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# The New Impact Factor of International Brazilian Journal of Urology Is 4.3

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In June 2026 Clarivate released the impact factor of 2026 (Figure-1). To our great satisfaction, The International Brazilian Journal of Urology achieved an impact factor of 4.3 (the cover in this edition). With this impact factor, The International Brazilian Journal of Urology establishes itself as one of the ten most important in the field of urology: a feat that would have been unthinkable in the past. In the present evaluation The International Brazilian Journal of Urology maintained your category ranking (Figure-2). This achievement was made possible only thanks to the Board of the Brazilian Society of Urology, the tireless work of the associate editors, and the prompt availability of the reviewers. Our journal is fully open-access—a unique service made possible by the pioneering spirit of the Brazilian Society of Urology. The Editor-in-Chief extends sincere thanks to everyone involved, especially the technical editorial team, who do outstanding work. We will discuss some articles from this edition below.

**Figure 1 - Impact factor of Int Braz J Urol in present year.**

$$\frac{\text{Citations in 2025 to items published in 2023 (253) - 2024 (224)}}{\text{Number of citable items in 2023 (54) + 2024 (56)}} = \frac{477}{110} = 4.3$$

**Figure 2 - Category Ranking of The International Brazilian Journal of Urology.**

| CATEGORY             |          |           |                |             |
|----------------------|----------|-----------|----------------|-------------|
| UROLOGY & NEPHROLOGY |          |           |                |             |
| 18/134               |          |           |                |             |
| JCR YEAR             | JIF RANK | QUART ILE | JIF PERCENTILE |             |
| 2025                 | 18/134   | Q1        | 86.9           | <div></div> |
| 2024                 | 16/133   | Q1        | 88.3           | <div></div> |
| 2023                 | 28/126   | Q1        | 78.2           | <div></div> |



The September-October number of International Brazilian Journal of Urology presents original contributions with a lot of interesting papers in different fields: Prostate cancer, Robotic Surgery, Kidney cancer, Testicular cancer, Infertility, Erectile dysfunction and Reconstructive Urology. The papers came from many different countries such as Brazil, China, France and India, and as usual the editor's comment highlights some of them. The editor in chief would like to highlight the work about robotic surgery in kidney cancer

Dr. Pal and colleagues from India, presented in page xxxx (1) a nice study about the Suture versus Sutureless Retroperitoneal Robot- assisted Partial Nephrectomy (RAPN) using Veriset™ Hemostatic Patch and concluded that Veriset™ hemostatic patch during retroperitoneal RAPN can be considered as a safe and feasible alternative to conventional cortical renorrhaphy to achieve hemostasis and the trifecta outcome. It can bring down warm ischemia time, console time, and blood loss without increasing the complications and reducing the renal function. However, as the study population predominantly comprised low nephrometry score tumors, the role of this approach in moderate- and high-complexity renal masses remains to be established and warrants validation in larger studies.

Robotic surgery has revolutionized the urologic surgery, resulting in better outcomes and faster recovery (2-9). The present study is interesting and will greatly assist the urologist in treatment of kidney cancer.

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

## CONFLICT OF INTEREST

None declared.

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**ARTICLE INFO**

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# Beyond Oral Therapies: A Practical Approach to Overcoming Barriers to Intracavernosal Injection Therapy in Clinical Practice

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## ABSTRACT

The objective of this manuscript is to present intracavernous therapy to readers, serving as a model and guide for physicians on how to introduce and manage it in their patients. Furthermore, we propose a strategy designed to ensure maximum safety with minor complications and provide an effective implementation of intracavernosal injection (ICI) therapy for the management of erectile dysfunction (ED). While phosphodiesterase type 5 inhibitors (PDE5i) are recognized as first-line therapy, approximately one-third of patients do not achieve satisfactory clinical outcomes, highlighting the importance of ICI as a highly effective second-line option. This comprehensive review details patient selection, drug formulation, structured patient education, stepwise dose titration, management of adverse events, and longitudinal follow-up. This approach is intended to minimize treatment-related complications, enhance patient confidence and adherence, and optimize long-term therapeutic outcomes. By suggesting a standardized clinical application of ICI therapy, this review aims to address key barriers that currently restrict its broader adoption in routine clinical practice.

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## INTRODUCTION

Erectile dysfunction (ED), defined as the recurrent or persistent inability to achieve and maintain an erection sufficient for satisfactory sexual performance, is a prevalent condition affecting millions of men globally. The prevalence and severity of ED increase significantly with age, impacting more than 50% of men in older age groups (1-3). Treatment modalities include oral pharmacotherapy, vacuum devices, and penile prostheses (4, 5).

Phosphodiesterase type 5 inhibitors (PDE5i), such as sildenafil, tadalafil, and vardenafil, are considered first-line therapies due to their established efficacy, ease of administration, and favorable safety profiles (6). These agents enhance the nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway by inhibiting PDE5, thereby promoting smooth muscle relaxation and increasing penile arterial inflow during sexual stimulation (7). However, up to 30–40% of patients do not achieve satisfactory erectile responses, being candidates for 2nd and 3rd line therapies. Additionally, PDE5i are contraindicated in patients taking nitrates, those with unstable cardiovascular disease, or those who have experienced recent major cardiovascular events. Adverse effects commonly include headache, flushing, nasal congestion, and dyspepsia (8).

Intracavernosal injection (ICI) therapy involves the direct injection of vasoactive agents into the corpora cavernosa, including prostaglandin E1, phentolamine, and papaverine, administered individually or in combination (called bimix or trimix) (9, 10). It is an effective second-line treatment, with reported success rates exceeding 85%, even among PDE5i non-responders (7, 11). Despite that, it is striking that the regular use of ICI therapy is underrated and underused by healthcare professionals who deal directly with patients with ED, frequently skipping directly to penile prosthesis after failure of PDE5i therapy, precluding patients from the chance of trying this less-invasive therapy.

Reasons for the underutilization of such an effective tool include restricted access to medical education and proper physicians' training on how to reduce the risk of adverse events, strategies to initiate and titrate the dosage, as well as patients' training to

overcome psychological and objective difficulties in self-administration, needle-related anxiety, logistical challenges related to drug handling and storage, and high cost (12, 13).

This review outlines the main concepts behind ICI, pharmacological agents, proper patient selection, and training. The purpose is to share an institutional protocol, developed and tested over years of use in a Tertiary Care Hospital, to address limitations that currently restrict its broader clinical adoption and to establish a safe, standardized, and practical approach to ICI therapy.

## MATERIALS AND METHODS

A narrative review format was employed to educate readers on the central concepts of ICI therapy, while providing clinicians with a pragmatic, evidence-based framework for its safe and effective application in real-world clinical practice. Rather than systematically aggregating all available data, the review prioritized key studies and influential publications that have significantly shaped the development and current use of ICI therapy, as well as our own experience.

A targeted literature search was conducted in the PubMed database in August 2025, covering studies published during the previous 25 years. The search strategy utilized the Medical Subject Headings (MeSH) term "Intracavernosal Injection Therapy" in combination with the keywords "Self-Injection Therapy for Erectile Dysfunction." Bibliographies of selected articles were also manually reviewed to identify additional relevant references.

Due to the descriptive nature of the review, neither quantitative data synthesis nor formal assessment of methodological bias was performed. Article selection was based on clinical applicability and the relevance of findings to real-world practice.

We present an institutional clinical strategy for ICI therapy implementation at a tertiary referral center. The protocol was developed through integration of contemporary evidence, structured consensus among experienced sexual medicine urologists, and retrospective evaluation of routine clinical outcomes. It standardizes key aspects of care, including drug selection, patient training, stepwise dose titration, and management

of treatment-related complications. This structured approach is designed to help clinicians safely initiate and optimize ICI therapy to improve efficacy and long-term adherence. No formal external validation was conducted.

## RESULTS AND DISCUSSION

As previously mentioned, ICI therapy may be administered as monotherapy or combination therapy (bimix, trimix, or quadrimix) to promote erection. Each pharmacological compound has distinct mechanisms of action and potential adverse effects, and combining them enables a multi-mechanistic approach, enhancing synergistic efficacy while allowing lower individual drug concentrations. This strategy may improve tolerability and reduce the incidence of dose-dependent adverse events associated with higher single-agent doses (9). The four vasoactive agents for ICI combinations are prostaglandine, papaverine, phentolamine, and atropine

## AGENTS AND SOLUTIONS

### Prostaglandin E1 - (PGE1)

The use of prostaglandin E1 for erectile dysfunction has been described since 1986 (14). In recent decades, prostaglandin E1 has become the most extensively studied intracavernosal vasoactive agent, being the most common agent in monotherapy.

The PGE1 mechanism of action involves stimulating adenylate cyclase and locally blocking  $\alpha$ -1 receptors, thereby promoting smooth muscle relaxation and arterial dilatation. The effective dose varies with the severity of the ED and its etiology, ranging from 2.5  $\mu$ g to 40  $\mu$ g when used as monotherapy. The most common monotherapy dose is between 10 and 20  $\mu$ g (15). This agent is commercially available in a lyophilized formulation, marketed under the brand name Caverject® (Pfizer), and can be obtained through standard retail pharmacies with a prescription.

The most frequent adverse effect of prostaglandin injections is penile pain, particularly at doses exceeding 15 $\mu$ g. Additionally, once reconstituted into active form—or when incorporated into compounded solutions such as trimix—the medication must be stored at 2-8°C (36-46°F) and has a stability period of up to 30 days.

### Papaverine

Papaverine was the first pharmacological agent identified as effective for treating erectile dysfunction. Discovered in 1848 as an opium alkaloid from *Papaver somniferum*, a plant, papaverine is frequently used in combination with other vasoactive agents in ICI therapy due to its adverse effect profile. Its mechanism of action includes phosphodiesterase inhibition, increased cAMP levels, reduced smooth muscle contraction, and promotion of arterial dilatation (16).

Papaverine monotherapy is typically administered at doses ranging from 10 to 60 mg (17). One of the most significant agent-specific adverse effects is penile fibrosis, which is thought to be related to the solution's acidic nature. Regarding penile fibrosis, Lakin et al. reported in a study of 100 men receiving ICI therapy with papaverine, with or without phentolamine, for 29 months, that nodules or plaques were associated with penile fibrosis. Nodules were defined as round areas at the injection site without other symptoms and were observed in 9 patients, typically resolving spontaneously and not being associated with penile curvature. Plaques occurred in 6 patients, further from the injection site, were indistinguishable from Peyronie's plaque and were, in some cases, associated with significant penile deformity, interfering with intercourse (18).

Although this cohort of men with severe ED lacked a control group to compare the rate of spontaneous Peyronie's disease development and establish causality, there remains a reluctance to use papaverine as monotherapy. Combination therapy with other vasoactive agents allows lower total papaverine doses, potentially reducing the risk of dose-related adverse effects (19).

### Phentolamine

Phentolamine's vasoactive function was discovered in 1978. The mechanism of action is a reversible, competitive antagonist at  $\alpha$ -adrenergic receptors. It causes vasodilation of vascular smooth muscle and reduces the adverse sympathetic effects on erection (20).

Phentolamine is primarily used as an adjuvant in combination with other vasoactive agents, as its efficacy as a single agent is limited, even at higher doses (15).

## Atropin

The use of atropine in erectile dysfunction has been reported by Virag et al. since 1985 (21). Atropine at low concentrations ( $10^{-8}$  M) blocks muscarinic receptors and regulates neurogenic corporal smooth muscle relaxation. In contrast, higher concentrations ( $10^{-3}$  M) may release endothelium-derived relaxing factor, a neurotransmitter involved in penile erection (22). Atropine should not be used as a single agent; typical doses range from 0.075 mg/mL to 0.15 mg/mL of atropine sulfate, most commonly in combination with other vasoactive agents, particularly in the quadrimix formulation (23). Figure-1 summarizes the mechanism of penile erection and the pharmacological action of intracavernosal agents.

## Combination

The nomenclature for combinations of vasoactive drugs is based on the number of vasoactive agents in the formula, not on their concentrations. Below are some examples of commercially available formulations in compounding pharmacies in our country:

Bimix – a combination of two vasoactive agents (e.g., Papaverine 30mg/mL + Phentolamine 1mg/mL; Prostaglandin 20 mcg/mL + Phentolamine 2mg/mL).

Trimix – a combination of three vasoactive agents (e.g., Papaverine 30mg/mL + Phentolamine 1mg/mL + Prostaglandin 10mcg/mL) \* most referred formula in the literature.

“Super” Trimix - higher concentration of three vasoactive agents (e.g., Papaverine 25mg/mL + Phentolamine 4mg/mL + Prostaglandin 20mcg/mL).

Quadrimix – a combination of four vasoactive agents (e.g., Papaverine 20mg/mL + phentolamine 3,3mg/mL + prostaglandin 44mcg/mL + Atropine 0,11mg/mL).

Combinations and dosages of these agents vary by pharmacy and can be selected based on the patient's response, side effects, and preferences. The effective dose represents the effect of available agents, their concentration in a given solution, and, of course, the injected volume. Accordingly, dosing discussions should focus on the delivered pharmacological dose rather than volume alone. To standardize communication

and reduce ambiguity, the use of international units (IU)—analogous to insulin syringes—is recommended, with 1 IU corresponding to 0.01 mL.

Clinical efficacy should be interpreted as a function of the administered dose in the setting of patient-specific variables, including cavernosal tissue integrity, arterial integrity, veno-occlusive function, and psychological well-being. Erectile response, therefore, reflects a dynamic interaction between pharmacologic stimulation and biologic capacity, while a stressful environment and consequent adrenergic influence will act negatively.

## Adverse Effects

The majority of side effects of the intracavernous injection are related to the puncture site or local complications. Otherwise, the rates of side effects are conflicting in the literature and range from 5% to 94% (24–26).

## About starting the treatment for erectile dysfunction

A comprehensive evaluation of the patient's sexual history, emphasizing a patient-centered approach, is essential. As with all patients with ED, this assessment should include a thorough medical, sexual, and psychological history, a physical examination, and basic laboratory and hormonal testing (7). Patients should be informed about the association between ED, endothelial dysfunction, and cardiovascular disease. If appropriate, according to cardiovascular risk stratification (27), complementary investigations must be conducted (28). Education regarding lifestyle modifications, such as dietary changes and increased physical activity, can improve overall and sexual health. A detailed history of ED, previous treatments, including previous exposure to ICI, such as in previously performed penile duplex doppler with induced erection, should be inquired, and alignment of patient expectations is fundamental to effective management (29). Patients with contraindications, failure to respond, or intolerance to PDE5i are candidates for ICI therapy.

## The Patient Selection

Shared decision-making, incorporating a comprehensive assessment of patient needs, comorbidities, and potential barriers to treatment, is essential to optimize outcomes, reduce dropout rates, and minimize adverse events.



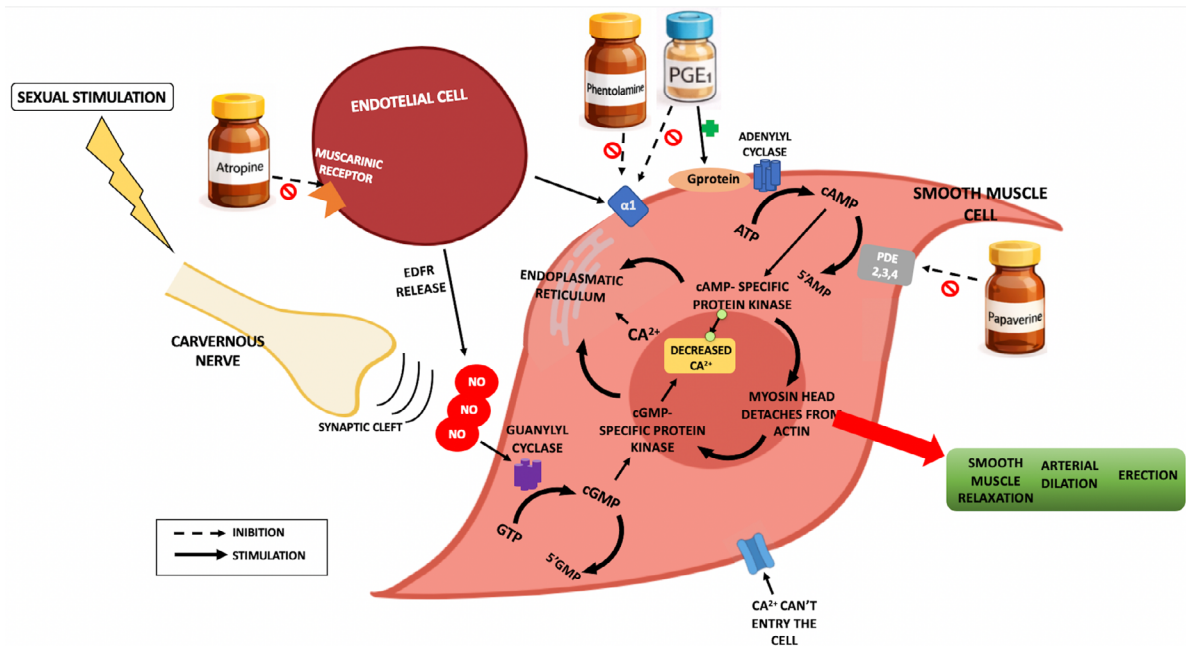
**Figure 1 - Mechanisms of penile erection and pharmacological action of intracavernosal agents.**

Diagram illustrates the intracellular pathways regulating penile smooth muscle tone and the principal sites of action of commonly used intracavernosal pharmacotherapies. Sexual stimulation activates parasympathetic signaling, promoting nitric oxide (NO) release from endothelial cells via endothelium-derived relaxing factor (EDFR). NO stimulates guanylyl cyclase, leading to increased cyclic guanosine monophosphate (cGMP) production. Cyclic adenosine monophosphate (cAMP) and cGMP, the key intracellular second messengers mediating smooth muscle relaxation, activate their respective protein kinases. These kinases phosphorylate downstream target proteins, resulting in potassium channel opening, calcium channel inhibition, and sequestration of intracellular calcium by the endoplasmic reticulum. The consequent reduction in intracellular calcium ( $\text{Ca}^{2+}$ ) levels promotes smooth muscle relaxation, arterial dilation, and erection. Prostaglandin E1 (PGE1) activates adenyl cyclase via G protein-coupled receptors, increasing cAMP levels and further contributing to  $\text{Ca}^{2+}$  reduction and smooth muscle relaxation. Papaverine acts as a nonspecific phosphodiesterase inhibitor, enhancing cyclic nucleotide accumulation. Phentolamine is a competitive  $\alpha$ -adrenergic receptor antagonist that attenuates sympathetic-mediated smooth muscle contraction. Solid arrows represent stimulatory pathways, whereas dashed arrows indicate inhibitory effects. GTP denotes guanosine triphosphate; ATP denotes adenosine triphosphate.

Although there are generally no absolute contraindications to intracavernosal injection (ICI) therapy—making it a feasible option for most patients (30)—careful patient selection remains critical. Evaluation should include manual dexterity, tremor, visual acuity, penile exposure, abdominal circumference, and the ability to perform self-injection or to receive assistance from a partner (31), as these factors may significantly impact treatment adherence and effectiveness.

Additionally, needle anxiety, substance abuse, and psychiatric disorders may represent important limitations to therapy. In this context, partner involvement in injection training may help mitigate some of these barriers and improve overall treatment adherence.

### Contraindications

Contraindications to intracavernosal therapy primarily involve hypersensitivity to vasoactive agents or conditions that elevate the risk of priapism, fibrosis, or bleeding. The literature identifies absolute contraindications as a history of priapism, hemoglobinopathy, severe penile fibrosis, penile implants, and bleeding diathesis (9, 15, 17, 31, 32).

However, some clinical experiences suggest these may not always constitute absolute contraindications. Intracavernosal injection therapy has been used in patients receiving antiplatelet agents, such as acetylsalicylic acid (ASA), and anticoagulants with an overall favorable safety profile. Available data indicate that the

main concern in this population is an increased risk of minor bleeding complications, including ecchymosis or hematoma at the injection site, rather than major hemorrhagic events (32). In this context, pragmatic measures derived from clinical practice—such as rigorous patient training in injection technique, use of the smallest effective needle (0,30 x 8mm), proper site selection, and prolonged local compression after injection—may help mitigate bleeding risk. With appropriate patient selection and adherence to these precautions, ICI can be performed safely in many individuals, and current evidence does not support considering antithrombotic therapy as an absolute contraindication. However, caution remains warranted (7, 17, 33). It remains essential to inform patients about potential complications and to engage in shared decision-making (30).

### Injection training

Adequate training for safe and confident self-administration of ICI therapy is essential. The initial administration must be performed in the clinical setting by a physician assistant or a trained nurse under a urologist's supervision (5, 7, 15, 17, 34).

The primary goal of the initial visit is not to repeatedly administer injections in the office until the ideal dose is reached, but rather to familiarize the patient with the entire therapeutic process. This includes preparing the syringe, understanding the use of international units (IU) as the standardized language for dose communication, anatomical orientation, proper penile positioning for injection, and experience with the first intracavernosal injection (17). During this first visit, a standardized low initial dose, selected based on the individual patient's clinical profile, is administered in the office. This dose serves both as a safety measure and as a baseline assessment of pharmacologic responsiveness.

At the second visit, the patient is expected to independently prepare the medication and perform the injection under the supervision of the training team. At this stage, adjustments - including modification of the drug formulation and/or the administered volume - may be made based on the response observed in the initial visit, always balancing efficacy and safety.

Although many patients are discharged after the second supervised injection and begin home administration, the optimal therapeutic dose is often achieved progressively over the first months of treatment. Ongoing communication between the patient and the prescribing team is essential to allow careful dose titration, minimize adverse effects—particularly prolonged erections—and ensure long-term adherence and confidence with therapy.

Comprehensive counseling regarding potential complications is mandatory. Patients must commit to strict adherence to prescribed dosing, maintain direct access to the medical team for guidance, and have clear instructions on how to seek emergency care in the event of adverse outcomes such as prolonged erections or priapism.

Nowadays, two injection delivery systems are available through compounding pharmacies in our country. The first—commonly used worldwide—consists of a multidose vial and a disposable syringe. In this method, the patient must aspirate the prescribed dose of the vasoactive agent from the vial and administer it using a disposable syringe and an insulin needle. In our practice, we use the 0,30 x 8mm needle. It is essential to verify the syringe calibration, as some are marked in international units (IU), while others are calibrated in milliliters (mL) or cubic centimeters (cc).

