows ***no evidence*** of

recurrence or residual retroperitoneal masses. Renal function and hormonal profile are stable. Given prior chemotherapy exposure, cardiovascular monitoring is advised. Follow-up will continue with clinical exams and tumor markers every 3-4 months, with the next CT scan planned at 12 months, unless symptoms warrant earlier imaging.

Conclusions: As far as we know this is the first reported case of SP-rRPLND in Europe. The LAA provides safe access while minimizing morbidity, potentially improving recovery (8). A unilateral approach, avoiding transperitoneal access, may further reduce morbidity (9). Future studies should validate long-term oncological outcomes and compare SP-rRPLND with multiport and open approaches. SP-rRPLND represents a promising advancement in minimally invasive testicular cancer surgery.

Data Availability

https://zenodo.org/records/14841220

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CONFLICT OF INTEREST

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Correspondence address:
Gianluca Spena, MD
Department of Urology, Istituto Nazionale Tumori IRCCS
Fondazione G. Pascale,
Via Mariano Semmola 53.
80131, Naples, Italy
E-mail: spena.dr@gmail.com

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ARTICLE INFO

Gianluca Spena
https://orcid.org/0000-0002-6714-9315

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VIDEO SECTION

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Robotic-assisted Laparoscopic Ureterocalicostomy (RALUC): How we do it

Jens-Uwe Stolzenburg [1], Doreen Trebst [1], Theodoros Spinos [2], Toni Franz [1], Anja Dietel [1], Stefan Siemer [3], Matheus Miranda Paiva [4], Evangelos Liatsikos [2], Ho Thi Phuc [1]

[1] Department of Urology, University of Leipzig, Leipzig, Germany; [2] Department of Urology, University of Patras, Patras, Greece; [3] Department of Urology, University of Saarland, Homburg, Germany; [4] Serviço de Urologia, Hospital Irmandade da Santa Casa da Misericórdia de Santos, Santos, SP, Brasil

ABSTRACT

Purpose: Ureterocalicostomy refers to the anastomosis of the lower pole calyces with the ureter after excision of the hydronephrotic lower renal pole (1, 2). Indications for ureterocalicostomy include previous failed pyeloplasty, ureteropelvic junction obstruction (UPJO) with anatomical abnormalities, such as intrarenal pelvis or short ureter (3) and proximal ureteral strictures (4). The purpose of this video is to demonstrate the technique of Robotic-Assisted Laparoscopic Ureterocalicostomy (RALUC) in a patient with UPJO and intrarenal pelvis.

Materials and Methods: Preoperatively, a retrograde ureteropyelography was performed. A transperitoneal approach with the Hassan technique was used, followed by the introduction of four additional DaVinci® trocars. The first step of the procedure is dissection of the retroperitoneum, the proximal ureter and lower part of the kidney including the renal hilum. The proximal ureter is dissected below the stricture. The lower pole artery is selectively bulldogged, and the lower pole of the kidney is resected in a circular manner to get broad based access to the lowest calix. The "Garland" suture technique is used to control hemostasis of the lower pole of the kidney. Therefore, a running, "low tension", circular suture is performed along the whole renal defect. This provides sufficient parenchymal hemostasis without narrowing the access to the lower calix. The ureter is then spatulated and sutured to the lower calix. The video shows step by step the ureterocalical anastomosis in single knot technique and explains tips and tricks.

Results: Total operative time was 114 minutes, while estimated blood loss was 25 mL. The JJ catheter was removed at 40 days postoperatively, while an ultrasound was performed after the JJ removal, showing no hydronephrosis. No intraoperative or postoperative complications were reported. The creatinine count and GFR after JJ removal were 92 μmoL/L and 70 ml/min, respectively. During the last follow-up the patient remained asymptomatic and had a mild chronical dilatation of the caliceal system but no hydronephrosis.

Conclusions: This video demonstrates the effectiveness and repeatability of RALUC for reconstructing UPJO in patients with very narrow or intrarenal pelvis. RALUC is a feasible, safe and efficient approach for selected patients requiring reconstruction of the upper urinary tract.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Jens-Uwe Stolzenburg, MD
Department of Urology,
University of Leipzig,
Liebigstraße 20, 04103 Leipzig, Germany.
Telephone: + 49 341-9717600
E-mail: Jens-Uwe.Stolzenburg@medizin.uni-leipzig.de

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https://orcid.org/0000-0003-2547-8329

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LETTER TO THE EDITOR

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Editorial Comment: Is the Effectiveness of Self-Visualization During Flexible Cystoscopy Gender-Dependent in Patients with no Previous Cystoscopy History?