The second system comprises medication cartridges for use with injection pens. This format has gained popularity due to its numerical dose display in international units, which facilitates dose titration and enhances patient confidence.

In this system, disposable needles are attached to the pen before administration, eliminating the need for manual dose preparation once the medication is in the cartridge. Consequently, patients can focus primarily on proper injection technique rather than dose measurement, simplifying the procedure and potentially reducing dropout rates (31, 35).

Before the injection, it is essential to clean the area with alcohol swabs, then stretch the penis by the glans and insert the needle completely, in the dorso-lateral of the penile shaft at a 90° angle to avoid missing injections and perform an adequate and safe intracavernous administration (15). It is important to instruct patients to administer the injection laterally at the 3 o'clock



or 9 o'clock position, while avoiding blood vessels, and always alternate the puncture side. Immediately after the injection, the puncture site should be compressed for 30 to 60 seconds. It's not recommended to compress or use a tourniquet at the base of the penis (17). Figures 2 and 3 illustrate the technique for intracavernosal injection.

### Choosing a vasoagent and starting dose

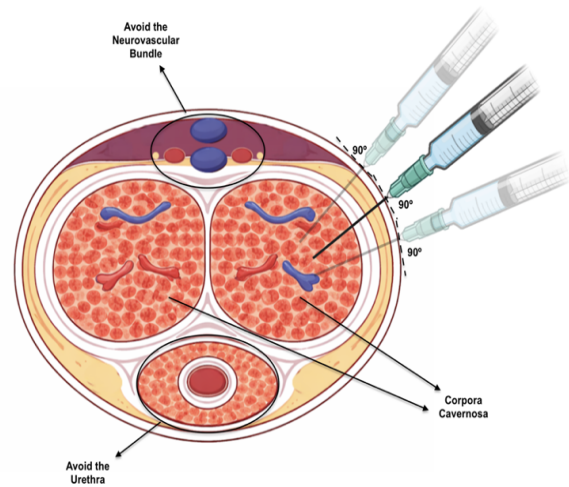
After determining that a patient is a candidate for intracavernous therapy, titration of the dose and selection of an appropriate vasoactive agent should consider the etiology of erectile dysfunction, risk factors, comorbidities, previous failed attempts, and residual erectile function. During this phase, the risks of prolonged erections and insufficient dosing are elevated, underscoring the importance of initiating treatment in a clinical setting under urologist supervision (29, 36).

The preferred vasoactive agents are typically Bimix (Papaverine 30 mg/mL and Phentolamine 1 mg/mL) or Trimix (Papaverine 30 mg/mL, Phentolamine 1 mg/mL, and Prostaglandin 10 mcg/mL). For organic erectile dysfunction, the Trimix dose should be determined based on previous erectile response or erection quality. PDE5i should also be considered. For neurogenic erectile dysfunction, a low dose of Bimix is recommended.

In patients following radical prostatectomy, with normal pre-procedure erectile function, a low dose of Bimix is advised. For patients with reduced pre-procedure erectile function after radical prostatectomy or those who have undergone pelvic irradiation, a low dose of Trimix is initially recommended (29).

If the patient has previously undergone Penile Doppler Duplex Ultrasonography (PDDU) with an adequate redosing protocol and achieved a Best Quality Erection or an Erection Hardness Score (EHS) of 3 or greater, the recommended initial dosage for training should be the exam dose or 20% lower to mitigate the risk of prolonged erections. This dosage reduction accounts for the anxiety and adrenergic response associated with PDDU, which can diminish the vasoactive response (30). The initial dosing should be tailored to the patient's current erectile function and the response to PDE5i. Dosing categories are defined as low (1-10 units), moderate (11-50 units), and high (>50 units).

**Figure 2 - Transversal anatomy of the penis and recommended intracavernosal injection technique.**



Cross-sectional representation of the penile shaft demonstrating the corpora cavernosa as the target structures for intracavernosal drug administration. Safe needle placement is performed at the mid-shaft level at the 10 o'clock (left lateral) or 2 o'clock (right lateral) position, using a perpendicular (90°) angle relative to the penile surface. The dorsal neurovascular bundle and urethra must be avoided during injection. Drug delivery is illustrated using a 29-gauge, ½" needle on a 100-unit syringe, consistent with standard intracavernosal injection practice.

**Figure 3 - Schematic representation of intracavernosal injection.**

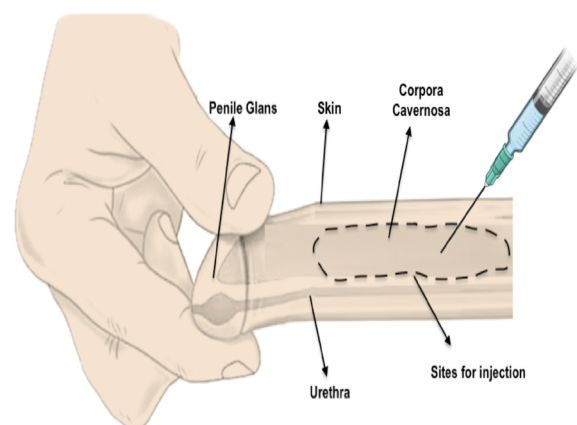


Illustration of the penis demonstrating the relationship between the corpora cavernosa, corpus spongiosum, urethra, and penile glans. The recommended intracavernosal injection sites are illustrated within the cavernosal bodies, emphasizing proper needle placement. This diagram highlights the structural basis underlying safe intracavernosal pharmacotherapy.

### Dose adjustment

Dose adjustments should be guided by the hardness and duration of the erection achieved after the injection. The primary goal is to achieve an EHS of  $\geq 3$  or a numerical score of 7 out of 10, indicating an erection sufficient for vaginal intercourse, with a duration of approximately 60 minutes (30). Table-1 provides a suggested safe dose-titration protocol.

### Management of adverse events and complications

Reported complication rates are variable and predominantly involve minor injection-site events. Among men who discontinue treatment, penile pain or discomfort is the most commonly reported adverse effect, most frequently associated with prostaglandin doses exceeding 15 $\mu$ g (25).

According to the literature, the prevalence of pain associated with PGE1 ranges from 9% to 34%. According to Sung et al., 45.9% of patients who discontinued with ICI cited pain as the primary adverse event (24). Cost is an additional consideration for the treatment modality and dropout rates. Mulhall et al. reported that 28% of men discontinued treatment due to high cost (25).

To ensure the treatment success, some pain management strategies include reducing the prostaglandin concentration or altering the formulation to exclude this agent. Pain typically decreases over the course of treatment, and slower injection rates are associated with reduced discomfort (24, 25, 37).

Priapism is a particularly concerning adverse effect, as it constitutes a urological emergency that can result in tissue damage, fibrosis, and loss of erectile function. The risk of priapism varies by vasoactive agent formulation, but it is mostly determined by the dose used. Priapism is most commonly observed during the initial dose-titration phase, with reported rates ranging from 2% to 15% (36). A prolonged erection is defined as one that persists for between two and four hours, whereas priapism refers to an erection lasting more than 4 hours. Ischemic priapism (low-flow, veno-occlusive) constitutes a medical emergency due to the risk of corporal fibrosis and irreversible erectile dysfunction if not treated promptly. Several conservative treatments have been described, including exercise,

ejaculation, ice packs, cold baths, and cold-water enemas (38). The success rates for these measures alone are variable and infrequently reported (39); however, they should be attempted, particularly in patients without immediate access to drainage or injection of a sympathomimetic agent.

For priapism treatment, the first step is injection of a sympathomimetic agent (phenylephrine, etilephrine, or adrenaline) into the corpora cavernosa. Etilephrine is often selected in our country due to the limited availability of phenylephrine. Repeat injections may be administered as needed, and treatment is discontinued once detumescence is achieved. In the absence of detumescence, corporal aspiration is performed following a penile nerve block. Table-2 summarizes the medical treatment.

A 19-G scalp needle should be introduced into one of the corpora cavernosa to facilitate blood outflow and reduce intracavernous pressure. Although most urologists prefer to place the butterfly needle from the side of the shaft, insertion through the glans has been reported to reduce the risk of ecchymosis and hematoma formation (40). Placement of an additional 19-G butterfly needle in the contralateral corpora cavernosa with cold saline irrigation may also be performed (Figure-4) (41, 42). If patients do not respond, shunt surgery is considered the next treatment option (43).

Penile shunt surgery is rarely required to treat ICI priapism. The main objective of the procedure is to create an outflow of ischemic blood from the corpus cavernosum into the corpus spongiosum, thereby restoring normal circulation within these structures (44). Four categories of shunt procedures have been described: percutaneous distal shunts, such as Winter's procedure, Ebbehøj's technique, and T-shunt (45-47); open distal shunts, including Al-Ghorab's procedure and Burnett's technique (48); open proximal shunts, such as Quackles's technique (49), and vein anastomosis shunts, like Grayhack's procedure (50). The choice of shunt procedure may be influenced by surgeon preference and familiarity (42).

In addition to priapism and prolonged erections, the development of plaques and penile curvature is a significant concern. These complications are strongly

**Table 1 - Dose adjustment algorithm for intracavernosal injection therapy.**

| DOSE        | RIGIDITY | DURATION      | ADJUSTMENT       |
|-------------|----------|---------------|------------------|
| 1-5 UNITS   | ≤ 20%    | Irrelevant    | Increase 5 units |
| 1-5 UNITS   | 30-50%   | Irrelevant    | Increase 5 units |
| 1-5 UNITS   | 60-70%   | ≤ 15 minutes  | Increase 2 units |
| 1-5 UNITS   | 60-70%   | 15-60 minutes | Maintain dose    |
| 1-5 UNITS   | 60-70%   | > 60 minutes  | Reduce 1 unit    |
| 1-5 UNITS   | > 70%    | ≤ 60 minutes  | Maintain dose    |
| 1-5 UNITS   | > 70%    | > 60 minutes  | Reduce 2 units   |
| 6-10 UNITS  | ≤ 20%    | Irrelevant    | Increase 5 units |
| 6-10 UNITS  | 30-50%   | Irrelevant    | Increase 5 units |
| 6-10 UNITS  | 60-70%   | ≤ 15 minutes  | Increase 2 units |
| 6-10 UNITS  | 60-70%   | 15-60 minutes | Maintain dose    |
| 6-10 UNITS  | 60-70%   | > 60 minutes  | Reduce 2 units   |
| 6-10 UNITS  | > 70%    | ≤ 60 minutes  | Maintain dose    |
| 6-10 UNITS  | > 70%    | > 60 minutes  | Reduce 2 units   |
| 11-30 UNITS | ≤ 20%    | Irrelevant    | Increase 5 units |
| 11-30 UNITS | 30-50%   | Irrelevant    | Increase 5 units |
| 11-30 UNITS | 60-70%   | ≤ 15 minutes  | Increase 2 units |
| 11-30 UNITS | 60-70%   | 15-60 minutes | Maintain dose    |
| 11-30 UNITS | 60-70%   | > 60 minutes  | Reduce 2 units   |
| 11-30 UNITS | > 70%    | ≤ 60 minutes  | Maintain dose    |
| 11-30 UNITS | > 70%    | > 60 minutes  | Reduce 2 units   |

Recommended dose adjustment strategy based on erectile rigidity and duration of erection following intracavernosal injection. Dose modifications are expressed in units, where 1 unit corresponds to 0.01 mL (0.01 cc). The algorithm is based on a standard trimix formulation containing papaverine 30 mg/mL, phentolamine 1 mg/mL, and prostaglandin E1 (alprostadil) 10 µg/mL.

associated with frequent injections and higher doses of papaverine. Retrospective studies have reported such alterations in 5% to 30% of patients (31), and they account for treatment discontinuation in 24% of cases (24).

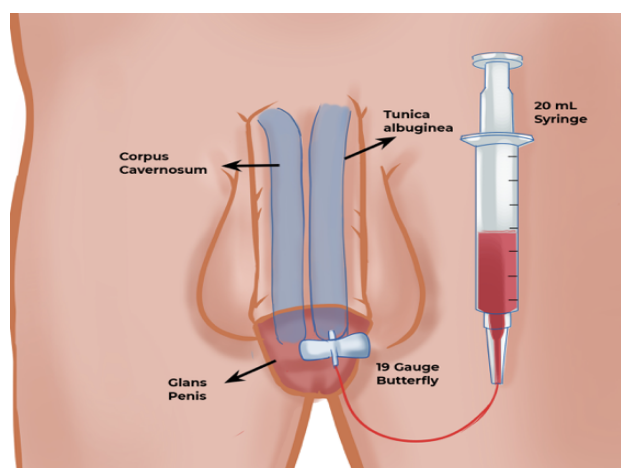
Other minor local side effects include nodules at the injection site and small hematomas that do not require intervention. Unusual adverse effects such as inadvertent urethral injection, foreskin swelling, and

loss of local sensation have also been reported. In these cases, discontinuation of injections until symptom resolution and reassessment of injection technique are recommended (18, 24). Infection is a possible but rare adverse effect, with only a single case reported in one study (51). Proper injection techniques, single-use of syringes and needles, and strict hygiene at the injection site are essential to minimize this risk.

**Table 2 - Sympathomimetic agents for the management of prolonged erection and priapism.**

| Drug          | Dose/Instructions for use                                                                                   |
|---------------|-------------------------------------------------------------------------------------------------------------|
| Phenylephrine | Intracavernous injection of 200 µg every 3-5 minutes.<br>The maximum dosage is 1 mg within 1 hour.          |
| Etilephrine   | Intracavernosal injection at a concentration of 2.5 mg in 1-2 mL of normal saline.                          |
| Adrenaline    | Intracavernous injection of 2 mL of 1/100,000 adrenaline solution up to five times over a 20-minute period. |

Recommended sympathomimetic agents and dosing protocols used for intracavernosal administration in the acute management of prolonged erection and ischemic priapism. Doses reflect commonly reported clinical practice and guideline-based approaches aimed at achieving detumescence while minimizing systemic adverse effects.

**Figure 4 - Drainage technique of prolonged erection.**

Schematic representation of corporal aspiration performed through the penile glans. A 19-gauge butterfly needle is inserted above the coronal sulcus, in the midglans, into one of the corpora cavernosa. The needle is connected to a 20-mL syringe to aspirate stagnant blood from the corpus cavernosum, facilitating detumescence.

Systemic side effects are infrequent and mainly include hypotension and dizziness. At higher doses of papaverine, elevations in liver transaminases have been reported, most commonly in patients with a history of alcohol consumption (19, 31).

### Practical Considerations

Several considerations are important to optimize therapeutic outcomes. Penile pain following injection may result from the prostaglandin dose, as some patients exhibit intolerance. Reducing the prostaglandin dose or utilizing a formulation without this vasoactive agent are potential alternatives.

Additionally, the requirement to refrigerate prostaglandin can lead to dissatisfaction and increased rates of treatment discontinuation.

Patients with Peyronie's disease or palpable plaques should be informed about the potential risk of exacerbating fibrosis when using papaverine. Consideration should be given to formulations that do not contain papaverine. Patients with coagulation disorders or those receiving anticoagulant therapy are at increased risk for small hematomas and bleeding. Therefore, practitioners should be proficient in injection techniques, and compression should be applied to the injection site for at least 60 seconds in these

individuals (30). When the administered dose exceeds 0.5 mL, switching to a more concentrated formulation is recommended (31).

### Follow-up Protocol

Following treatment initiation and dose titration, monthly follow-up is recommended for the first three months. Regular assessment should include erection score, erection duration, administered dose, application technique, and necessary dose adjustments. All patient concerns should be addressed during these visits.

After establishing treatment efficacy and completing the initial follow-up period, office visits every six months are advised. Ongoing evaluation should include monitoring for side effects, penile examination, injection-related difficulties, patient concerns, and overall satisfaction with therapy.

### CONCLUSIONS

Intracavernous injections are highly effective and safe. The implementation of standardized formulations and dosing protocols is essential to optimize outcomes, minimize adverse effects, and reduce therapy discontinuation. ICI should be considered the second-line therapy for ED after failure of PDE5i and should be considered before the indication of penile prosthesis surgery.

### ABBREVIATIONS

ED = Erectile dysfunction

ICI = Intracavernosal Injection

PDE5i = Phosphodiesterase type-5 inhibitors

NO-cGMP = Nitric oxide-cyclic guanosine monophosphate

PGE1 = Prostaglandin E1

ASA = Acetylsalicylic acid

PDDU = Penile Doppler Duplex Ultrasonography

EHS = Erection Hardness Score

IU = International units

mL = milliliters

CC = Cubic centimeters

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### CONFLICT OF INTEREST

None declared.

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# Clitoris Anatomy Applied to Aesthetic, Reconstructive and Transgender Surgery: A Narrative Review

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## ABSTRACT

This review aims to provide a comprehensive analysis of the anatomy of the clitoris, focusing on its complex internal structure, topographic relationships, and neurovascular supply highlighting its morphological features and clinical implications in aesthetic, reconstructive and transgender surgery. We analyzed papers published in the past 70 years in the databases of Pubmed, Embase and Scielo. We excluded case reports, editorials and opinions of specialists. Studies were excluded if they lacked clear anatomical descriptions of the clitoris, if full-text access was unavailable, or if they were published in languages other than Portuguese, English, or Spanish. Long overshadowed by other anatomical studies, the clitoris is now understood as a multi-planar organ with significant depth and extensive innervation with several applications and surgical techniques, such as clitoral hood reduction (hoodectomy) or labiaplasty. The clitoris is a very important structure to female physiology, specially orgasm. Knowledge of clitoris anatomy is a fundamental step in aesthetic surgery and in reconstruction. In aesthetic and reconstructive clitoroplasty, Buck's fascia is a critical anatomical landmark. The neurovascular bundle resides just beneath this fascia on the dorsal aspect of the clitoris. By staying superficial to or carefully dissecting within this layer, surgeons can ensure that the blood supply and sensory fibers remain intact, preventing glans necrosis and desensitization. This narrative review addresses the anatomical integration, surgical techniques, and functional importance of the clitoral complex in the transgender population and transgender surgery.

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## INTRODUCTION

The vulva consists of a series of structures located in the anterior region of the perineum. It is the site where the main procedures in regenerative gynecological surgery are performed. The vulva can be didactically divided into 6 regions or complexes: Pubic area; Clitoral complex; Clitorolabial interface; Labia minora; Labia majora and Perineal region. This division is of great importance in the study of the perineal and vulvar region (1). In the field of aesthetic surgery, the primary goal is to enhance the appearance of the vulva while strictly preserving sensation and function. In this review we will describe the anatomy of clitoral complex and clitorolabial interface.

Understanding clitoral topography is vital in surgical procedures such as vulvectomies, pelvic floor reconstructions, and gender-affirming surgeries. The clitoris is not merely a superficial glans; it is a complex, tri-dimensional structure composed of the glans, the body (corpus), and the bilateral crura (2). Understanding the precise pathways of the dorsal nerves and the deep arteries is critical to avoid complications like chronic pain, numbness, or tissue necrosis and to preserving sexual function and sensation. In this review we show the most important aspects of the clitoris surgical anatomy applied to aesthetic, reconstructive and transgender surgery.

## CLITORIS EMBRIOLOGY

In embryology of the female genital tract, both the external and internal genitalia differ before the end of the first trimester. The female genitals are made up of the gonads, fallopian tubes, uterus, cervix, vagina and external genitalia. A male fetus develops in the presence of a Y chromosome that encodes the SRY protein. The SRY protein allows for testicular differentiation and androgen production, including testosterone. In its absence, this process will not occur, leading to the formation of a female fetus (3, 4).

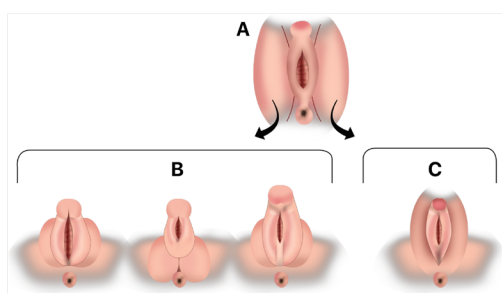
Embryological development of the female reproductive tract is a process rich in its complexity in which fetal structures are differentiated in an orchestrated way to form external genitalia (4, 5). Any impairment at this stage can lead to a slight difference, resulting in congeni-

tal anomalies that affect the female genital tract. The genital tubercle is the anlage of the external genitalia in both males and females. Congenital abnormalities frequently result from abnormal formation of this structure and its subsequent development (3-6). The most important parameter in female genitalia to evaluate the fetal androgen exposure and gender detection between 11 and 13 weeks post conception (WPC) is the AGD (anogenital distance) (6). The relationship between AGD and serum testosterone in both genders was reported, meaning that a long distance is associated with elevated serum testosterone levels (5). The female external genitalia do not require fetal ovarian hormones in their development (4-6) as occurs in male fetuses that requires hormones for their development.

In early development, the external genitalia are undifferentiated. The genital tubercle initiates differentiation into a penis or clitoris at 8 WPC. The female external genitalia develop due to hormonal stimuli between the third and fifth month of gestation (5-7). The genital tubercle elongates, giving rise to the clitoris; the urethral folds do not fuse and give rise to the labia minora. The genital folds elongate and form the labia majora; the urogenital sulcus remains open and forms the vaginal vestibule (Figure-1). In an interesting paper with human female fetuses using reconstruction and histological techniques shows important aspects of the clitoris development (7). The authors show that the mesenchymal inside the clitoris soon divides into the glans and the cavernous bodies (7). The clitoral hood forms between 10 and 14 WPC as a fold of tissue that extends from proximal to distal over the glans. The labia majora gradually cover the clitoris after 14 WPC. The labia minora form at 8 WPC from the ridges of thick-skin epithelium that flank the genital exit. In this paper the authors proposed that the clitoris "disappears" between both labia majora because the 50% of decline in its length between 15 and 20 WPC (7). However, when we analyzed our sample in a previous publication with 22 female fetuses we observed that there are no significant differences in clitoris length and width between 12 and 22 WPC and the glans clitoris is easily observed in female human fetuses during the 2nd gestational trimester (Figure-2) (8). Normative curves about the clitoris development are scarce in literature but has great importance to identify clitoromegaly in neonatal period (9).