Hinpetch Daungsupawong [1], Viroj Wiwanitkit [2]

[1] Private Academic Consultant, Phonhong, Laos; [2] University Centre for Research & Development Department of Pharmaceutical Sciences, Chandigarh University, Mohali, Punjab, India

To the editor,

We would like to comment on "Is the Effectiveness of Self-Visualization During Flexible Cystoscopy Gender-Dependent in Patients with no Previous Cystoscopy History? A Prospective Randomized Study (1)". This study looks into the effects of real-time self-visualization (SV) during flexible cystoscopy (FC) on discomfort, anxiety, patient satisfaction, and willingness to repeat the procedure. Male patients in the SV group had considerably lower pain scores and anxiety levels than those in the non-SV group, as well as higher satisfaction and readiness for future cystoscopy. However, no significant variations in pain outcomes were detected across groups among female patients. Although this study provides fascinating insights, there are several questions about its design and approach.

The biggest limitation of this study is the possibility of gender bias. According to the study, the SV group included an equal number of male and female patients, however the findings indicated that the SV intervention had a stronger effect on pain reduction in men than in women. This raises the question of whether gender-related variables such as pain perception, anxiety levels, and tolerance for medical procedures were not sufficiently controlled or examined. Differences in baseline features and psychological aspects between male and female patients may influence the results, but these variables were not controlled for in this investigation. Furthermore, selection bias may have been introduced by the randomization strategy, which assigned male patients to the SV and non-SV groups sequentially, as well as women. Although the 1:1 ratio was maintained, further randomization may not have adequately compensated for confounding variables.

The statistical analysis in this study may have been insufficient to determine the significance of pain scores in female patients. Although the pain difference among women was not statistically significant, the tiny effect size could have resulted in a type II error due to sample size or insufficient statistical power for this subgroup. The lack of multivariate analysis to account for potential confounding factors, such as prior medical procedures or experience with anxiety disorders, further limits the study's ability to make definite results.

Future research should include bigger and more diverse groups with thorough stratification for confounding factors (e.g., gender, baseline anxiety level, medical history) to improve the validity of the results. Furthermore, a longitudinal study assessing the long-term effects of self-visualization on anxiety, pain tolerance, and patient satisfaction over numerous cystoscopy sessions could give additional evidence of its efficacy. Alternative approaches that combine self-visualization with other pain-relieving techniques may also provide useful insights for enhancing the patient experience during cystoscopy. Finally, blinded study design may reduce bias in outcome evaluation, particularly for subjective variables like pain and satisfaction.

COMPLIANCE WITH ETHICAL STANDARDS

AI declaration

The authors used language editing computational tools in preparation of the article.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Hinpetch Daungsupawong, MD
Private Academic Consultant, Phonhong, Laos
E-mail: dramnuaykleebayoon@gmail.com

ARTICLE INFO

Hinpetch Daungsupawong
https://orcid.org/0009-0002-5881-2709

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Refining Methodological Approaches in Pediatric Neurosurgery: Considerations for Future Research

Shengyi Chen [1], Yuekun Fang [1], Bin Cheng [2]

[1] Department of Andrology, Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine, Wenzhou, China;
[2] Department of Urology, Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine, Wenzhou, China

To the editor,

We are writing to express our appreciation for the recently published study titled "The Effect of Detethering Surgery on the Bladder Function and Psychology of Children with Primary Tethered Cord Syndrome" in the International Braz J Urol (1). This study provides valuable insights into the impact of detethering surgery (DS) on bladder function and psychological behavior in pediatric tethered cord syndrome (TCS) patients. The authors' meticulous approach to evaluating postoperative outcomes has significantly contributed to the understanding of neurogenic bladder management and post-surgical recovery. In particular, the study's emphasis on both functional and psychological parameters offers a comprehensive perspective on the multifaceted nature of TCS management. Despite the study's commendable contributions, we would like to offer constructive suggestions for future improvements.

First, the choice of statistical models warrants further refinement. The study employs standard comparative analyses to evaluate bladder function outcomes; however, incorporating cluster analysis could provide additional insights (2). By grouping patients based on preoperative bladder characteristics or surgical response patterns, researchers could better identify subgroups that benefit most from DS. This stratified approach would enhance the study's applicability and clinical relevance.