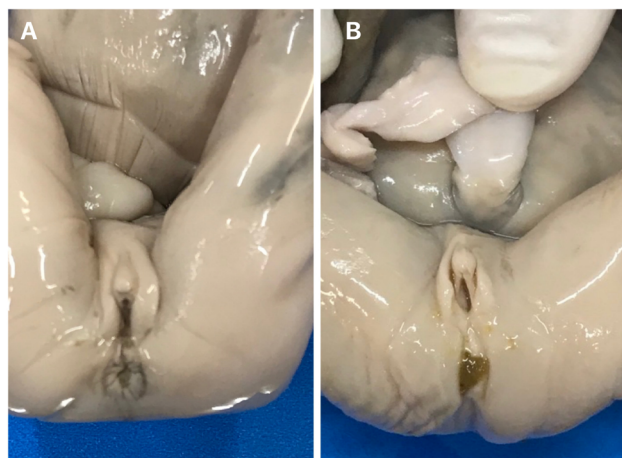
A nice basic research study of human fetal genital tubercles during the first trimester after elective termination of pregnancy showed that the distinction of glans and shaft begins at 9 WPC and the formation of the prepuce starts to cover the dorsal aspect of the glans clitoris at 11 to 12 WPC. The authors also identified the development of the clitoral ridge as a well vascularized structure at the midline of the vestibular groove with the presence of the neurovascular band during the 1st gestational trimester (10).

**Figure 1 - Clitoris Embryology.**



Schematic drawing showing the genital development in male and in female. A) Undifferentiated stage; B) Male genitalia development, we can observe the elongation of genital tubercle, to form the penis and C) Female genitalia totally developed.

**Figure 2 - Clitoris in 2nd gestational trimester in human fetuses.**

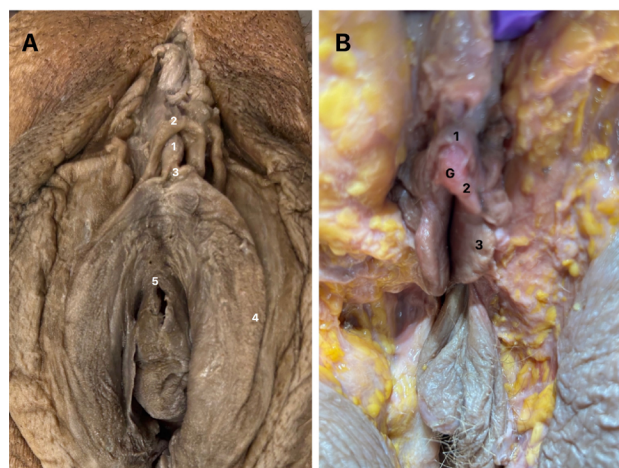


The figure shows two female fetuses with 16 weeks post-conception (A) and 18 weeks post-conception (B). We can observe the clitoris aspect during the 2nd gestational trimester. In this period the glans and clitoris frenulum are easily identified.

## TOPOGRAPHIC ANATOMY OF THE CLITORIS

The clitoris is an erectile organ homologous to the penis, responsible for the sensation of pleasure during female orgasm; knowledge of the anatomy of the clitoris is of fundamental importance in regenerative gynecology (2, 11). This organ is formed by erectile tissue, composed of the glans, the body (*corpora cavernosa*), and the vestibular bulbs. The glans and the bulb of the vestibule correspond to the corpus spongiosum. The clitoris is partially covered by structures derived from the labia minora – the prepuce and the frenulum of the clitoris. It is in contact with the supero-anterior portion of the pubic arch to which it is attached by the suspensory ligament of the clitoris (9, 11, 12). The labia minora are small mucous folds located between the labia majora, approximately 4 to 4.5 cm in length, with the space between them being called the vestibule of the vagina (13). Superiorly, the labia minora are related to the clitoris, dividing to form an upper portion that partially covers the glans, called the clitoral prepuce, and inferiorly the clitoral frenulum, which attaches to the lower portion of the glans (Figure-3). Inferiorly, the labia minora unite to form the labial frenulum or fork (13-15).

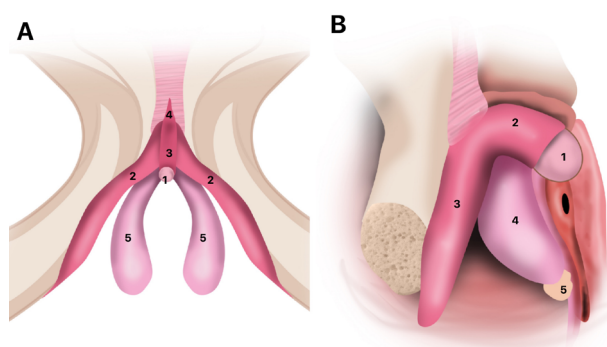
The relationship between the clitoris and the labia minora is one aspect of importance of anatomical continuity and functional synergy. In gynecology, these structures are often viewed together as the clitoral-labial complex (16, 17). Understanding how they transition into one another is the most critical factor in achieving natural-looking and sensation-preserving results in aesthetic and reconstructive surgery. The labia minora do not simply end near the clitoris; they bifurcate (split) into two distinct cutaneous folds as they travel superiorly: Superior Fold (Prepuce or Hood): The upper portions of the labia minora fuse together over the clitoral glans to form the clitoral hood; Inferior Fold (Frenulum): The lower portions fuse beneath the clitoral glans, forming the frenulum, similar to the frenulum of the penis and the lateral connection: The lateral walls of the labia minora are tethered to the clitoral body. When the labia are pulled or stimulated, this tension is transmitted directly to the clitoral glans, facilitating the “gliding” mechanism during sexual activity (Figure-3) (16-20).

**Figure 3 - Glans of the clitoris.**

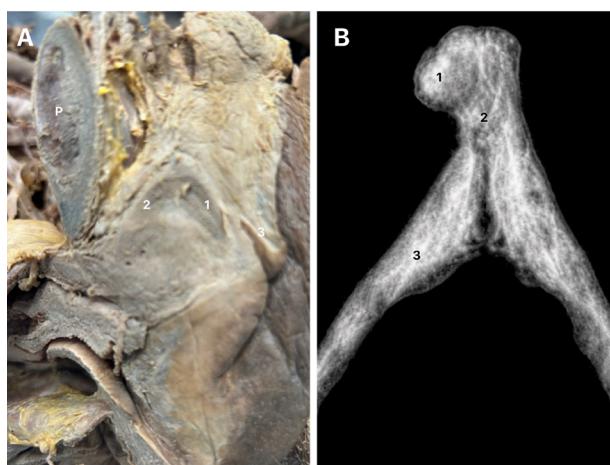
A) The photo shows the perineal region of a formalized human corpus, we can observe: 1- clitoris glans, 2- clitoris hood, 3- clitoris frenulum, 4 - labia minora and 5 - urethra; B) Photograph of the perineal region of a fresh cadaver showing the relationship of the glans of the clitoris (G) with the labia minora (3), 1- Prepuce of the clitoris and 2- Frenulum of the clitoris.

The clitoris has a shape similar to an inverted Y with the following portions: glans, body and crura (Figure-4). The glans is a protuberance that is partially exposed in the vulva, which has intimate contact with the clitoral body. The glans is the only externally visible portion, located at the superior junction of the labia minora. It is highly sensitive and covered by the clitoral hood (prepuce) (20-22). The clitoral body is located in the median plane immediately below the pubic arch and is composed of two *corpora cavernosa* covered by a tunica albuginea that sends a septum separating the *corpora cavernosa*. These are cylinders of erectile tissue that extend posteriorly and inferiorly (20-22). Each of the erectile bodies of the clitoris is attached to the ischiopubic ramus by a root, also called clitoral crura. These are the "legs" of the clitoris, extending along the pubic rami, a very important anatomical relationship for the interpretation of the image exams specially MRI (Figure-5).

The vestibular bulb, homologous to the corpus spongiosum, is located below the bulbospongiosus muscle (Figure-6). The clitoris and the vestibular bulb are considered distinct erectile structures that neverthe-

**Figure 4 - Anatomy of the Clitoris.**

A) Schematic drawing of a frontal view of the clitoris and its relations with the pelvic bones. We can observe: 1- glans of the clitoris, 2- crura of the clitoris, 3- body of the clitoris, 4 - suspensory ligament of the clitoris and 5 - bulb of the vestibule; B) Schematic drawing of a lateral view of the clitoris, we can observe: 1- glans of the clitoris, 2- body of the clitoris, 3 - crura of the clitoris, 4 - suspensory ligament of the clitoris and 5 - bulb of the vestibule.

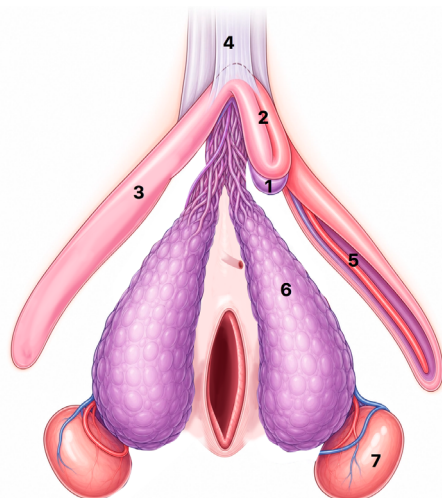
**Figure 5 - Sectional view of the clitoris. A) Sagittal section of a fresh frozen cadaver showing the shaft (1) and root (2) of the clitoris, p - pubis; B) A reconstruction of the clitoris showing the glans (1), shaft (2) and root (3).**

A) Sagittal section of a fresh frozen cadaver showing the shaft (1) and root (2) of the clitoris, p - pubis; B) A reconstruction of the clitoris showing the glans (1), shaft (2) and root (3).

less act together at the moment of female orgasm. Often considered the internal "wings," these masses of erectile tissue flank the vaginal opening and are embryologically homologous to the bulb of the penis (18-20).



**Figure 6 - Clitoris vestibular bulb. Schematic drawing showing the most important clitoris structures. 1- Glans, 2- Shaft, 3- root, 4-suspensory ligament, 5- deep artery of the clitoris (cavernosa), 6- vestibular bulb and 7- Bartholin gland**



Schematic drawing showing the most important clitoris structures. 1- Glans, 2- Shaft, 3- root, 4-suspensory ligament, 5- deep artery of the clitoris (cavernosa), 6- vestibular bulb and 7- Bartholin gland

## CLITORAL HOOD

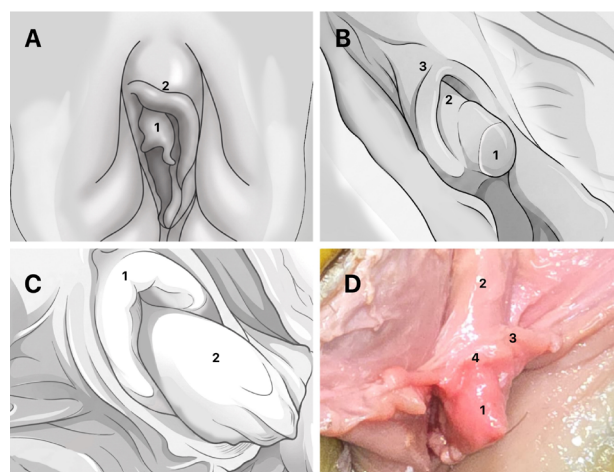
Knowledge of the anatomy of the glans and clitoral hood is clinically important in cosmetic and reconstructive surgeries (23). The clitoral hood is formed by the superior fusion of the labia minora. The clitoral hood is a fold of skin that surrounds and protects the glans of the clitoris and is also called preputium clitoridis, clitoral prepuce, and clitoral foreskin (24). The upper (superior) folds fuse to form the prepuce (hood), while the lower (inferior) folds fuse beneath the glans to form the frenulum. The hood is composed of thin, highly elastic layer of skin and mucosal tissue (23, 24). It contains a high density of sebaceous glands that produce lubricating oils, preventing the sensitive glans from drying out or becoming irritated by friction. Some women have large clitoral hoods that completely cover the clitoral glans. Some of these can be retracted to expose the clitoral glans, such as for hygiene purposes or for pleasure; others do not retract. Other women have smaller hoods that do not cover the full length of the

clitoral glans, leaving the clitoral glans exposed all the time (23).

The clitoral hood varies in size, shape, and thickness and usually has two distinct parts: a deep part - referred to as collar (present in more than 92% of cases) and a superficial part, referred to as hood (Figure-7) (25). Anatomical variations of the clitoris hood are frequent. The clitoris hood collar itself, especially the frenular part, could be continuous with the skin overlying the body of the clitoris, thus forming a pseudo-hood (Figure-7) (25). Zdilla in a very important paper described the clitoral hood anatomy and propose that the clitoral prepuce may exist as a unique structure distinct from the labia minora across the life cycle (25). The hood may join the crest of the labium minus, join at the lateral aspect of the labium minus, or not join at the labium minus at all (25).

Clitoral hood is a frequent focus in aesthetic and functional gynecology. Some women experience "clitoral phimosis" or have redundant (excess) hood tissue that may interfere with hygiene or sexual sensation (26). The presence of clitoral adhesion and phimosis can trap smegma, causing pain (clitorodynia) or a significant

**Figure 7 -Clitoris Hood.**



A) Schematic drawing showing the clitoris hood (2) and its relationship with clitoris glans (2); B) Schematic drawing showing the hood retracted (3) to expose the clitoris glans (1) and shaft (3); C) Schematic drawing showing another case of hood retraction (1) with the exposition of the clitoris glans (2) and D) Fresh frozen cadaver with dissection of hood (3) with the glans (1) and clitoris shaft (2) exposition, we can observe the hood deep part - the collar (4).

decrease in sexual pleasure because the “gliding” mechanism is lost. Treatment involves manually or surgically releasing these adhesions to restore mobility (26).

Hood innervation has a great importance during surgical procedures. The dorsal nerves of the clitoris run just beneath the deep fascia of the clitoral body. Surgeons performing a hoodectomy must remain strictly in the superficial subcutaneous plane to avoid permanent desensitization (27, 28). Often performed alongside a labiaplasty, the goal is to create a proportional appearance where the glans is visible but still protected. Sensory Mapping: High-resolution scans show that sensory branches of the pudendal nerve extend into the preputial tissue (27, 28). While not as sensitive as the glans, the hood is a legitimate erogenous zone. Over-resection during surgery can lead to a loss of the “pre-orgasmic” build-up provided by hood movement (27-29).

## CLITORIS GLANS

The glans clitoris is the most visible and highly sensitive part of the clitoral complex. While historically often mistaken for the entirety of the clitoris, it represents the distal termination of the clitoral body (corpus) and serves as the primary epicenter for sexual sensation in the female body (Figure-3). The glans is a small, rounded structure, typically measuring 3 to 6 mm in diameter, though there is significant natural anatomical variation (16, 30). It is situated at the anterior junction of the labia minora, partially or fully covered by the clitoral hood. Unlike the clitoral body and crura, which are composed of cavernous erectile tissue, the glans is primarily made of highly vascularized connective tissue and an extremely dense concentration of nerve endings.

Glans effectively is a sensory cap for the erectile bodies (31, 32). It is connected to the clitoral body that engorges with blood during arousal; the glans is pushed forward and becomes more prominent (27, 28). The glans is the destination for the terminal branches of the dorsal nerves of the clitoris (DNC) (32). According to the landmark 2026 synchrotron mapping studies, the glans contains over 10,000 sensory nerve fibers (27, 28, 32). This density is roughly 15 times higher than that of the glans penis relative to its size. The 2026 data revealed

that the DNC branches into a tree-like network within the glans, ensuring that even the slightest touch triggers a significant neurological response (27, 28, 32). The glans has important sensory receptors that are packed with specialized receptors, specifically Meissner's corpuscles (light touch) and Pacini corpuscles (vibration), which are tuned to the frequencies often used in manual or mechanical stimulation.

During the female sexual response cycle, the glans undergoes distinct changes (29, 31, 32): Engorgement: While the glans does not contain the same large blood-filled spaces as the *corpora cavernosa*, it becomes tumescent (swollen) due to increased blood flow in its dense capillary network. Retraction: Interestingly, as a woman nears orgasm, the glans often retracts under the clitoral hood. This is a protective mechanism; the glans becomes so sensitive that direct, high-intensity contact may become painful or overwhelming. Sensitivity Peaks: The glans acts as the “trigger” for the somatic reflex arc that leads to the rhythmic pelvic floor contractions of an orgasm (29, 31).

During gynecological surgery the glands need to be preserved because of its extreme sensitivity and critical role in pleasure (30, 33). In procedures like clitoral hood reduction, the surgeon must ensure that no incisions or sutures interfere with the blood supply to the glans or the terminal nerve branches entering it. In some cases, the prepuce can become adhered to the glans (clitoral phimosis) due to inflammation or hygiene issues, which can trap debris (smegma) and lead to pain or decreased sensation (13, 14, 26). In the field of aesthetic and reconstructive gynecology, surgical techniques involving the clitoris focus on two main objectives: improving anatomical harmony (aesthetic) and restoring function or alleviating pain (reconstructive) (13, 14, 26). A common mistake in aesthetic surgery is performing a significant labiaplasty without addressing the clitoral hood. This can lead to a “clitoral unmasking” or a top-heavy appearance. If the labia minora are resected too aggressively near the clitoris, the natural “tugging” sensation that contributes to arousal may be lost. High-quality aesthetic surgery aims to preserve the frenulum (the inferior connection), as this area is rich in sensory receptors and maintains the structural integrity of the clitoral-labial unit.

In some cultures, female genital mutilation (FGM) is practiced as a rite of passage into womanhood, is perceived as an improvement to the appearance of the genitalia or is used to suppress or reduce female sexual desire and pleasure (including masturbation). In cases of genital mutilation reconstruction, the "pull-down" technique aims to bring the buried clitoral body to the surface to create a "neo-glans" that can once again interface with external stimuli (34). If the labia minora have been partially preserved, these flaps of skin are often used to reconstruct a new clitoral hood (prepuce) over the newly transposed clitoral stump (35). The goal is to re-create the "hood-glans" interface, allowing for the protective and stimulatory gliding motion to occur once again (34-36).

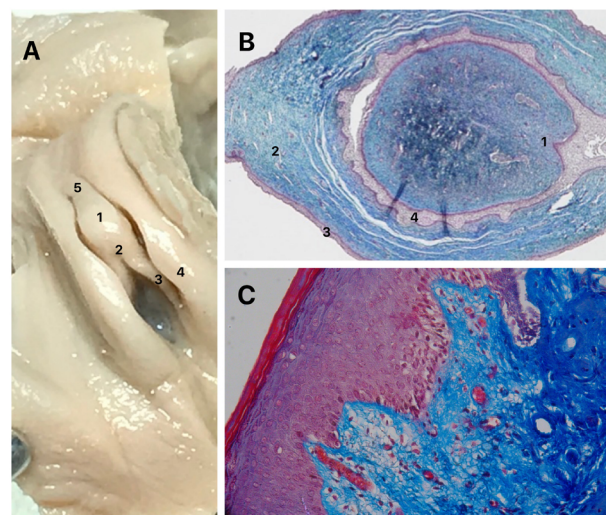
## CLITORIS HISTOLOGY

Histology of the human clitoris reveals a highly specialized organization of erectile tissue and neurovascular structures, similar in several aspects to the penis, but with functions exclusively related to sexual pleasure. The clitoris is composed of three main parts: glans, body (or shaft), and crura (37, 38). Histologically, these regions are formed mainly by erectile tissue of the corpus cavernosum type, surrounded by dense connective tissue (2). The erectile tissue of the clitoris consists of vascular spaces (sinusoids) lined by endothelium and trabeculae of connective tissue containing collagen fibers, elastic fibers, and smooth muscle. These elements allow blood engorgement during arousal, promoting clitoral erection. Unlike the penis, the clitoris does not have a corpus spongiosum or associated urethra, being formed exclusively of cavernous tissue.

The clitoral glans is lined by stratified squamous epithelium, which can vary from keratinized to non-keratinized depending on the region (Figure-8). Rich sensory innervation is seen just below the epithelium (37, 38). The clitoris presents: Helicine arteries, responsible for filling the sinusoids, venous network that regulates blood flow during tumescence and detumescence (2). The erectile tissue is enveloped by a tunica albuginea, composed of dense connective tissue rich in collagen, which provides structural support and aids in maintaining intracavernous pressure during erection. One of the most

striking aspects of clitoral histology is its extreme density of nerve endings: Abundant presence of Meissner's corpuscles (tactile sensitivity), Pacinian corpuscles (pressure and vibration) and free nerve endings. This organization explains the high sensitivity of the clitoral glans.

**Figure 8 -Clitoris Histology.**



A) The figure shows the clitoris of a fetus with 16 weeks post-conception, we can observe the clitoris glans (1), clitoris frenulum (2), labia minora (3), labia majora (4) and clitoris shaft (5); B) Photomicrography of a female human fetus with 17 weeks post-conception. We can observe the histology arrangement in clitoris, 1- clitoris glans, 2 - clitoris hood, 3- epithelium of the clitoris and 4 - preputial lamella of clitoris, Masson Trichrome X400. C) The figure shows a photomicrography of clitoris hood, and we can observe the clitoris epithelial height measurement. Masson Trichrome X400.

## CLITORIS SUSPENSORY LIGAMENT

The suspensory ligament of the clitoris is a condensation of connective tissue and deep fascia that connects the clitoral body to the pubic symphysis and anterior pelvic structures. It supports and stabilizes the clitoris, transmits tension during erection, and is related to the deep dorsal vein, arteries and neurovascular bundles (37, 38). It is often described as having superficial and deep components that merge with the suspensory apparatus of the mons pubis and the deep fascia of the urogenital diaphragm. Knowledge of its anatomy is rel-



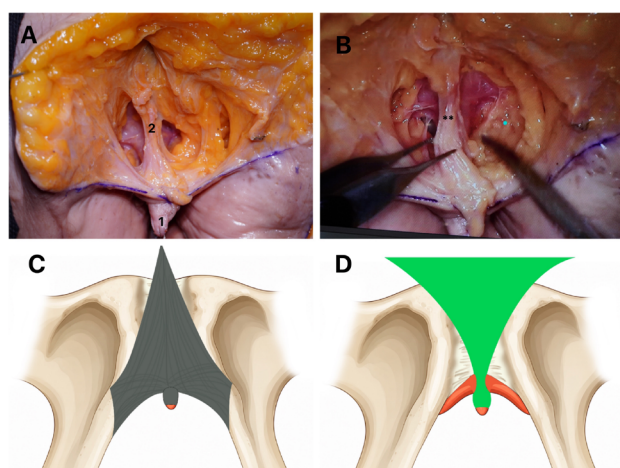
evant in genital surgery (cosmetic and reconstructive), pelvic trauma and pelvic floor dysfunction.

The suspensory ligament is located in midline, extending from the dorsum of the clitoral body to the pubic symphysis/retro-pubic region (37, 38) (Figure-9). It lies deep to the mons pubis, continuous with deep fascia, intimately associated with the deep dorsal vein and dorsal nerves of the clitoris. It is described as fibrous band(s) with variable thickness; authors report superficial and deep laminae or a single suspensory plate depending on dissection technique and specimens and has the function of mechanical support of the clitoral body; contributes to positional stability and may influence biomechanical transmission during sexual arousal (37, 38). The suspensory ligament is an important land-

mark in female genital aesthetic and reconstructive procedures (labiaplasty, clitoral hood reduction, suspensory release) and may be considered in evaluation of pelvic pain after trauma surgery.

A relevant anatomical-histological study introduced a new three-dimensional interpretation of the clitoral suspensory ligament by describing three components (superficial, intermediate, and deep) of which the intermediate component appears to be functionally the most relevant (39) (Figure-9). It arises from the anterior abdominal wall, courses over the pubic symphysis without full fixation to it, envelops the clitoral body, and gives off lateral extensions resembling airplane wings, which traverse the labia majora and insert into the fascia lata in the ipsilateral inguinal region. Because this component is composed of dense connective tissue rich in collagen fibers, it plausibly contributes to the barrier effect suggested by the findings of this study (39).

**Figure 9 - Clitoral suspensory ligament.**



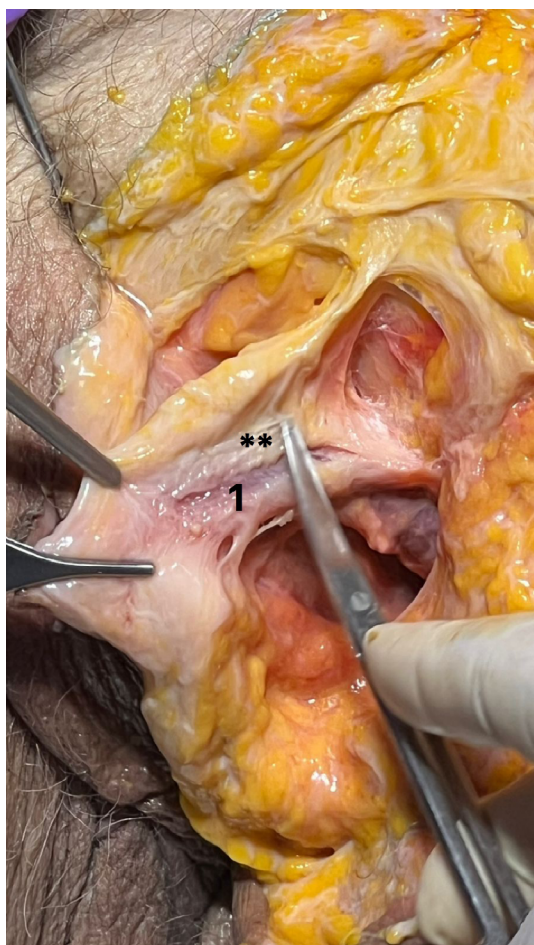
A) Photograph of the perineal region of a fresh-frozen cadaver showing the clitoral suspensory ligament (2), 1 - clitoris glans; B) Photograph of the same fresh-frozen cadaver showing the suspensory ligament after dissection; C) Schematic drawing showing the superficial component of the clitoris suspensory ligament (Black). This superficial component arises from the anterior abdominal wall, courses over the pubic symphysis without full fixation to it, envelops the clitoral body, and gives off lateral extensions resembling airplane wings, which traverse the labia majora and insert into the fascia lata in the ipsilateral inguinal region, we can observe the clitoris glans in orange and D) Schematic drawing showing the Intermediate component of clitoris suspensory ligament (green). This component is located in midline, extending from the dorsum of the clitoral body to the pubic symphysis/retro-pubic region. This component completely encloses the clitoral body and sends lateral extensions to the labia majora. We can observe the clitoris glans and clitoris root in orange; the clitoris shaft is not observed because the intermediate component involves this portion.

## CLITORIS BODY AND BULBUS

The clitoral body (shaft) lies beneath the skin, extending inward from the glans. The shaft is composed of two *corpora cavernosa* (erectile tissues), similar in structure to the penis, surrounded by a fibrous sheath called the tunica albuginea, separated by an incomplete septum. The septum is an extension of the tunica albuginea, which is a fibrous connective tissue sheath that surrounds the *corpora cavernosa* superficially (Figure-10) (37, 38). The body bifurcates laterally into the left and right crura that follow the inferior border of the ischiopubic rami and are located deep to the respective ischiocavernosus muscles (40). During arousal, it fills with blood and becomes engorged, contributing to increased sensitivity and rigidity; and it connects the external glans to the internal crura. Functionally, the body acts as a central conduit of erectile tissue, transmitting pressure and stimulation from internal movement to the glans (2).

The vestibular bulbs are often overlooked but are key to sexual function and are composed of erectile tissue (Figure-5). They are located on either side of the vaginal opening, beneath the labia and made of spongy erectile tissue (similar to corpus spongiosum in males).

**Figure 10 - Clitoris shaft with albuginea.**



Photography of a dissection in female fresh frozen cadaver showing the clitoris shaft after the dissection of the tunica albuginea (1). We can observe the neurovascular bundle in clitoris dorsal portion (\*\*).

They swell during arousal, narrowing the vaginal opening and increasing friction and are connected to the clitoral body via vascular and neural networks and maintain a consistent relationship with the clitoral complex and can completely or partially fill the space between labia minora, body, and crura (2). These bulbs are partly responsible for the sensation of fullness and pressure during arousal and penetration.

Measurements of the clitoris vary a lot from person to person, and they can also change depending on factors like arousal, age, and hormonal influences. Therefore, anatomical studies give us useful average ranges for the glans and shaft (body). A recent meta-

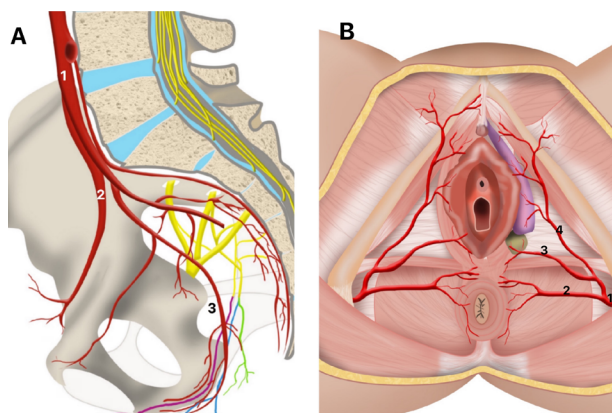
analysis presented important information about the clitoris measures (40). The average length and width of the glans was 6.40 mm (range 1.00-21.00 mm) and 5.14 mm (range 2.00-32.00 mm), respectively. The average length and width of the body was 25.46 mm (range 5.00-59.00 mm) and 9.00 mm (range 5.00-20.00 mm), respectively. The average length and width of the crura was 52.41 mm (range 23.00-90.00 mm) and 8.71 mm (range 2.00-13.00 mm), respectively. The average length and width of the bulb was 52.00 mm (range 13.00-70.00 mm) and 10.33 mm (3.00-29.00 mm), respectively (40). The authors of this metaanalysis concluded that the clitoral components vary in size and shape, whilst remaining within the normal range (40).

## CLITORIS VESSELS

Knowledge of the vascularization and innervation of the clitoris has great application in surgical procedures in regenerative gynecology. The clitoris and labia minora share more than just skin; they share a blood and nerve supply derived from the same source. Both receive blood from branches of the internal pudendal artery. Specifically, the labial arteries and the dorsal artery of the clitoris arise from the same perineal trunk.

The blood supply to the clitoris is primarily derived from the internal pudendal artery, which is a branch of the internal iliac artery (Figure-11). The pudendal artery originates 3 arteries which has the clitoris as its irrigation area (Figure-12): 1) Dorsal artery of the clitoris, that runs along the dorsal surface of the clitoral body, deep to the Buck's fascia. It provides the primary blood supply to the glans and the overlying prepuce (hood); 2) Deep artery of the clitoris, that runs through the center of the *corpora cavernosa* and is essential for tumescence (erection) and 3) Bulbar artery that supplies the vestibular bulbs and the surrounding erectile tissue.

In aesthetic surgery, particularly during a clitoral hoodectomy, surgeons must remain superficial to the deep fascia to avoid compromising these terminal branches, which could lead to ischemia of the glans. Venous drainage mirrors the arterial supply, primarily through the dorsal vein of the clitoris, which eventually drains into the vesical or vaginal venous plexuses.

**Figure 11 - Internal Pudendal artery distribution.**

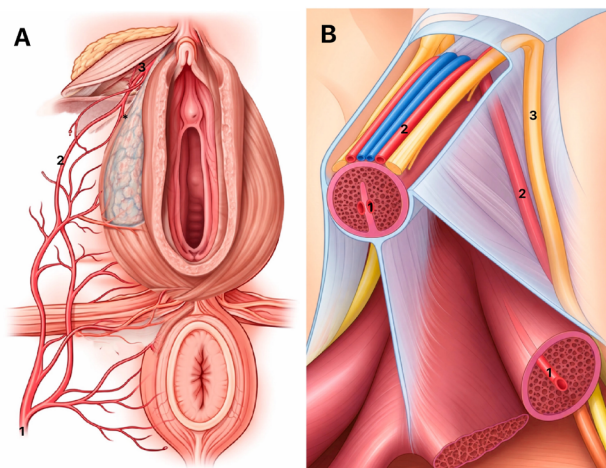
A) Schematic drawing of the vessels responsible for the vascularization of the pelvic viscera in women in a lateral view, 1- Internal iliac artery, 2 - internal iliac artery and 3 - internal pudendal artery, branch of the anterior trunk of the internal iliac artery and B) Schematic drawing showing the branching of the internal pudendal artery (1), 2- inferior rectal branch, 3- transverse perineal branch and 4 - perineal branch.

These structures, together with the dorsal nerve of the clitoris, which will be described in the next topic, form a neurovascular bundle located in the dorsal region of the clitoris (Figure-13). The dorsal region of the clitoris is therefore a region of great importance during surgeries of this organ (9, 41). Preservation of the clitoral bundle is a key point in surgical interventions such as clitoroplasty or clitoropexy.

## CLITORIS NERVES

Clitoris is one of the most densely innervated structures in the human body, specifically designed for sensory reception. While the sensory innervation of the clitoris (via the pudendal nerve) is responsible for the "feeling" of touch, the autonomic innervation is the "engine" that drives the physiological changes of sexual arousal, such as vasocongestion and tumescence. This system operates largely outside of conscious control, through the complex interaction of the sympathetic and parasympathetic pathways (42).

The pudendal nerve is the primary source of somatic sensation. Specifically, the dorsal nerve of the clitoris (the terminal branch of the pudendal nerve)

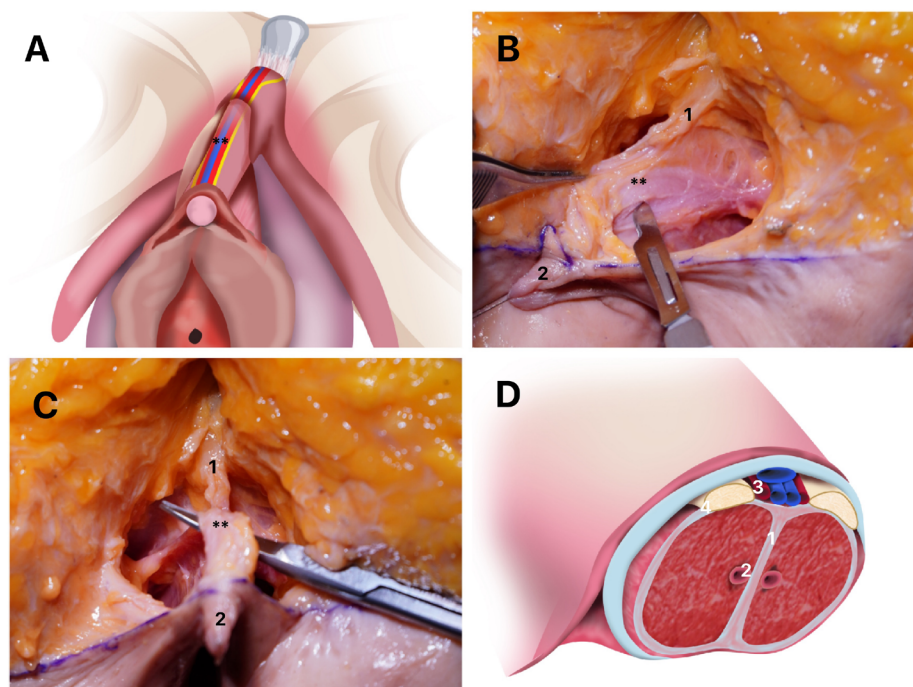
**Figure 12 - Clitoris Arteries.**

A) Schematic drawing showing the pudendal internal artery (1) distribution. The clitoris arteries origin from the perineal artery (2). We can observe the dorsal clitoris artery (3) and clitoris deep artery origin (\*) and B) Schematic drawing of the clitoris arteries: The clitoris deep artery (1) penetrates the root of the clitoris and follows a path through the central region of the entire clitoris, including the body, where it can also be called the cavernous artery of the clitoris (1), the superficial clitoral artery (2) is a branch of the perineal artery and runs closely and superficially to the tunica albuginea of the clitoris. It is one of the elements that constitute the neurovascular bundle in the dorsal region of the clitoris and is of great surgical importance. The dorsal nerve of the clitoris (3) is also observed in this figure.

travels along the clitoral body to reach the glans. This nerve provides the high-resolution tactile sensitivity required for sexual arousal (28, 32, 42). The clitoris also receives autonomic fibers from the cavernous nerves, which originate from the uterovaginal plexus (Frankenhäuser's ganglion). The nerve travels along the ischio-pubic ramus and emerges beneath the pubic symphysis. It runs along the dorsal aspect of the clitoral body, typically located at the 11 o'clock and 1 o'clock positions. These nerves are highly sensitive and relatively superficial near the glans (32, 43). During labiaplasty (especially the "wedge" technique) or hood reduction, incisions made too deeply or too medially toward the midline of the dorsal body can result in permanent desensitization (anorgasmia) or the formation of painful neuromas (Figure-14).

The somatic innervation of the clitoris is responsible for the transmission of acute sensory information—touch, pressure, temperature, and, most importantly, erogenous pleasure—to the central nervous system. Unlike the autonomic system, which handles the "involuntary"



**Figure 13 – Clitoral neurovascular bundle.**

A) Schematic drawing showing the relationship of the clitoral neurovascular bundle (\*\*) with the region of the clitoral body (3); B) The figure shows a dissection in a fresh frozen cadaver of the clitoral neurovascular bundle (\*\*) and its relation to the dorsal region of the clitoral body, 1 – suspensory ligament of clitoris, 2- clitoris glans; C) The figure shows in the same fresh frozen cadaver the individualization of the clitoral neurovascular bundle (\*\*), 1 – suspensory ligament of clitoris, 2- clitoris glans and D) Schematic drawing of a transverse section of the clitoral body showing the topography of its components: 1- Septum between the erectile (cavernous) bodies of the clitoris, 2- deep artery of the clitoris, 3- dorsal artery of the clitoris, 4- dorsal nerve of the clitoris.

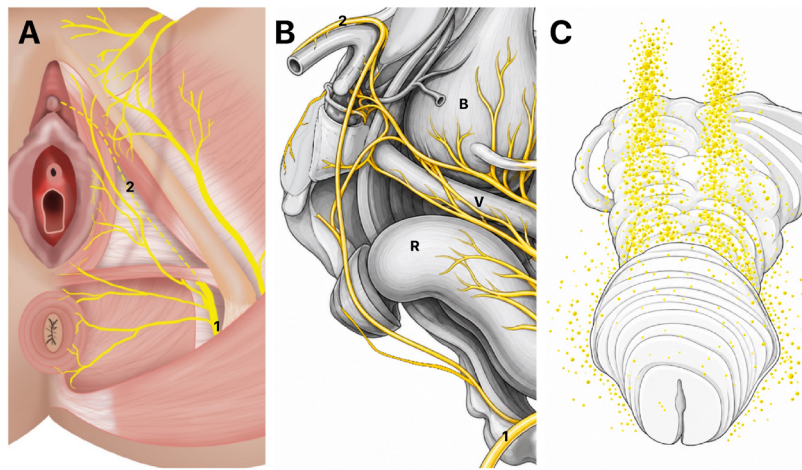
vascular response, the somatic system provides the “voluntary” and conscious perception of stimulation. The clitoris receives its somatic sensory supply almost exclusively from the pudendal nerve, which originates from the ventral rami of the S2, S3, and S4 sacral spinal nerves.

As the pudendal nerve travels through the pelvis, it enters Alcock’s canal (pudendal canal) and eventually divides into three terminal branches: The inferior rectal nerve, The perineal nerve and The Dorsal Nerve of the Clitoris (DNC) (Figure-14). The DNC is the most critical branch for sexual function. It is a purely sensory nerve (in some models, it carries minor sympathetic fibers, but its primary role is somatic) that travels forward along the ischiopubic ramus.

The DNC emerges from beneath the pubic symphysis and enters the clitoral complex at the level of the suspensory ligament. It runs along the dorsal (top) surface of the clitoral body, deep to the Buck’s fascia but

superficial to the tunica albuginea of the *corpora cavernosa*. Classically, the two bilateral nerves are described as running at these specific “clock” positions along the clitoral shaft (Figure-14). The Glans “Tree”: As confirmed by 2026 synchrotron mapping, once the DNC reaches the glans, it does not stop; it branches into an extremely dense network of terminal fibers. This “nerve tree” ensures that every micron of the glans is highly sensitive (28, 29, 32).

The somatic system in the clitoris is unique due to the concentration of specialized mechanoreceptors: Pacini Corpuscles: Sensitive to vibration and deep pressure; Meissner Corpuscles: Sensitive to light touch; Free Nerve Endings: Responsible for temperature and pain (nociception). With over 10,000 sensory axons (28, 29, 32), the clitoris has the highest density of these receptors in the human body. This allows for the phenomenon of spatial summation, where stimulation across the

**Figure 14 – Somatic Innervation of Clitoris.**

A) Schematic drawing showing the innervation of the female perineum: 1- pudendal nerve, 2 - dorsal Nerve of the Clitoris (dotted line) originates from the perineal branch; B) Schematic drawing showing the pudendal nerve (1) originating the dorsal nerve of the clitoris (2) and its path in perineum, B- bladder, V- vagina, R- rectum and C) Schematic drawing showing the dorsal nerve of clitoris distribution (yellow) in clitoris shaft and glans.

surface of the glans rapidly builds to the threshold required for a somatic reflex—the orgasm.

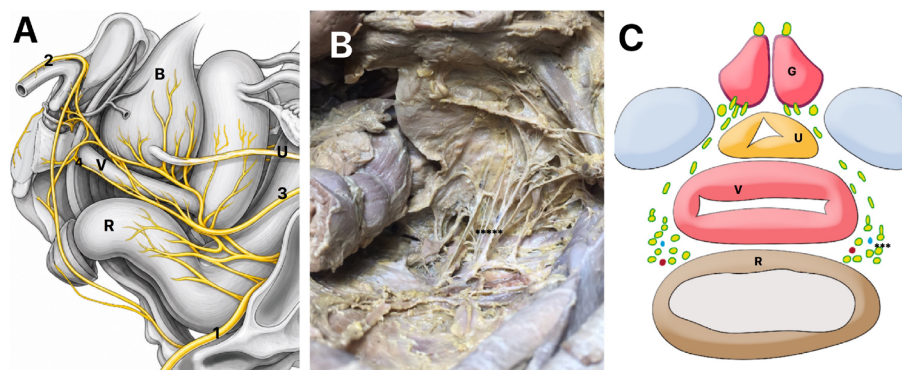
The Parasympathetic fibers has a function of trigger the relaxation of smooth muscles in the erectile tissue, allowing for increased blood flow and engorgement. The Sympathetic fibers are involved in the resolution phase and smooth muscle contraction. The sensory innervation of the clitoris is provided by the dorsal nerve of the clitoris, the terminal branch of the pudendal nerve (27, 32, 43). The autonomic fibers that reach the clitoris originate from the inferior hypogastric plexus (also known as the pelvic plexus). This plexus is a dense network of nerves located on the lateral walls of the rectum and vagina (Figure-15). The parasympathetic input arises from the pelvic splanchnic nerves (nerve roots S2 through S4). The sympathetic input arises from the hypogastric nerves (nerve roots T10 through L2 (27, 32, 43).

From this plexus, the autonomic fibers travel along the vaginal wall and the urethra to reach the erectile bodies of the clitoris. The specific autonomic nerves destined for the clitoris are the cavernous nerves (Figure-15). These are small, delicate fibers that travel along the posterolateral aspect of the urethra and the vaginal wall. They penetrate the tunica

albuginea of the *corpora cavernosa* and the vestibular bulbs. They regulate the smooth muscle tone of the deep clitoral arteries and the trabecular tissue within the erectile chambers.

An interesting recent study provides a quantitative mapping of clitoral innervation and structure (44). The authors shows that while the absolute number of nerve fibers is ~60% lower in the clitoris, albeit with a higher proportion of myelinated fibers, the innervation density is markedly higher than in the penis. These data will inform not only our understanding of differences and similarities between female and male genitals and their sensory function but also reveal some of the neglected aspects of female sexuality. The original figures in this paper are very interesting and shows the nerves distribution around the clitoris, specially in the glans (44).

In 2026 some important papers show anatomical aspects about the clitoris innervation (19). Previous textbooks suggested the dorsal nerve of the clitoris (DNC) simply tapered off as it reached the glans. The 2026 mapping reveals that the DNC actually branches out into a complex, tree-like structure within the glans, maintaining significant diameter (0.2 mm to 0.7 mm) even at distal points (19).