Second, potential confounding variables merit additional consideration. While the study adjusts for age, gender, and baseline bladder function, other factors—such as socioeconomic status, prior interventions (e.g., pharmacological treatments or catheterization practices), and the severity of spinal cord tethering—may significantly impact postoperative outcomes. Incorporating these variables into the analytical framework would strengthen the study's robustness and improve result interpretation.

Third, the duration and sustainability of treatment effects warrant further exploration. The study assesses bladder function within a relatively short follow-up period. However, the long-term progression of neurogenic bladder dysfunction in TCS patients remains uncertain. Future studies should extend the follow-up duration to evaluate whether initial improvements persist over time or if secondary complications arise. Additionally, standardized postoperative management strategies should be considered to ensure consistent patient outcomes.

In conclusion, this study provides compelling evidence on the effects of DS in pediatric TCS patients, particularly regarding bladder function and psychological outcomes. However, refining statistical methods, accounting for additional confounding factors, and extending follow-up periods could further enhance the study's impact. We commend the authors for their valuable contribution and look forward to continued advancements in this field.

The Authors

CONFLICT OF INTEREST

None declared.

Correspondence address:
Bin Cheng, MD
Department of Urology, Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine, Wenzhou, China
E-mail: bincheng591@gmail.com

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Bin Cheng
https://orcid.org/0009-0003-6405-6150

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Integrating Clinical Insights and Methodological Refinement: Addressing Key Limitations and Future Directions in Imaging Biomarkers

Yuekun Fang [1], Shengyi Chen [1], Bin Cheng [2]

[1] Department of Andrology, Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine, Wenzhou, China;
[2] Department of Urology, Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine, Wenzhou, China

To the editor,

We read with great interest the article by Vieira et al., titled "Comparison of Morphological and Functional MRI Assessments of Periprostatic Fat for Predicting Prostate Cancer Aggressiveness," published in the International Brazilian Journal of Urology (1). The authors present valuable insights by highlighting the apparent diffusion coefficient (ADC) of periprostatic fat as a potential functional imaging biomarker associated with adverse outcomes in prostate cancer (PCa). This innovative approach adds a physiological dimension to imaging interpretation, potentially enhancing traditional risk stratification methods.

While the study is both timely and thought-provoking, several limitations not addressed by the authors warrant further discussion to enhance the translational applicability of their findings. First, the analysis did not adjust for key systemic metabolic factors—such as body mass index (BMI), insulin resistance, lipid profile, and chronic inflammation—which are known to influence adipose tissue characteristics (2). These factors may independently affect ADC values, potentially confounding their relationship with tumor aggressiveness. Future studies should incorporate these variables to more accurately assess the independent prognostic value of periprostatic fat ADC.

Second, ADC values were derived from a single small region of interest (ROI) placed in the anterior periprostatic fat, assuming tissue homogeneity. However, adipose tissue can be spatially heterogeneous, particularly in patients with obesity or metabolic syndrome, where regional variations in fat composition and inflammation are common. Employing multi-slice or volumetric ADC analysis across anterior, lateral, and posterior regions could provide a more comprehensive and representative assessment of periprostatic fat, thereby enhancing the robustness and generalizability of this imaging biomarker (3, 4).

Third, while the proposed ADC-based approach is promising, its clinical implementation hinges on measurement reproducibility and operational simplicity. The current study does not evaluate inter-observer agreement or outline standardization procedures. In this context, recent advances in artificial intelligence (AI), radiomics, and machine learning offer promising avenues to improve measurement consistency and predictive accuracy (5, 6). Automated segmentation, texture analysis, and AI-driven risk models could minimize

reader variability and facilitate the development of reproducible, clinically actionable tools for the early identification of aggressive PCa phenotypes.

In conclusion, Vieira et al. introduce a potentially impactful imaging biomarker for prostate cancer risk stratification. To maximize its clinical utility, future research should address metabolic confounding, adopt more extensive imaging protocols, and leverage AI-based technologies to improve reproducibility and integration into clinical workflows. These steps are essential for advancing personalized care in prostate cancer management.

The Authors

CONFLICT OF INTEREST

None declared.

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ARTICLE INFO

Bin Cheng
https://orcid.org/0009-0003-6405-6150

Correspondence address:
Bin Cheng, MD
Department of Urology, Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine,
Wenzhou, China
E-mail: bincheng591@gmail.com

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