**Figure 15 – Autonomic innervation of clitoris.**

A) Schematic drawing showing the autonomic innervation of the female perineum: 1- pudendal nerve, 2 - dorsal Nerve of the Clitoris, 3- Left hypogastric nerve, 4 - origin of cavernous nerve of clitoris, B- bladder, V- vagina, R- rectum; B) Dissection of fixed female pelvis showing the inferior hypogastric plexus distribution (\*\*\*) and C) Schematic drawing showing the autonomic innervation of clitoris distribution (yellow), we can observe the autonomic neurovascular bundle of clitoris (\*\*\*), G- glans, U- urethra, V- vagina, R- rectum.

New data shows that clitoral nerves are not confined strictly to the glans. Sensory branches extend significantly into the clitoral hood and the mons pubis. This suggests that surgeons must rethink “safe zones” in aesthetic procedures like hoodectomies (19, 25). A study by Zdilla (25) identified a previously undescribed anatomical subdivision called the “clitoral collar”—a distinct band of preputial tissue around the neck of the clitoris that likely plays a role in stabilizing the neurovascular bundle. Research published by Wolf-Vollenbröcker (28) found that clitoral innervation is often not bilaterally symmetrical, which is a critical consideration for reconstructive microsurgery.

Female genital cosmetic surgery has gained significant importance in both plastic surgery and gynecology, with labia minora reduction and clitoral hood reduction among the most common procedures. Recent literature emphasizes the need for precise surgical techniques involving the clitoris, given its dual role in aesthetics and sexual function with careful manage of the “safe zones” of the clitoral complex (40, 45). In clitoral hoodectomy the excision should be limited to the redundant skin of the prepuce. Dissection must remain subcutaneous, avoiding the deep dorsal fascia where the neurovascular bundle resides. In labiaplasty when extending the reduction toward the superior commissure, the surgeon must be wary of the “nerve entry point” near

the clitoral body (30). The dorsal midline of the clitoral body is considered a high-risk area. Most modern techniques advocate for lateral incisions or “Y-V” plasty to avoid the central neurovascular highway (28, 30).

## ROLE OF THE CLITORIS IN FEMALE ORGASM

Clitoris is the only human organ evolved for the sole purpose of providing sexual pleasure. While historically overshadowed by vaginal-centric theories of reproduction, modern anatomical studies—particularly since the late 1990s—have redefined it as the powerhouse of the female orgasm (16, 19). The most significant shift in understanding the clitoris is the realization that what is visible externally (the glans) is merely the tip of the iceberg.

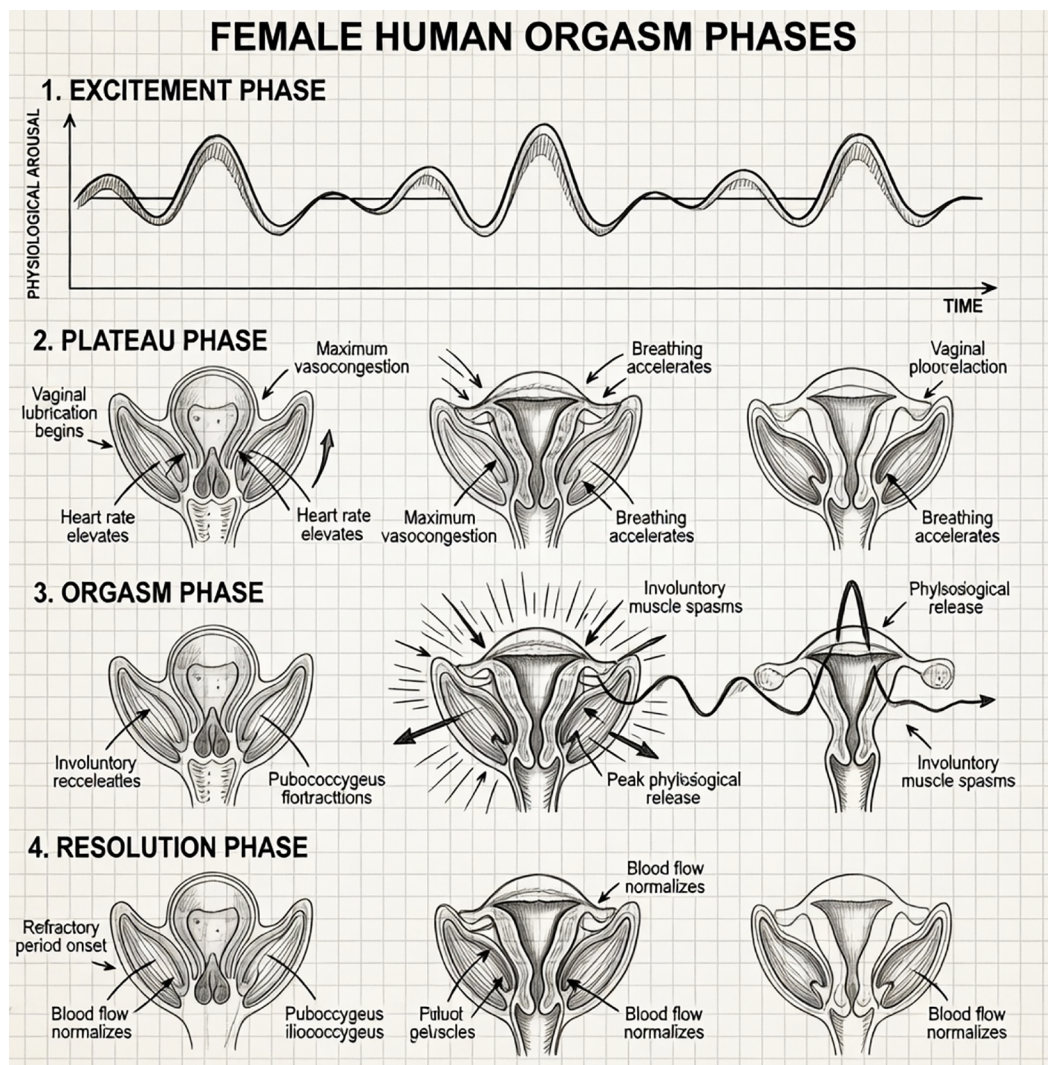
The Glans contains approximately 8,000 to 10,000 sensory nerve endings, a density higher than any other part of the human body, including the penis (29, 32, 43). The internal complex beneath the surface, the clitoris extends into two crura (legs) and two vestibular bulbs. These structures hug the vaginal wall and engorge with blood during arousal. Because the internal parts of the clitoris wrap around the vagina, most “vaginal” orgasms are actually the result of indirect stimulation of the clitoral internal structures.



The clitoral orgasm is a complex neuro-vascular event. It follows a specific physiological sequence: Vasocongestion: Upon stimulation, the dorsal and deep arteries increase blood flow to the corpora cavernosa and vestibular bulbs. This causes the clitoris to double or triple in volume. The Reflex Arc: Sensory input travels via the pudendal nerve to the sacral spinal cord and then to

the brain's pleasure centers (such as the paraventricular nucleus). The Climax: At the peak of arousal, a series of rhythmic contractions (every 0.8 seconds) occur in the pelvic floor muscles (ischiocavernosus and bulbospongiosus), releasing the accumulated neuromuscular tension (16, 19). We can observe in Figure-16 the physiological sequence of the female orgasm and the role of clitoris.

**Figure 16 – Clitoris and Orgasm.**



Schematic drawing showing the orgasm phases. PHASE 1 – Excitement (Blood flow ↑↑, Sensitivity ↑). In this phase we observe a high neural activation with glans erection, clitoris body engorgement, initial expansion of vagina and lubrication; PHASE 2 – Plateau (Sustained high arousal). In this phase we can observe an extremely clitoris sensibility and glans retraction under hood, perineal muscle tension and faster breathing; PHASE 3 – Orgasm. In this phase we observe a dopamine peak, oxytocin release and intense brain activation with rhythmic contractions of pelvic floor, typically in 3 to 12 pulses, the clitoris (orgasm center) has high nerve density, integrative stimulation and primary pleasure source and PHASE 4 – Resolution. The pelvic muscles present relaxation, we observe arousal decrease, the clitoris return to baseline and may remain sensitive during variable period of time in this phase.

The somatic innervation is the afferent (incoming) limb of the orgasmic reflex (16, 19). Afferent Limb: Sensory signals travel from the glans via the DNC to the Sacral Spinal Cord (S2–S4). Integration: The signal is processed in the spinal cord and sent to the brain (sensory cortex). Efferent Limb: If the threshold is reached, the spinal cord sends a motor signal back via the perineal branch of the pudendal nerve to the pelvic floor muscles (ischiocavernosus and bulbospongiosus), causing the rhythmic contractions characteristic of climax.

## CLITORIS AND AESTHETIC SURGERY

Clitoris anatomy knowledge is a prerequisite for understanding its function. These findings are being applied immediately in three areas (46, 47): Providing a roadmap to restore sensation for survivors of female genital mutilation; Gender-Affirming Surgery: Improving the “gold standard” for clitoroplasty by ensuring the neurovascular bundle is mobilized without damaging the newly mapped “tree” branches and Pelvic Cancer Radiotherapy: Using the 3D maps to spare clitoral nerves from radiation damage, preserving sexual function after cancer treatment.

### 1. Clitoral Hood Reduction (Hoodectomy)

This is the most common aesthetic procedure (30, 45). It addresses “clitoral unmasking” or redundant preputial skin that can cause discomfort or hygiene issues. Extended Lateral Wedge Technique: Instead of a simple vertical excision (which carries a risk of midline scarring over the glans), a wedge is removed from the lateral aspects of the hood. This preserves the central neurovascular highway. Y-V Plasty: Used when the hood is narrow but long. A Y-shaped incision is converted into a V-shape to shorten the hood while maintaining the protective function of the skin over the glans. Safety Landmark: Surgeons must remain superficial to the Buck’s fascia, where the dorsal nerves are located.

### 2. Nerve-Sparing Clitoroplasty (For Clitoromegaly)

Used in cases of clitoral enlargement (hypertrophy), the goal is to reduce size without sacrificing sensitivity. Reduction and Recession: Rather than re-

moving tissue, the clitoral body is “folded” (plicated) or shortened by resecting a middle segment of the *corpora cavernosa*. Dorsal Nerve Mobilization: The most critical step. The surgeon carefully dissects the neurovascular bundle away from the erectile tissue before any reduction is performed. Glans Preservation: The glans is reduced only if absolutely necessary, usually through a small ventral wedge resection that avoids the high-density dorsal nerve “tree”.

### 3. The Foldes Technique (Reconstruction after FGM/C)

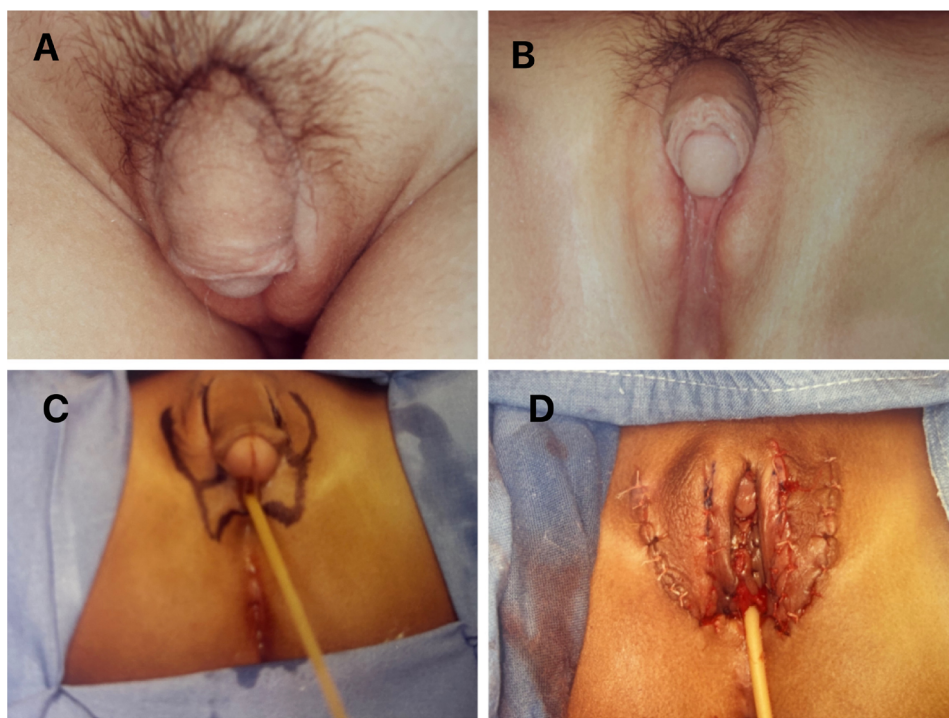
This is the gold standard for reconstruction in survivors of Female Genital Mutilation/Cutting (30, 33, 34). Uncovering the Stump: The surgeon identifies the buried clitoral body (the “stump”) behind the scar tissue. Ligamentous Release: The suspensory ligament is partially cut to allow the buried portion of the clitoris to be brought forward. Transposition: The healthy, sensitive tissue is moved to the surface to create a new visible glans. This technique restores erogenous sensation in the majority of patients by reconnecting the internal anatomy with external stimulation.

### 4. V-Plasty for Labial-Clitoral Integration

Often performed during labiaplasty, this technique ensures the labia minora and the clitoral hood transition smoothly. Superior Commissure Refinement: By creating a V-shaped flap where the labia meet the hood, surgeons avoid the “dog-ear” deformity (bunched skin) and protect the frenulum of the clitoris. Functional Importance: Maintaining the frenulum is essential for the “tugging” sensation that transmits labial movement to the clitoral glans during sexual activity.

## CLITORIS AND TRANSGENDER SURGERY

The preservation or construction of the clitoris (clitoroplasty) is often considered the “gold standard” for success in gender-affirming surgeries, particularly in feminizing genitoplasty (vaginoplasty) (48-50).

**Figure 16 – Clitoris and Orgasm.**

A) Clitoromegaly in patient with 1 year-old and CAH; B) A view of the perineal region of the same patient; C) Other patient 9 months-old with CAH during the preparation for the surgical correction and D) Final aspect of this patient after clitoroplasty.

In feminizing surgeries, the clitoris is not merely an aesthetic addition but the primary organ for sexual gratification and sensory feedback. The transition from a phallus to a vulva requires a sophisticated “repurposing” of erectile tissue. Sensation Preservation: The dorsal nerve of the penis is homologous to the dorsal nerve of the clitoris. Successful surgery relies on the mobilization of the neurovascular bundle to ensure the neo-clitoris retains its sensitivity. Psychological Well-being: Research indicates that the presence of a functional, aesthetically pleasing clitoris significantly correlates with reduced gender dysphoria and improved post-operative quality of life.

The most common technique for creating a clitoris in trans women is the glans-based clitoroplasty. The Neurovascular Bundle (NVB) is the lifeline of the neo-clitoris. During surgery, the glans penis is reduced in size while remaining attached to its original nerve and blood supply (the dorsal arteries and nerves). This pedicle is then tunneled and positioned superior to the

neo-urethral orifice. A critical challenge is the partial resection of the *corpora cavernosa*. While some erectile tissue is removed to create a feminine contour, enough must be preserved to allow for the physiological engorgement of the neo-clitoris during arousal, mimicking cisgender female anatomy.

The importance of the clitoris is further highlighted by the risks associated with its surgical construction: Glans Necrosis: If the blood supply via the dorsal arteries is compromised during the stripping of the penile shaft, the neo-clitoris may undergo necrosis. Desensitization: Excessive tension on the neurovascular bundle or direct trauma to the dorsal nerves can lead to permanent loss of erogenous sensation. Chronic Pain: Improper burial of the nerves can lead to the formation of neuromas or chronic hypersensitivity.

### Metoidioplasty

In transmasculine individuals, the clitoris itself is the primary focus of metoidioplasty. Through testosterone



therapy, clitoral hypertrophy (clitoromegaly) occurs. Surgery involves releasing the clitoral ligaments (suspensory and chordee) to allow the enlarged clitoris to project forward, functioning as a small phallus. This procedure preserves the high density of sensory nerve endings, ensuring that the patient maintains peak sexual sensation (51, 52).

In the context of gender-affirming surgery for transmasculine individuals, metoidioplasty is a surgical option that relies entirely on the pre-existing anatomical structures of the clitoris, which have been modified by androgen therapy (testosterone). Unlike phalloplasty, which uses tissue grafts, metoidioplasty focuses on the "release" and repositioning of local tissues (51, 52).

The foundation of a metoidioplasty is the androgen-induced clitoromegaly. Before surgery, patients typically undergo 1-2 years of testosterone therapy, which causes the clitoral glans and *corpora cavernosa* to hypertrophy. The final length of the "metoidio-phallus" is strictly limited by the individual's biological response to testosterone. These erectile bodies remain functional, allowing the neo-phallus to become engorged during arousal, preserving the patient's natural erectile capacity. A key anatomical barrier to the projection of the clitoris is the suspensory ligament and the ventral tethering known as chordee.

The most significant anatomical priority in metoidioplasty is the protection of the dorsal neurovascular bundle. Because the nerves are located on the dorsal aspect (top) of the clitoral body, surgeons must be extremely precise during the ligamentous release. Preservation of the deep and dorsal arteries ensures that the hypertrophied tissue remains viable and responsive to stimulation. The high success rate of erogenous sensation post-metoidioplasty is due to the minimal manipulation of these specific nerves compared to other phallic constructions.

In cases of clitoromegaly—the abnormal enlargement of the clitoris—surgical intervention via clitoroplasty is often indicated when the condition causes physical discomfort, psychological distress, or functional interference. Modern surgical philosophy has shifted from "clitoral reduction" to "clitoral preservation," prioritizing the maintenance of neurovascular integrity.

Clitoromegaly can result from various conditions, and the surgical approach must consider the underlying

cause: Congenital Adrenal Hyperplasia (CAH): The most common cause, where excess androgens lead to virilization of the genitalia (Figure-17); Polycystic Ovary Syndrome (PCOS): Severe cases can lead to mild-to-moderate enlargement.; Androgen-secreting tumors: Rapid onset of enlargement often points to adrenal or ovarian tumors and Exogenous Steroids: Use of anabolic steroids can lead to irreversible clitoral growth (51, 52).

Historically, clitoromegaly was often treated with a clitorectomy (total removal), which resulted in permanent loss of sexual sensation. Contemporary techniques focus on reduction and recession while preserving the glans and its innervation. Degloving: An incision is made around the clitoral hood and the skin is "degloved" to expose the clitoral body and the neurovascular bundles (NVB). Mobilization of the NVB: Utilizing the anatomical data confirmed in recent 2026 studies, the surgeon carefully separates the dorsal nerves and arteries from the erectile bodies (*corpora cavernosa*). Partial Corporoplasty: A portion of the erectile tissue is excised or plicated (folded) to reduce the length and girth of the clitoral shaft. Glans Reduction: If the glans itself is excessively large, a "wedge resection" may be performed. However, surgeons must be extremely conservative here to avoid damaging the high-density nerve endings mapped in the glans. Recession and Fixation: The shortened clitoris is recessed back toward the pubic symphysis to create a more feminine and comfortable anatomical position.

The success of a clitoroplasty is measured by three main pillars: Sensation: Post-operative testing should ideally show preserved erogenous sensitivity. Aesthetics: The goal is a clitoris that is proportional to the labia majora and minora, typically partially covered by the clitoral hood. Function: Reducing the size of the clitoris can alleviate "chafing" or pain caused by friction against clothing, which is a common complaint in patients with significant clitoromegaly.

## CONCLUSION

The clitoris is a very important structure to female physiology, specially the orgasm. The knowledge of clitoris anatomy is the fundamental step in aesthetic surgery and in reconstruction, specially in transgender procedures.

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## CONFLICT OF INTEREST

None declared.

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# Suture versus Sutureless Retroperitoneal Robot-assisted Partial Nephrectomy using Veriset™ Hemostatic Patch: A Propensity Score Matched Comparative Analysis from a Single Centre

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## ABSTRACT

**Objective:** To evaluate the efficacy of Veriset™ hemostatic patch as a substitute for conventional renorrhaphy in retroperitoneal robot-assisted partial nephrectomy (RAPN).

**Materials and Methods:** A total of 113 patients underwent retroperitoneal RAPN between January 2024 and January 2025. After propensity score matching on age, BMI, and R.E.N.A.L. nephrometry score, 32 and 40 patients underwent Veriset™ placement and renorrhaphy, respectively, were included for final analysis. The clinico-demographic data, R.E.N.A.L. nephrometry score, blood loss, hemoglobin-drop, hospital stay, complications, and renal function on follow-up were prospectively recorded.

**Results:** The mean age, body-mass-index, and R.E.N.A.L. score were  $52.6 \pm 9.86$  years,  $27.41 \pm 4.06$  kg/m<sup>2</sup>, and  $5.24 \pm 1.17$ , respectively. As per the low, intermediate, and high-risk categories of nephrometry, the patients were evenly distributed. The console time and warm ischemia time (WIT) were significantly less in the Veriset group ( $47.26 \pm 17.51$  vs.  $71.67 \pm 22.6$  minutes, and  $12.86 \pm 6.14$  vs  $17.48 \pm 5.40$  minutes, respectively,  $p < 0.001$ ). Blood loss was significantly higher in the renorrhaphy group ( $57.74 \pm 22.83$  vs.  $87.34 \pm 33.81$  mL,  $p = 0.008$ ). The change in GFR was significantly less in the Veriset group on postoperative day-1 ( $p = 0.008$ ), but became comparable after six months. The postoperative pain score at 6, 12, and 24 hours, blood transfusion, hospital stay, and readmission rates were similar in both groups.

**Conclusion:** As compared to the renorrhaphy group, Veriset group patients had less console time, WIT, blood loss and immediate reduction of GFR. Sutureless retroperitoneal RAPN can produce good perioperative results without increasing complications.

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## INTRODUCTION

Management of small renal masses has evolved toward an individualized approach incorporating active surveillance, nephron-sparing surgery, and ablative therapies (1, 2). Robot-assisted partial nephrectomy (RAPN) remains the most widely adopted and preferred surgical option (3). Since its introduction in 2009, the retroperitoneal approach has offered rapid and direct access to the renal hilum, early identification and control of the renal artery—often encountered before the renal vein—without colon mobilization. Avoidance of intraperitoneal dissection reduces the risk of postoperative ileus and facilitates earlier recovery of bowel function. Additionally, in the patients with prior abdominal surgery, it minimizes the challenges associated with intra-abdominal adhesions (4). Retroperitoneal approach (RAPN) provides excellent perioperative, oncological, and functional outcomes (5). The ‘trifecta outcome’ [warm ischemia time (WIT) less than 25 minutes, negative surgical margins, and the absence of complications] can be consistently attained (6). In recent meta-analyses, retroperitoneal RAPN has shown less blood loss, blood transfusion, complication rates, and length of stay (7, 8). It also achieved satisfactory results in the renal tumours with higher preoperative RENAL scores (9).

Preservation of viable renal parenchyma remains the fundamental principle of partial nephrectomy (PN). Several surgical strategies—such as tumor enucleation, enucleo-resection, off-clamp PN, early unclamping, and selective arterial clamping—have been developed. Renorrhaphy has traditionally been an integral component of PN, serving to achieve hemostasis and maintain parenchymal integrity. However, the compressive forces applied during renorrhaphy may result in strangulation of viable renal tissue and inadvertent ligation of intrarenal parenchymal arteries (10). Furthermore, inner renorrhaphy may injure or lacerate interlobar and segmental vessels, leading to intimal disruption and focal ischemia. The delayed vessel wall erosion, slippage of sliding clips or bolsters, and impaired vascular healing may ultimately result in pseudoaneurysm formation (11). To address these technical limitations, various topical hemostatic agents have been increasingly utilized,

as they were associated with reductions in warm ischemia time, operative duration, and estimated blood loss, without an increase in postoperative complications (12).

Veriset™ was developed by Covidien (Mansfield, MA, USA), composed of polyethylene glycol (PEG), tri-lysine, buffer salts, and oxidized cellulose. It has dual mode of action on the tumour bed: it can produce a tamponade effect by giving mechanical compression after getting soaked in the blood due to its self-adhesive hydrogel properties, and at the same time, it concentrates platelets and other clotting factors. The patch gets absorbed within four weeks of application (13). This hemostatic patch achieved hemostasis irrespective of bleeding severity or the surface area during hepatic resection (14). Veriset™ also demonstrated good hemostasis in cardiovascular procedures (13).

There has been limited literature regarding the utility of Veriset™ as an alternative to conventional renorrhaphy while performing minimally invasive PN. Few studies have demonstrated the efficacy of this hemostatic patch to control bleeding in transperitoneal partial nephrectomy, but so far, the use of Veriset™ in retroperitoneal PN has not been evaluated. In this article, we analysed the feasibility of Veriset™ in retroperitoneal RAPN and compared it with the conventional renorrhaphy.

## MATERIALS AND METHODS

The study included 113 patients who received retroperitoneal RAPN between January 2024 and June 2025. These patients' data were gathered in a prospective manner. Ethical clearance was obtained from the Internal Review Board (IRB) of the institute ethics committee (IEC) (Ref. AM/EC/356-2023). The patients with a contralateral normal-functioning kidney and who had a single renal tumour on imaging and were planned for retroperitoneal RAPN were included. The exclusion criteria were patients with numerous renal masses, chronic liver disease, on dual antiplatelets, significant breaches of the pelvicalyceal system (PCS), such as breaches of two or more renal calyces or pelvis. The clinico-demographics, tumour size and location, number of renal vessels, blood parameters before and after surgery, the R.E.N.A.L nephrometry score, intraoperative

findings, blood loss, transfusion, post operative course, hospital stay, complications and follow up of 6 months duration along with postoperative serum creatinine and estimated GFR (eGFR) were recorded. For nephrometry, the R.E.N.A.L. score was used, and GFR was assessed using the Modification of Diet in Renal Disease (MDRD) formula. The two groups underwent propensity score matching based on age, body mass index (BMI), and R.E.N.A.L nephrometry score.

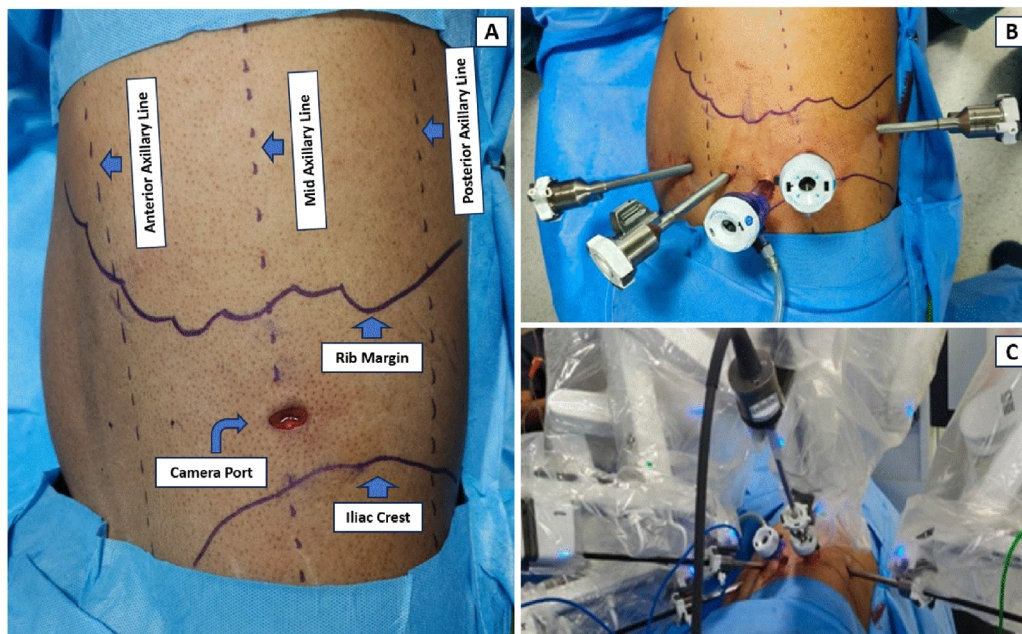
## SURGICAL TECHNIQUE

The patient was positioned laterally as per the site of the tumour. Superiorly, the costal margin, inferiorly the anterior superior iliac spine (ASIS), and anterior, mid, and posterior axillary lines were marked. The camera port was placed under vision (Figure-1A). A reniform-shaped balloon was inserted to create the retroperitoneal space under vision. All the retroperitoneal RAPNs were performed using the Da Vinci X and Xi robot (Intuitive Surgical, Sunnyvale, CA, USA) (Figures 1B, 1C).

**Veriset™ Group (VG):** The lateroconal fascia was divided to approach the hilum. The renal artery and vein were skeletonised. The tumour was located with intraoperative ultrasonography, dissected, and scored. The artery was clamped with bulldog clamps and the tumour was enucleated (Figure-2A). In some cases, enucleo-resection was performed. Spot coagulation was used on the tumour bed. Stratafix 3-0 was used to seal any pelvicalyceal system breaches (Ethicon, Inc., NJ, USA). After that Veriset™ was placed over the tumour bed and compressed with a moist saline-soaked gauze for 1-2 minutes (Figures 2B, 2C, 2D). Depending on the size of the tumour bed after excision, the patch's dimensions varied from 2 X 4 cm to 5 X 5 cm. In a few cases, two patches were used.

**Renorrhaphy Group (RG):** (Figure-3A). Spot coagulation was used after tumour removal (Figure 3A, 3B). The sliding clip technique, renorrhaphy was carried out with a single-layer Vicryl 1-0 (Ethicon, Inc., NJ, USA) (Figures 3C, 3D). No drain was placed in any group of patients.

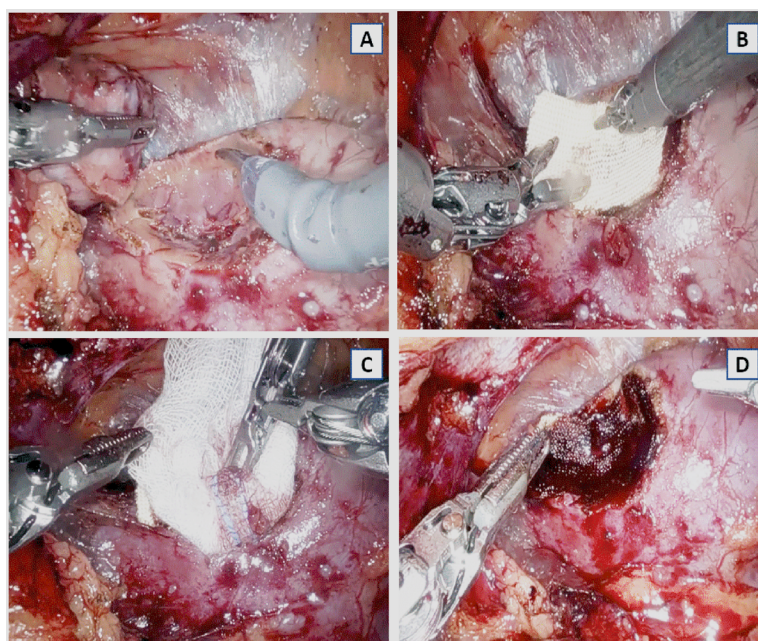
**Figure 1 - Retroperitoneal port placement.**



A) The landmarks and the area of the camera port placement; B) Four robotic and one assistant port placement; C) The final picture after docking the robotic system.

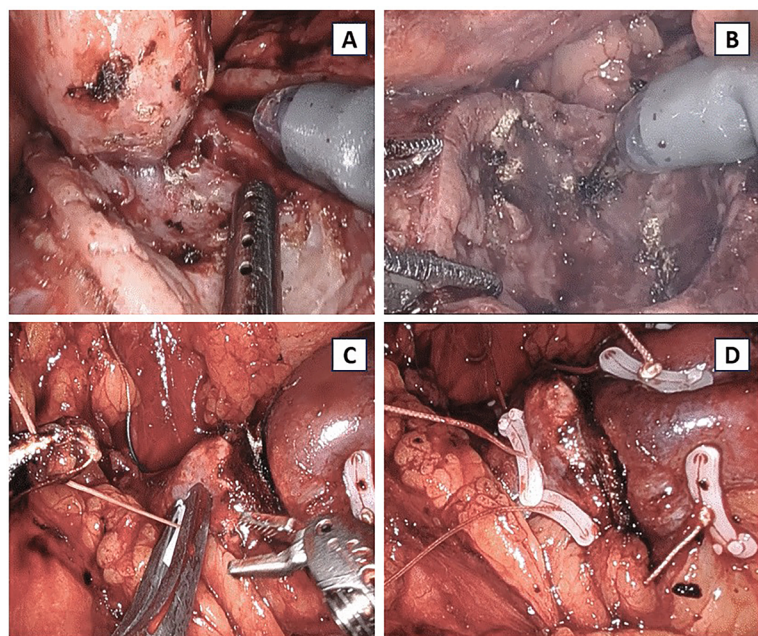


**Figure 2 - Veriset™ hemostatic patch placement.**



A) Tumour bed after enucleation; B) Placement of Veriset™; C) Compression with moist saline gauze; D) Final picture after hemostasis with Veriset™ patch.

**Figure 3 - Renorrhaphy.**



A) Enucleation of the tumour; B) Spot coagulation of the bleeders on the tumour bed; C) Sliding-clip renorrhaphy; D) Final picture after hemostasis with renorrhaphy.

## Statistical Analysis

R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria) was used to conduct the statistical analysis. For continuous variables, descriptive statistics were shown as means with standard deviations; for categorical variables, they were shown as frequencies and percentages. Categorical variables were compared using the Chi-squared test or Fisher's Exact test. Independent sample t-tests were used to compare continuous variables. The statistical significance was considered at a p-value of <0.05.

## RESULTS

A total of 113 patients underwent retroperitoneal RAPN during the study period. Of these patients, 32 patients had Veriset patch placed (VG). Eighty-one patients underwent conventional renorrhaphy (RG). The mean age, BMI, and R.E.N.A.L. nephrometry score were  $54.3 \pm 12.4$  vs.  $52.08 \pm 15.96$  years,  $26.95 \pm 7.24$  vs.  $27.27 \pm 4.26$  kg/m<sup>2</sup>,  $5.3 \pm 1.12$  vs.  $5.27 \pm 1.23$ , respectively (Table-1).

After propensity score matching, 32 patients in the VG and 40 patients in the RG were taken for the final analysis (Propensity score  $0.25 \pm 0.05$ ). The tumour size was comparable ( $3.33 \pm 1.2$  vs.  $3.34 \pm 0.9$  cm, respectively). As per the R.E.N.A.L. Nephrometry Score Category, low, intermediate, and high-risk tumours were evenly distributed in both groups (65.6 vs. 67.6%, 25 vs. 21.6%, and 9.4 vs. 10.8%, respectively). The warm ischemia time ( $12.86 \pm 6.14$  vs.  $17.48 \pm 5.40$  minutes,  $p < 0.001$ ), console Time ( $47.26 \pm 17.51$  vs.  $71.67 \pm 22.6$  minutes,  $p < 0.001$ ), and blood Loss ( $57.74 \pm 22.83$  vs.  $87.34 \pm 33.81$  mL,  $p = 0.008$ ) were significantly less in the VG. Three patients in the VG required suturing of the large bleeding vessels in tumour bed before patch application. Although hemoglobin drop was less in the VG ( $0.84 \pm 0.21$  vs.  $1.15 \pm 0.3$  gm/dL), it was not statistically significant ( $p = 0.075$ ). The immediate drop in GFR on postoperative day-1 was significantly less in the VG ( $0.07 \pm 11.15$  vs.  $4.68 \pm 11.66$  mL/min/1.73 m<sup>2</sup>,  $p = 0.008$ ). Although at 6-month follow-up, the change in GFR becomes similar in both groups ( $-7.21 \pm 10.51$  vs.  $-7.68 \pm 11.09$ , mL/min/1.73 m<sup>2</sup>,  $p = 0.237$ ). The

postoperative pain score, length of hospital stays, and margin positivity rate were not affected by either group. Overall, two patients in the RG developed hematuria. One of them had readmission and undergone angioembolisation. None of the patients had any urine leak; one patient in the RG had a pseudoaneurysm on follow-up (Table-1).

## DISCUSSION

RAPN is a well-established and feasible minimally invasive approach for renal tumours (15). The transperitoneal approach is still used most commonly as it provides quick access, simple port insertion, a larger workspace with familiar anatomy. However, the retroperitoneal approach has provided non-inferiority in achieving Trifecta outcome along with shorter operating and ischemia times, hospital stays, less intra-operative blood loss, and fewer complications without compromising the GFR (16). Renorrhaphy continues to remain the cornerstone for re-approximation of the renal parenchyma following tumor excision. Techniques like running knotless suturing with Lapra-Ty (absorbable Polyglactin) clips, Suture-clips, Endoclips, or Hem-o-lok clips were invented to minimise the parenchymal compression. Barbed suture, like V-Loc further simplified the renorrhaphy by providing uniform tension distribution. Novel suturing strategies—including V-hilar repair, ring renorrhaphy, and off-clamp renorrhaphy—have been developed (17). Renorrhaphy has been associated with pseudoaneurysm in at least 1-5% patients within the first 90 days after RAPN (18). Gill et al. proposed two mechanisms: firstly, the inadvertent vascular injury during suturing, and secondly, the increased blood flow and accumulation at the injured site after the patient resumes daily activity (19). Renorrhaphy, along with excision of viable renal parenchyma and prolonged WIT causing ischemia-perfusion damage, can decrease up to 20% of the renal function (20).

To overcome these challenges, the use of various hemostatic agents has been suggested. Grossly four types of agents have been explored: mechanical agents like bovine collagen, polysaccharide spheres, cellulose, and gelatin (Bioglue) form a matrix over the tumour bed

**Table 1 - Comparison of different perioperative, oncological and renal function parameters between the Veriset™ group (VG) and the renorrhaphy group (RG).**

| Parameters                                      |                         | Retroperitoneal Robot assisted Partial Nephrectomy |                               | p-value |
|-------------------------------------------------|-------------------------|----------------------------------------------------|-------------------------------|---------|
|                                                 |                         | Veriset Group<br>(n = 25)                          | Renorrhaphy Group<br>(n = 40) |         |
| Age (Years)                                     |                         | 53.5 ± 10.2                                        | 52.08 ± 15.96                 | 0.92    |
| Gender                                          | Male                    | 15 (60%)                                           | 28 (75.6%)                    | 0.87    |
|                                                 | Female                  | 10 (40%)                                           | 9 (24.4%)                     |         |
| Laterality                                      | Right                   | 11 (44%)                                           | 21 (56.7%)                    | 0.59    |
|                                                 | Left                    | 14 (56%)                                           | 16 (43.3%)                    |         |
| BMI (kg/m <sup>2</sup> )                        |                         | 27.84 ± 5.12                                       | 27.27 ± 4.26                  | 0.9     |
| Tumour Size (cm)                                |                         | 3.32 ± 1.15                                        | 3.34 ± 0.9                    | 0.78    |
| Number of Renal Arteries                        |                         | 1.35 ± 0.24                                        | 1.43 ± 0.33                   | 0.32    |
| Number of renal Veins                           |                         | 1.46 ± 0.42                                        | 1.21 ± 0.18                   | 0.43    |
| Nephrometry Score                               |                         | 5.32 ± 1.29                                        | 5.27 ± 1.23                   | 0.75    |
| R.E.N.A.L. Nephrometry Score<br>Category        | Low Risk (4-6)          | 17 (68%)                                           | 25 (67.6%)                    | 1.000   |
|                                                 | Intermediate Risk (7-9) | 6 (24%)                                            | 8 (21.6%)                     |         |
|                                                 | High Risk (10-12)       | 2 (8%)                                             | 4 (10.8%)                     |         |
| Blood Loss (mL)                                 |                         | 59.45 ± 24.64                                      | 87.34 ± 33.81                 | 0.008   |
| Blood Transfusion                               |                         | 0 (0.0%)                                           | 1 (2.7%)                      | 0.394   |
| Console Time (Minutes)                          |                         | 45.34 ± 16.21                                      | 71.67 ± 22.6                  | <0.001  |
| Warm Ischemia Time (Minutes)                    |                         | 12.73 ± 5.83                                       | 17.48 ± 5.40                  | <0.001  |
| Pain Score- VAS                                 | at 6th hour             | 1.87 ± 0.43                                        | 1.72 ± 0.25                   | 0.56    |
|                                                 | at 24th hour            | 1.63 ± 0.43                                        | 1.53 ± 0.42                   | 0.83    |
| Hemoglobin (g/dL)                               | Preoperative            | 13.42 ± 4.5                                        | 13.81 ± 1.75                  | 0.35    |
|                                                 | Postoperative           | 12.92 ± 1.85                                       | 12.66 ± 1.72                  | 0.73    |
| Change in Hemoglobin (g/dL)                     |                         | -0.95 ± 0.38                                       | -1.15 ± 0.3                   | 0.075   |
| Serum Creatinine<br>(mg/dL)                     | Postoperative day 1     | 1.04 ± 0.34                                        | 1.16 ± 0.39                   | 0.72    |
|                                                 | At 6 Months             | 1.18 ± 0.27                                        | 1.28 ± 0.25                   | 0.67    |
| GFR<br>(mL/min/1.73 m <sup>2</sup> )            | Preoperative            | 90.43 ± 23.15                                      | 87.52 ± 23.28                 | 0.63    |
|                                                 | Postoperative day 1     | 87.44 ± 25.34                                      | 83.54 ± 18.89                 | 0.83    |
|                                                 | at 6 months             | 82.78 ± 30.15                                      | 80.29 ± 25.63                 | 0.325   |
| Change in eGFR<br>(ml/min/1.73 m <sup>2</sup> ) | Postoperative day 1     | -0.07 ± 10.27                                      | -4.68 ± 11.66                 | 0.008   |
|                                                 | At 6 Months             | -7.01 ± 12.78                                      | -7.68 ± 11.09                 | 0.237   |
| Margins (Positive)                              |                         | 1 (5.0%)                                           | 0 (0.0%)                      | 0.567   |
| Length of Stay (Days)                           |                         | 3.25 ± 0.93                                        | 3.38 ± 1.28                   | 0.587   |
| Postoperative Hematuria                         |                         | 0 (0.0%)                                           | 2 (5.4%)                      | 0.54    |
| Urine Leak                                      |                         | 0 (0.0%)                                           | 0 (0.0%)                      | 1.000   |
| Pseudoaneurysm                                  |                         | 0 (0.0%)                                           | 1 (2.7%)                      | 0.394   |
| Angioembolisation                               |                         | 0 (0.0%)                                           | 1 (2.7%)                      | 0.394   |
| Hospital Readmission                            |                         | 0 (0.0%)                                           | 1 (2.7%)                      | 0.279   |
| Propensity Score                                |                         | 0.25 ± 0.05                                        | 0.25 ± 0.05                   | 0.775   |

BMI = Body mass index; VAS = Visual analogue scale; GFR = Glomerular filtration rate

and activate the extrinsic coagulation pathway. The active substance, like thrombin, works on the intrinsic pathway to convert fibrinogen into fibrin. The flowable agents (gelatin-based, e.g., Surgiflo, FloSeal, Flogel, and collagen-based, like Collastat) swell after being sprayed from a syringe and create a tamponade effect. Lastly, fibrin based like sealants, foams, and glue (Tachosil: fibrin and thrombin) promote fibrin mesh formation at the end of the coagulation cascade (15). Although initial experience with hemostatic agents was not encouraging for blood loss and hemoglobin drop in RAPN (21). However, recently only 4.4% patients were reported to have failure with Hemopatch (Baxter) (22). Tiscione et al. reported a six-minute and 18-minute reduction in median WIT and operating time respectively, without affecting the renal function (23). Improved functional (operative time [110 vs 150 min;  $p < 0.01$ ] and length of stay [2 vs 3 d;  $p = 0.02$ ] and trifecta safety (86% vs. 70%,  $p=0.1$ ) were seen by Farinha et al. during transperitoneal RAPN when they compared the selective-suturing or sutureless technique with Veriset and Tachosil with standard renorrhaphy (24).

Veriset™ (Covidien; Mansfield, MA, USA) is composed of absorbable oxidized cellulose and hydrogel components without any human or animal component. Along with providing mechanical compression by forming a cross-linked PEG-based gel while interacting with blood, it can concentrate platelets and other clotting factors over the tumour bed to accelerate coagulation (13). The oxidised cellulose may provide anti-microbial cover. It requires at least 30 seconds of pressure with a moist saline gauze and gets absorbed after four weeks of application. It is very easy to insert through the assistant port. As described by Brassetti et al., we perform high-precision coagulation of the bleeders on the tumour bed before placing the Veriset™ (20). To lower WIT and postoperative pseudoaneurysm rates, we have changed our practice from two-layer renorrhaphy to single-layer outer cortical renorrhaphy (SLOCR) (25). Our study result still shows significantly less WIT ( $12.86 \pm 6.14$  vs.  $17.48 \pm 5.40$  minutes,  $p<0.001$ ), console Time ( $47.26 \pm 17.51$  vs.  $71.67 \pm 22.6$  minutes,  $p<0.001$ ) in the VG. Erne et al. found similar results, with 35 and six minutes less mean operating time and WIT, respectively, in the

patients who underwent laparoscopic partial nephrectomy (26). In our patients of VG, we released the arterial clamp immediately after the patch placement at the start of the compression, while in RG, we only released it after the renorrhaphy, which we feel attributed to the shorter WIT in the VG.

In our study, VG had significantly less blood Loss ( $57.74 \pm 22.83$  vs.  $87.34 \pm 33.81$  mL,  $p=0.008$ ). Although the hemoglobin drop was less in VG, it was not significant. Maurice et al. recorded 2.4% blood transfusions. After covariate adjustment, they found no alteration in postoperative bleeding outcome by the hemostatic agents in nonanemic patients (27). However, in our propensity-matched analysis between VG and RG in transperitoneal RAPN, we found less blood loss in VG (28). Guo et al. found a similar result of almost 80 mL less mean estimated blood loss (12). As the retroperitoneum is a less distensible compartment compared to the peritoneal cavity, the pneumoperitoneum can create more compression on the tumour bed. This effect helps in more precise resection or enucleation of the tumour, and Veriset patch, along with pneumoperitoneum, secures the hemostasis in a more efficient manner. Two patients in RG had hematuria. One of them had readmission and was diagnosed to have pseudoaneurysm formation and underwent angioembolisation. None of the patients had such an outcome in the VG. In our earlier study evaluating the use of Veriset™ in transperitoneal robot-assisted partial nephrectomy, three failures were observed, necessitating additional renorrhaphy. These failures occurred due to bleeding following clamp release, which was attributed to overlooked arteries within the tumor base. In contrast, no failures were encountered in the retroperitoneal group. This difference may be explained by improved visualization of intratumoral arteries during tumor resection in the retroperitoneal approach, facilitated by effective tamponade of small renal veins, resulting in a clearer surgical field.

Renorrhaphy produces parenchymal ischemia and damage, and thereby produces a reduction in eGFR. In our study, the immediate rise in serum creatinine and eGFR drop was more pronounced in the RG, but this effect faded with time, and the renal function became comparable between both groups at 6 months.



This could be explained by the fact that the WIT in both our study groups was less than 20 minutes, which led to such a functional outcome. In a recent analysis, duration of ischemia did not affect the renal function in RAPN if the WIT was below 30 minutes (29).

The Veriset™ patch was used across all R.E.N.A.L. nephrometry grades. The mean tumour size in both groups was similar ( $3.33 \pm 1.2$  vs.  $3.34 \pm 0.9$  cm, respectively). Not any patient in these two groups suffered from urine leak, which signifies proper watertight closure of the pelvicalyceal system. Neither approach resulted in significant margin positivity. Complication rates were also comparable. Erne et al. recorded a similar outcome in their patients after laparoscopic PN (26). Based on these findings, Veriset is non-inferior in achieving the 'Trifecta outcome' while compared to renorrhaphy.

Hemostatic agents are associated with additional cost. Durant et al. analysed that the cost difference with renorrhaphy was greatest during 2010 (30). However, as Veriset™ hemostatic patch eliminates the need for consumables needed for renorrhaphy, i.e., sutures and hemo-lock clips, our rough estimation suggests that the cost of clips and sutures is largely comparable to a single Veriset patch, with costs increasing only when multiple patches are required. The cost factor warrants re-evaluation, and a detailed comparative analysis is required to understand the economic impact.

The indications for conventional renorrhaphy and hemostatic patch placement should be clearly defined. Veriset™ may be particularly advantageous where minimizing WIT and preserving viable renal parenchyma are of paramount importance, such as in patients with multiple renal tumors, syndromic conditions including von Hippel-Lindau disease (VHL), a solitary kidney, prior contralateral nephrectomy, or pre-existing chronic kidney disease. Conversely, as Veriset™ relies on an intact coagulation pathway to achieve optimal efficacy, its use should be avoided in patients with chronic liver disease, bleeding diathesis, or clotting factor deficiencies. In addition, cases with extensive pelvicalyceal system breach or a grossly irregular tumor bed following resection may not be suitable for this approach.

There are a few limitations in this study. Firstly, the sample size is small, and from a single centre. With such a small sample size, the study lacks the necessary statistical power (Type II error) to generalise the conclusion of no difference between the two techniques. Secondly, this non-randomised study can give rise to selection bias. Although propensity scores were matched, confounding factors cannot be ruled out. Thirdly, as we initially adopted Veriset™ in retroperitoneal RAPN, its use was largely limited to tumors with low nephrometry scores, resulting in a relatively small proportion of high-complexity cases in our cohort. Therefore, drawing a definitive conclusion regarding its safety or efficacy in the high nephrometry score subgroup is not feasible. The follow-up was short without any formal cost analysis. We avoided Veriset™ in major PCS breaches, which may have introduced a selection bias. Despite these, this is the first study that did a head-to-head perioperative, oncological, and functional outcome comparison of Veriset™ hemostatic patch with renorrhaphy in retroperitoneal RAPN.

## CONCLUSIONS

This study indicates that Veriset™ hemostatic patch during retroperitoneal RAPN can be considered as a safe and feasible alternative to conventional cortical renorrhaphy to achieve hemostasis and the trifecta outcome. It can bring down warm ischemia time, console time, and blood loss without increasing the complications and reducing the renal function. However, as the study population predominantly comprised low nephrometry score tumors, the role of this approach in moderate- and high-complexity renal masses remains to be established and warrants validation in larger studies.

## COMPLIANCE WITH ETHICAL STANDARDS

All the patients included in the study have given the consent for the same.

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## CONFLICT OF INTEREST

None declared.

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# Malleable Penile Prosthesis Fractures: Lessons Learned from 17 Years of Experience at a Tertiary Center in Brazil

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## ABSTRACT

**Purpose:** To critically evaluate the clinical presentation, imaging performance and surgical findings of malleable penile prosthesis (MPP) fractures in a high-volume tertiary center.

**Materials and Methods:** Medical reports of men who underwent revision surgery with intraoperative confirmation of MPP fracture between January 2008 and January 2025 were reviewed. MPP from a single manufacturer (Promedon®, Cordoba, Argentina) were inserted, and no comparisons were possible. Demographic data, presenting symptoms, imaging findings, and fracture location were analyzed. Diagnostic performance of physical examination and imaging modalities was descriptively compared.

**Results:** Among 741 penile prosthetic procedures, 98 were revisions and 52 (53.1%) were due to MPP fracture. Median time from implantation to fracture was 59 months (IQR 24.8–84.0). Penile instability was the most common symptom (96.1%), while pain was reported in 21.1%. Physical examination correctly identified fractures in 88.5% of cases, outperforming radiography and magnetic resonance imaging. Bilateral fractures occurred in 51.9% of revisions, most commonly in the proximal segment. Recurrent fractures occurred in 28.2% of patients.

**Conclusions:** MPP fractures are more prevalent than expected and a clinically relevant complication in high-volume centers. Diagnosis relies primarily on clinical assessment, with physical examination outperforming imaging modalities. Increased awareness of typical presentation patterns may support earlier recognition and more efficient management. Prospective studies are needed to identify modifiable risk factors, improve device design and quality, and advise patients on use to potentially improve prosthesis lifetime.

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## INTRODUCTION

Erectile dysfunction (ED) affects over 50% of patients over the age of 40 (1), with prevalence increasing with aging, and a significant negative impact on both patients' and their partners quality of life (QoL) (2). Despite the widespread use of phosphodiesterase type 5 inhibitors (PDE5Is) (3) and other effective treatment strategies such as shock wave therapy (4) or intracavernosal injections (5), penile prosthesis (PP) implantation remains a well-established treatment option, with high satisfaction rates among both patients and partners, and is considered the gold standard in those who fail, reject, or have contraindications to less invasive therapies (6).

Since its first description in 1936 (7), advances in prosthetic design have improved durability, concealability and rigidity (8), leading to the development of inflatable penile prosthesis (IPP) (9), which has yielded higher satisfaction rates among patients and their partners than the malleable penile prosthesis (MPP) (10). Recent advances have enabled penile prosthesis implantation to be safely performed with concomitant non-reconstructive urologic procedures, without increasing adverse events (11).

Nevertheless, MPPs offer important advantages over inflatable devices, including a more straightforward surgical technique, a lower incidence of mechanical complications, lower cost, and broader availability in developing countries (8, 12, 13). In Brazil, IPPs are neither covered by private insurance nor by the public Brazilian Universal Health Care System (Sistema Unico de Saude [SUS]), whereas MPPs are covered by both systems at no additional cost to patients. Similar access limitations to IPPs have been reported in other countries (14).

Although MPPs are associated with lower overall revision rates than IPPs (15), they are not without complications, including mispositioning (e.g., cross-over), infection, extrusion, and fracture, all of which may ultimately lead to revision surgeries (8, 11, 14). Among these, MPP fractures remain poorly reported in the literature, with evidence largely limited to case reports, despite being relatively frequent in high-volume centers in developing settings.

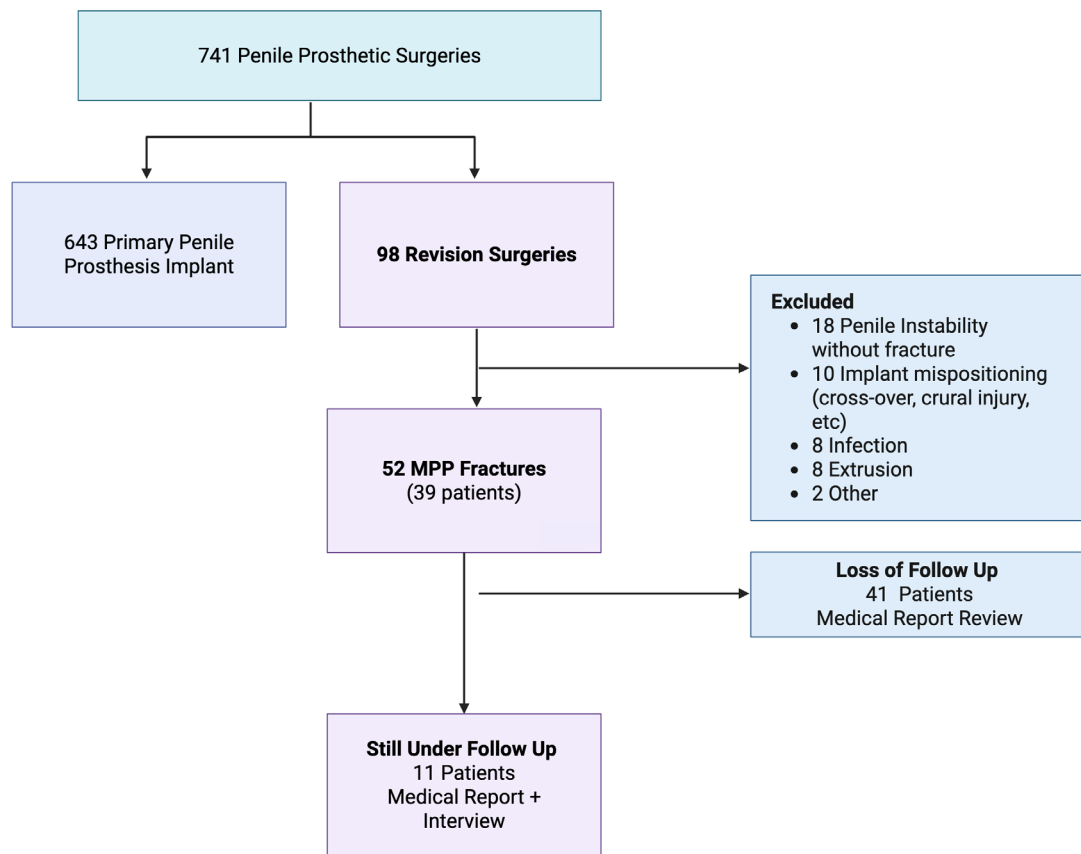
We hypothesized that malleable penile prosthesis (MPP) fractures present with consistent clinical features that may facilitate early diagnosis and management, while fostering the comprehension of this event and promoting strategies for its prevention. Therefore, this study aims to describe the characteristics of surgically confirmed MPP fractures treated at a tertiary university hospital over a 17-year period.

## MATERIALS AND METHODS

After institutional ethical approval (CAAE-26509), we conducted a single-center cross-sectional study based on retrospectively collected data from medical records of adult men who underwent revision surgery for MPP fracture between January 2008 and January 2025. Only cases with intraoperative confirmation of implant fracture were included. Patients with intact MPPs intraoperatively or incomplete medical records were excluded. The study design is depicted in Figure-1. In Brazil, the law requires companies to submit proposals in a blind auction to sell their devices to the State Government; the company with the lowest price and that meets the quality and legal requirements is declared the winner. At Hospital das Clinicas, University of São Paulo Medical School, primary MPP implantations were performed using a standardized penoscrotal approach by Urology residents under the supervision of an experienced prosthetic surgeon. Almost all patients received the Tube Malleable Implant (Promedon®, Cordoba, Argentina) one patient had been previously reviewed, and one patient had previously received a Medicone implant (Medicone®, Porto Alegre, Brazil) at an outside institution. All revision surgeries at our center involved replacement with the Tube Malleable Implant (Promedon®, Cordoba, Argentina), the only device routinely available in our service.

Routine postoperative follow-up was scheduled for two and six weeks, with clearance for sexual activity at the latter visit, followed by additional visits at three months and one year. Beyond this period, follow-up was patient-initiated as needed.

For patients with confirmed fracture, clinical and surgical data were collected, including age at implantation,

**Figure 1 - Flowchart of patient selection and study cohort.**

Flowchart illustrating patient selection and study design. A total of 741 penile prosthetic surgeries were performed during the study period, including 643 primary implantations and 98 revision procedures. Among revision surgeries, 52 cases were due to malleable penile prosthesis (MPP) fracture and were included in the study. Revision surgeries for penile instability without fracture, implant mispositioning, infection, and extrusion were excluded. Of the 52 patients with confirmed MPP fracture, 41 were lost to follow-up, and 11 patients were available for detailed postoperative assessment and interview.

erectile dysfunction etiology, comorbidities, prosthesis length and girth and post-operative complications.

Patients with confirmed fracture intraoperatively had clinical data of the implant procedure collected, including age at the time of implantation, etiology of erectile dysfunction (ED), comorbidities (eg, hypertension, diabetes, peripheral vascular disease, obesity, smoking history and chronic kidney disease), and intraoperative data, including prosthesis length and girth, the need for rear tip extensor utilization, and post-operative complications.

Fracture-related data were obtained from retrospective review of clinical records, including age at presentation, time from implantation to fracture and

presenting symptoms such as pain, penile instability (inability to maintain axial rigidity or alignment during sexual activity) and impairment of penetrative intercourse.

Imaging studies were requested at the discretion of the attending physician without a standardized imaging protocol and included pelvic X-ray and/or magnetic resonance imaging (MRI). Available images were reviewed and compared to intraoperative findings to assess diagnostic accuracy.

From March 2023 onward, a standardized surgical report was implemented for suspected fracture cases, documenting the number and location of fractures and evidence of contralateral metallic core fatigue in addition to prosthesis length, girth and use of extender tips.



Sexual behavior data were not routinely collected before June 2023. Thereafter, information on sexual and masturbation frequency, preferred sexual position, anal penetration practice, use of lubricants and resting position of the PP was obtained during scheduled visits or structured telephone interviews.

Data was analyzed descriptively. Continuous variables are presented as median and interquartile range (IQR), while categorical variables are presented as frequencies and percentages. Statistical analyses were performed using GraphPad Prism, version 10.0.0 (GraphPad Software, Boston, MA).

## RESULTS

Between January 2008 and January 2025, 741 penile prosthetic surgeries were performed at our institution, including 98 revisions. Malleable penile prosthesis (MPP) fractures were the leading indication for reoperation (53.1%; 52/98), followed by penile instability without fracture (18.4%; 18/98), implant mispositioning (10.2%; 10/98), and infection or extrusion (8.2%; 8/98).

Fifty-two revision surgeries for MPP fracture were performed in 39 patients. Recurrent fractures were observed in 11 patients: 9 (23.1%) had two events whereas 2 (5.1%) had three separate events.

Median age at initial MPP implantation was 60.5 years (IQR, 54.5–66.2). Underlying etiologies of erectile dysfunction included metabolic syndrome (43.5%; 17/39), oncological conditions (38.5%; 15/39), Peyronie's disease (10.5%; 4/39), and spinal cord injury (7.5%; 3/39). Hypertension (74.4%; 29/39) and diabetes (35.9%; 14/39) were the most frequent comorbidities; with all but 1 patient having HbA1c < 8.5%. Additional comorbidities included smoking (17.9%; 7/39), chronic kidney disease or kidney transplantation (15.4%; 6/39), peripheral vascular disease (7.7%; 3/39), and obesity (BMI > 30; 5.1%; 2/39). No intraoperative complications were reported, and two patients developed early superficial wound dehiscence without need for surgical intervention.

Symptoms of MPP fractures developed a median of 59 months (IQR, 24.8–84.0) after implantation. Penile instability was reported by 96.1% of patients (50/52), whereas pain by 21.1% (11/52) and penetrative difficulty

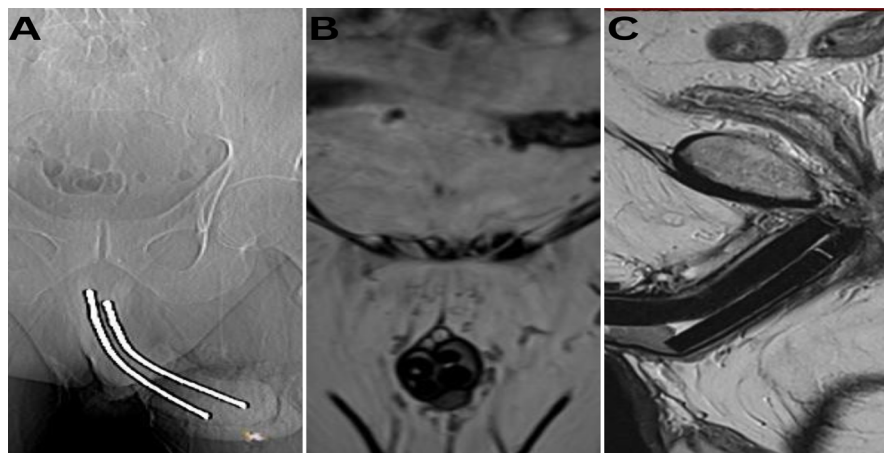
by 79.6% (40/52). Complete impossibility of penetration was reported by 15.4% (8/52), whereas 7.7% (4/52) reported no functional impairment.

Physical examination identified a palpable fracture in 88.5% (46/52) of cases. The evaluation consisted of systematic palpation of the penile shaft, combined with gentle axial compression and controlled bending of the prosthesis to assess discontinuity, abnormal angulation, or crepitus. Findings suggestive of fracture included a focal loss of rigidity, a palpable step-off, or crepitus along the shaft. Among patients who underwent X-ray, fracture was detected in 81.2% (26/32). Magnetic resonance imaging (MRI) was performed in 11 patients, but only 18.2% (2) of radiology reports described fractures. Representative imaging findings, including false-negative and discordant cases, are shown in Figure-2. Patient characteristics and diagnostic findings are summarized in Table-1.

All revision procedures were completed without intraoperative complications. Bilateral fractures were present in 51.9% (27/52). In 53.8% (28/48) of revisions, the replacement implant had greater girth and/or length. Fracture distribution by girth was: 9 mm (19.2%; 10/52), 10 mm (43.2%; 22/52), and 11 mm (21.1%; 11/52). No fractures occurred in 12 - 13mm prosthesis, which were unavailable before 2019. Median prosthesis length was 20cm (IQR 19-21.5). Rear tip extenders were used in only 15.4% (8/52) of cases. Sizing was primarily based on girth.

Forty-four surgical reports were available for detailed analysis (Figure-3), which illustrates representative intraoperative findings and fracture patterns. Up to four wear points per prosthesis were identified; and multiple wear points per cylinder were observed in 61.3% (27/44). Fractures were predominantly proximal (77.1%; 27/35), followed by distal (22.6%; 8/35) and mid-cylinder (17.1%; 6/35). Sexual behavior data were available for 11 patients. Most reported a single partner (72.7%; 8/11). None reported anal penetration. Lubricant use was routine in 55.0% (6/11). All patients routinely positioned the penis laterally for concealment. Median monthly penetrative intercourse before fracture was 2.0 (IQR 1.2–3.8), with a maximum of 12; two patients reported no intercourse. Among the 11 patients, the most

**Figure 2 - Imaging findings in malleable penile prosthesis (MPP) fracture (personal archive) highlighting discordance between imaging interpretation and intraoperative diagnosis.**



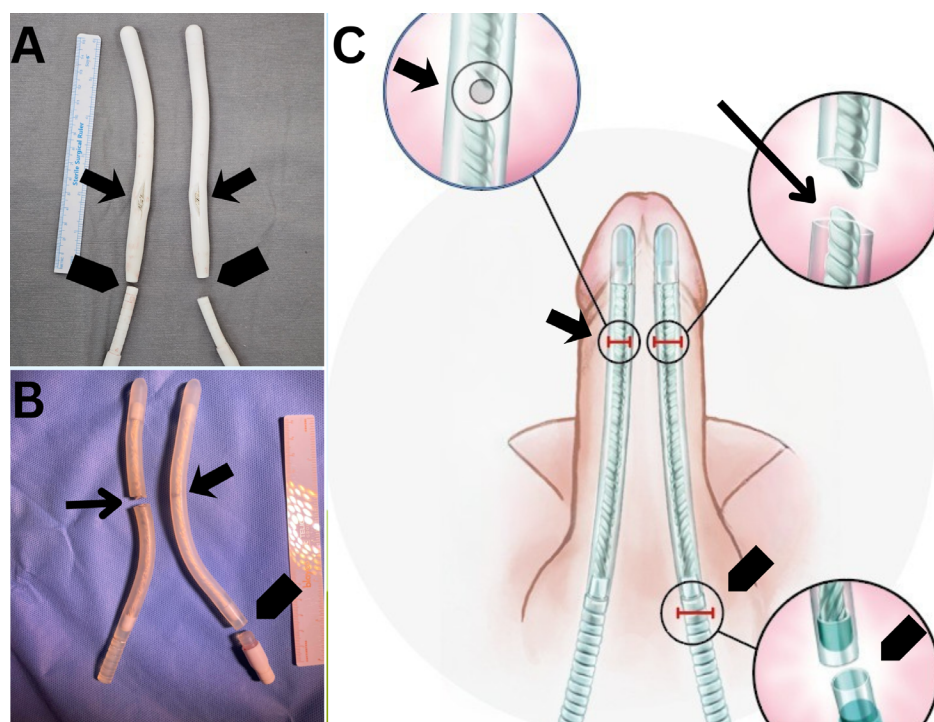
(A) Plain radiograph of the patient illustrated in Figure-3A, with surgically confirmed bilateral MPP fracture, showing no evident abnormalities. (B) Magnetic resonance imaging (MRI) of the same patient illustrated in Figure-3A, also without clear evidence of prosthesis fracture. (C) MRI of a different patient initially reported as disconnection of rear tip extenders; however, intraoperative findings confirmed prosthesis fracture, as illustrated in Figure-3B.A

**Table 1 - Signs and symptoms reported by patients with malleable penile prosthesis (MPP) fracture.**

| Variable                                        | Value          |
|-------------------------------------------------|----------------|
| Total Sample - MPP Fractures                    | (n = 52)       |
| Time from MPP Implant to MPP Fracture Complaint |                |
| < 1 year                                        | 11.5% (n = 6)  |
| 1 - 5 years                                     | 40.4% (n = 21) |
| 5 - 10 years                                    | 40.4% (n = 21) |
| > 10 years                                      | 7.7% (n = 4)   |
| MPP Fracture Symptoms                           |                |
| Instability                                     | 96.1% (n = 50) |
| Pain                                            | 21.1% (n = 11) |
| Challenge with Intercourse Penetration          |                |
| Difficulty with penetration                     | 76.9% (n = 40) |
| Impossibility of penetration                    | 15.4% (n = 8)  |
| Penetration not impaired                        | 7.7% (n = 4)   |
| MPP Physical Exam                               |                |
| Abnormal                                        | 88.5% (n = 46) |
| Normal                                          | 11.5% (n = 6)  |

Data are presented as n (%); MPP = malleable penile prosthesis; IQR = interquartile range

**Figure 3 - Intraoperative findings and fracture patterns of malleable penile prosthesis (MPP) (personal archive).**



(A) Medicone prosthesis demonstrating multiple bilateral fractures. (B) Promedon prosthesis demonstrating multiple bilateral fractures. (C) Schematic representation of fracture patterns identified intraoperatively. Across all panels, thick arrows indicate metallic core fatigue without disruption of the silicone covering; arrowheads indicate complete fractures external to the metallic core; and thin arrows indicate complete fractures involving both the silicone covering and the metallic core.

common position was the man in the superior position over the partner (72.7%; 8/11), followed by the same position with the partner's leg elevated (36.4%; 4/11). Less frequent positions included partner-on-top (9.1%; 1/11) and kneeling male with the partner supine and pelvis elevated (9.1%; 1/11).

## DISCUSSION

Penile prosthesis (PP) implantation is a well-established therapeutic option for erectile dysfunction (ED) and Peyronie's disease (14). Because implantation is irreversible, understanding complication patterns and failure mechanisms is paramount for patient counseling and long-term satisfaction.

In the United States, inflatable penile prosthesis (IPP) account for approximately 90% of implants, largely due to insurance coverage and higher patient

and partner satisfaction (7, 8, 10). In contrast, malleable penile prosthesis (MPP) remains widely used in developing countries owing to lower cost and easier of installation and functionality, demanding less steps for satisfactory sexual intercourse, but more prone to repeated bending (14). As a result, most available data derives from IPP-dominant populations, rendering MPP-related complications comparatively underexplored.

Large population-based studies suggest comparable overall revision rates between both prosthesis types. Lacy et al. (15) compared revision surgery rates among 6,586 patients undergoing primary penile prosthesis implantation with at least one year of follow-up, of whom 13.4% (883) received malleable penile prostheses (MPP). Their analysis demonstrated longer time to revision for MPP compared with IPP at 1-, 5-, and 10-year follow-up intervals (HR: 0.68; 95% CI 0.53–0.83;  $p < .001$ ), with a statistically significant divergence after 13 years,

suggesting favorable long-term durability of malleable devices. Similarly, Grewal et al. (12) analyzed 2,263 penile prosthesis implantations in California between 2006 and 2009, of which 19.4% (439) were MPP, and found no significant difference in overall reoperation rates (7.52% MPP vs 7.40% IPP;  $p = 0.94$ ), although complication patterns differed, with a higher proportion of infectious complications observed after MPP implantation (4.5% MPP vs 3.23% IPP;  $p = 0.18$ ) and a greater frequency of noninfectious complications following IPP placement (2.96% MPP vs 4.17% IPP;  $p = 0.25$ ). Importantly, neither study reported prosthesis manufacturer nor stratified early and late complications, limiting device-level interpretation.

Evidence regarding MPP-specific complications, particularly fracture, remains scarce and largely limited to case reports or secondary observations in studies designed for other outcomes. Despite this limited evidence base, our series demonstrates that MPP fracture was the leading cause for revision in our institution, accounting for 53.1% of reoperations. Our results, however, should be interpreted within the context of the study design. As only patients undergoing revision surgery with intraoperatively confirmed fractures were included, our findings reflect the relative contribution of fractures among revision cases in our institution and do not allow estimation of true incidence, prevalence or population-level occurrence.

In 2006, Minervini et al. (16) reported two cases of MPP rod fracture, one in the former model, the AMS 600 (Boston Scientific, Marlborough, MA) after 112 months and one Montor Malleable (Montor Medical, São Paulo, Brazil) after 79 months. Mohamed et al. (17) reported three revision surgeries due to MPP fractures in Promedon Tube Prosthesis after 13, 19, and 22 months of their implantation, being the cause of 23% (3/13) of prosthesis removal and 8.3% (3/36) of long-term complications in this cohort. Moreover, Pinheiro et al. (18) reported multiple site fractures on both cylinders of a 72-year-old patient, being the first to describe multiple fractures per cylinder.

Within the Brazilian Public Unified Health Care System (Sistema Unico de Saude [SUS]), device selection is determined by a public bidding process prioritizing cost-effectiveness once predefined technical criteria

are met. Consequently, the Promedon Tube Malleable Implant (Promedon®, Cordoba, Argentina) has been the primary device at our center. This prosthesis consists of a silicone elastomer body with a polytetrafluoroethylene-coated twisted silver wire core designed to provide axial rigidity (19, 20). A similar internal architecture is observed in the Medicone Penile Implant (Medicone®, Porto Alegre, Brazil) identified in one of our revision surgeries. Notably, both designs resemble earlier-generation MPP designs, such as the one by Dr Udo Jonas, introduced in the US marketplace in 1980 but soon replaced as the silver strands tended to fracture, rendering device failure (8).

Behavioral factors have been proposed as potential contributors to MPP fracture risk. Prior studies suggest that vigorous sexual activity, particularly positions where the woman is on top, may increase axial load (16, 17). Anal penetration has also been hypothesized as a contributing factor - according to Miller et al. (21), anal penetration requires a mean axial force of 2700 g (2640–4240 g), exceeding the approximately 1500 g required for vaginal penetration reported by Karacan (22). However, in our cohort, behavioral data were limited and did not allow confirmation or refutation of these proposed risk factors. Moreover, the small sample size ( $n = 11$ ) precludes any meaningful conclusions, and these findings should be interpreted as exploratory and hypothesis-generating, granting future data collection for clarification.

Beyond behavioral aspects, engineering and materials science principles are central to understanding device failure. From a biomechanical perspective, ED can be conceptualized as collapse or buckling of the penile column under an axial load during penetration (23). Manufacturers report varying axial load resistance thresholds across MPP models. The Promedon Tube Malleable Implant (Promedon®, Cordoba, Argentina) is designed to withstand axial loads exceeding 1,500 grams without bending (19), whereas the Tactra™ (Boston Scientific Corporation, Marlborough, MA) was engineered to provide a column strength from a pair of cylinders of 2,767 grams (24). Al Ansari et al. (25) utilized a digital inflection rigidometer (DIR) to assess the penile rigidity finding a mean DIR of 857g for a pair of cylinders

placed in patients of the Genesis® MPP (Coloplast Corp, Minneapolis, MN). These thresholds generally permit penetrative intercourse under physiologic conditions, but do not fully account for long-term mechanical fatigue.

Fracture susceptibility, however, depends not only on peak axial resistance, but also on geometry and material fatigue. Differences in device girth may alter resistance to bending forces, analogous to greater fragility of thinner rods compared to thicker ones of the same material (26; 27;28). In our series, no fractures were observed in 12 or 13mm rods; however, this finding should be interpreted with caution, as these devices had shorter follow-up, frequently below the median time to fracture in our cohort. While increased mechanical strength with larger diameters may be hypothesized, our design does not allow a robust comparison, as patients without fracture were not systematically analyzed.

More importantly, repetitive bending during concealment, voiding, or repositioning, exerts chronic stress particularly at the proximal shaft. In our cohort 77.1% occurred in this site, supporting cumulative fatigue as the predominant failure mechanism rather than acute overload. While the role of rear tip extenders (RTEs) in reducing axial rigidity and contributing to mechanical stress has been described in inflatable prostheses, these findings cannot be directly extrapolated to malleable devices. Unlike inflatable prostheses, malleable implants have a more homogeneous structure, and the difference in mechanical properties between the prosthesis and the extender is less pronounced. Taken together, these findings support a conceptual interpretation of failure mechanisms integrating cyclic fatigue, implant geometry, potential behavioral and manipulation (bending frequently) factors, grounded in both our data and established biomechanical principles. Future prospective studies with standardized reporting are warranted to further refine and validate these models.

Although a formal classification of fracture types was not feasible in our cohort due to limitations in intra-operative documentation, our findings support a conceptual model in which cyclic fatigue, implant geometry, and mechanical stress distribution contribute to device failure. The predominance of proximal fractures suggests a fatigue-related mechanism rather than acute overload.

These findings should be interpreted in the context of important methodological limitations. Imaging studies were non-standardized, performed at physician discretion, and not reviewed in a blinded fashion, limiting direct comparison of diagnostic performance across modalities. Proximal silicone fractures outside the metal axis were radiolucent on X-rays (Figure-2A). The low diagnostic yield of MRI observed in our cohort is unlikely to be explained by artifact-related blooming, as this effect is not prominent with the materials used in contemporary MPPs. Instead, the limited accuracy of MRI in this setting may reflect intrinsic methodological challenges, including difficulty in clearly delineating prosthesis discontinuity due to component overlap and subtle structural changes. In addition, limited familiarity of radiologists with prosthesis-specific failure patterns may further contribute to under-recognition. MRI interpretation was frequently limited by component overlaps without clear fracture visualization (Figure-2B).

Currently, no comparative studies systematically evaluated axial load tolerance and fatigue resistance across commercially available MPP brands (15). However, these results should be interpreted in the light of the fact that our cohort included a single device type (Promedon Tube Malleable Implant), characterized by a twisted silver wire core. Therefore, our findings may not be fully generalized to other MPP architectures such as Nitinol-based or helical-core designs, which may exhibit different mechanical properties and fatigue resistance profiles. These differences in internal architecture may influence long-term durability and fracturing patterns.

This study has limitations inherent to its retrospective, single-center design and absence of standardized long-term follow-up. As only patients undergoing revision surgery with confirmed fractures were included, the study is subject to selection bias and does not allow estimation of true incidence and prevalence. Routine annual follow-up is uncommon in prosthetic urology, limiting the ability to identify modifiable risk factors. Additionally, results primarily reflect experience with a single MPP model.

Nevertheless, this study represents, to our knowledge, the largest reported series of surgically confirmed MPP fractures, providing a comprehensive analysis



of clinical presentation, diagnostic performance, and intra-operative findings over 17 years of experience and may provide guidance for future more resilient implants.

## CONCLUSIONS

Malleable penile prosthesis fractures are an underreported yet clinically relevant complication and represented the leading indication for revision surgery in our cohort. Diagnosis relies primarily on careful physical examination, which outperformed conventional imaging modalities and may be sufficient to justify surgical revision in selected cases.

Fractures were frequently bilateral and predominantly located in the proximal segment, supporting cumulative material fatigue as the primary failure mechanism. Clinicians should maintain a high index of suspicion in patients presenting with penile instability or impaired penetrative intercourse and counsel patients accordingly.

Standardized and transparent reporting of mechanical performance, including axial load tolerance and resistance to cyclic fatigue, is needed to better inform clinical decision-making and device selection. Prospective, multicenter studies comparing different malleable penile prosthesis models are warranted to define modifiable risk factors and improve long-term outcomes and guide future development of more resilient models.

## CONFLICT OF INTEREST

Bruno C. G. Nascimento serves as a proctor for Boston Scientific.

All other authors declare no conflicts of interest

## ACKNOWLEDGEMENTS

Jorge Hallak and Bruno C. G. Nascimento contributed equally as senior authors.

## ETHICAL APPROVAL

The study was approved by the Institutional Review Board (CAAE-26509).

Written informed consent was obtained from all participants.

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# Focal Therapy for Prostate Cancer: A Treatment Option Reserved for the Ideal Candidate?

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## ABSTRACT

**Objectives:** To evaluate outcomes of FT (HIFU or cryotherapy) in prostate cancer (PCa) patients who do not meet the ideal focal therapy candidate profile, assessing whether expanding selection criteria beyond traditional parameters is safe. **Materials and Methods:** A retrospective analysis was performed on 282 patients treated with FT for ISUP 1 and 2 PCa at a single European center (2009–2020). Patients were categorized into three groups: G1 (ideal candidates: single lesion  $\leq 12$ mm, favorable biopsy features), G2 (ISUP 1 with minor deviations), and G3 (ISUP 2 with multiple lesions, larger tumor size, or positive cores outside the target zone). A secondary exploratory analysis compared ISUP 2 patients fully meeting criteria versus those with one deviating feature. Multivariable regression with propensity score matching was applied. **Results:** Overall recurrence occurred in 187 patients (66%): 77% in G1, 60% in G2, and 77% in G3. No significant differences were observed between G1 and G3 regarding in-field recurrence-free survival, clinically significant in-field recurrence-free survival, or out-field recurrence-free survival (all  $p > 0.05$ ). In the secondary analysis, lesion size  $\geq 12$ mm was the only feature associated with worse in-field recurrence-free survival ( $p = 0.04$ ) and clinically significant in-field recurrence-free survival ( $p = 0.001$ ). Multivariate Cox regression confirmed lesion size as an independent predictor (HR: 1.21; 95% CI: 1.05–1.40;  $p = 0.01$ ). **Conclusions:** Expanding FT selection criteria to include selected ISUP 2 patients with features outside traditional parameters appears safe. These preliminary findings highlight the need for multicenter studies to validate these results.

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## INTRODUCTION

Prostate cancer [PCa] is a prevalent disease characterized by significant clinical, morphological, and molecular heterogeneity (1). Consequently, treatment approaches also vary (2). Radical treatments for localized PCa, such as radical prostatectomy and radiotherapy, can adversely affect quality of life (3). Focal therapy (FT) has emerged as a promising alternative (4), demonstrating safety and potential benefits regarding genitourinary function and oncological outcomes. However, more extensive follow-up studies are required to move from hypothesis and preliminary findings to robust evidence (5, 6).

Advances in imaging and targeted biopsy have improved the ability to differentiate intermediate- and high-grade cancers from indolent ones. If accurately targeted, according to consensus meetings (5, 7-10), FT could optimize treatment for localized, small-volume cancers in intermediate-risk patients and selected high-risk individuals. Conversely, indolent cancer areas, such as Grade Group (GG) 1 lesions, can be monitored via active surveillance, particularly in patients with GG2 disease where only GG1 areas are targeted for active treatment. One of the latest consensus on the field suggests that in cases of clinically localized cancers with favorable single lesions, FT could be appropriate for men with ISUP 2 PCa, PSA <15 ng/mL, a single visible lesion ≤ 12 mm, with a maximum of one positive ISUP 1 core outside the target lesion (8-10).

Despite potential, recent literature displays significant variability in selection criteria, treatment methods, relapse definitions, follow-up protocols, and outcome reporting. While some studies advocate FT for higher-grade diseases without compromising metastasis or cancer-specific survival (5), optimal PSA levels and lesion size specifications remain debated. Consequently, current EAU and AUA guidelines advise caution, recommending FT within clinical trials or prospective registries (11, 12).

Identifying ideal candidates for FT thus remains a pivotal topic of discussion. We hypothesized that selected patients not strictly fulfilling the traditional FT inclusion criteria could still achieve oncological outcomes similar to those of ideal candidates. This study therefore aimed to evaluate selection criteria and the outcomes of patients not

meeting the ideal FT profile, to determine whether expanding the criteria is both safe and effective.

## MATERIAL AND METHODS

### Study population and design

This retrospective observational study relied on a prospectively maintained institutional database from a single European tertiary referral center, covering patients treated for low- to intermediate-risk PCa with FT between 2009 and 2020. According to local institutional policies for retrospective anonymized database analyses, formal ethics committee approval and informed consent were not required. Inclusion criteria included patients over 18, treatment-naïve, with mpMRI and subsequent biopsy confirming low- to intermediate-risk localized PCa (following the risk stratification of the "Guidelines on Prostate Cancer" proposed by the EAU and associated entities at the time of data analysis and patient follow-up, in 2023 (2)) having primary FT (Cryotherapy, Ablatherm® HIFU, Focal One® HIFU). Considering these criteria, out of 356 patients treated with FT, 282 were analyzed, and categorized into three groups. Both patients with MRI-visible and MRI non-visible lesions were included, as long as clinically localized PCa had been confirmed at targeted and/or systematic biopsy. The three groups were: Group 1 = perfect candidates (30 patients) following all the selection criteria recommended by the FT community, especially the International Delphi Consensus Project (2, 5, 8-10) (ISUP 2, PSA <15ng/mL, single visible lesions ≤12 mm at pre-treatment MRI, max 1 positive core ISUP 1 outside target lesion at pre-treatment biopsy); Group 2 (low-risk ISUP 1 patients, 181 patients); Group 3 (intermediate-risk not included in Group 1, 71 patients). Furthermore, a secondary exploratory analysis only considering ISUP 2 was conducted, comparing Group 1 to patients who were not ideal candidates for only one single criterion. These were divided into 3 groups: Sub-group 2 = with a single pre-treatment MRI lesion >12mm (5 patients); Sub-group 3 = with more than 1 lesion at pre-treatment MRI (9 patients); Sub-group 4 = with more than 1 positive core outside target lesion at pre-treatment biopsy (28 patients). Study design is summarized in Supplementary Table-1.

### Follow-up protocol

Because of the long inclusion period and the lack of dedicated guideline-based follow-up protocols for focal therapy during the years considered, follow-up was not fully standardized and changed over time according to institutional practice and to emerging evidence. In general, however, patients were followed with PSA every 3–6 months in the first 2 years and at least once a year afterwards. mpMRI was usually performed within the first year after treatment, and then repeated based on clinical suspicion. Follow-up biopsies were either protocol-driven (within 12–18 months after FT) or for-cause, triggered by a PSA rise, suspicious mpMRI findings or clinical concern. Retreatment or salvage therapy was offered in case of clinically significant recurrence, multifocal disease progression, radiological progression, or based on patient preference (Supplementary Figures 1, 2 and 3).

### Treatment protocol

Treatment was planned based on mpMRI findings together with targeted and systematic biopsy results. FT was delivered either as hemiablation or as quadrant ablation, depending on lesion location, size and laterality. Hemiablation was usually chosen for larger unilateral lesions, and quadrant ablation for smaller focal lesions. Whenever technically possible, a safety margin around the index lesion was included.

### Variables and outcomes definition

Data collected included patient demographics, baseline PCa features, and details on FT type and extent. Follow-up data included PSA values, PSA nadir, % of PSA reduction (defined as the ratio between PSA nadir and pre-treatment PSA), MRI and biopsies results. Recurrence was defined as any positive biopsy after FT. Infield recurrence referred to recurrence within the treated area, whereas outfield recurrence referred to recurrence outside the treated area. Clinically significant recurrence was defined as ISUP  $\geq 2$  disease. Local progression was defined as radiological and/or histological progression within the treated field.

The primary outcome was recurrence-free survival (time between FT and any positive biopsy during

follow-up), comparing Group 1 to Group 2 and Group 3. Recurrence-free survival was further analyzed in pre-specified subgroup analyses according to: (i) location of recurrence (infield vs outfield), and (ii) ISUP grade at recurrence (ISUP 1 only vs ISUP  $\geq 2$ , the latter defined as clinically significant recurrence). Secondary outcomes included progression-free survival (time between FT and local or distant disease progression, death, or end of follow-up), second treatment-free survival (time between FT and salvage/second treatment), and overall survival (time between FT and death or end of follow-up).

An exploratory secondary analysis compared Group 1 to Sub-group 2 (single pre-treatment MRI lesion  $>12$  mm), Sub-group 3 (more than 1 lesion at pre-treatment MRI), and Sub-group 4 (more than 1 positive core outside the target lesion at pre-treatment biopsy), in terms of recurrence-free survival, infield recurrence-free survival, clinically significant infield recurrence-free survival, outfield recurrence-free survival, second treatment-free survival, progression-free survival, and overall survival.

### Statistical analysis

Statistical methodologies followed validated guidelines (13). Comparisons involved chi-square tests, Fisher's exact tests, and Kruskal-Wallis tests as applicable. Multivariable regression analysis combined with propensity score matching minimized confounding among groups and Kaplan-Meier (KM) survival analysis was conducted. Covariates included: pre-treatment PSA (as a continuous variable), PSA<sub>d</sub> (as a continuous variable), MRI lesion dimension (as a continuous variable), presence of a single visible lesion, and presence of positive biopsies outside the target lesion (more than 1 positive core ISUP 1 outside target lesion). Furthermore, multivariate Cox regression model, between intermediate-risk patients, was fitted to predict how pre-treatment PSA, PSA<sub>d</sub>, MRI lesion dimension, presence of a single visible lesion and presence of positive biopsies outside target lesion might influence survival analysis. The R software environment for statistical computing and graphics (version 3.4.3) was used for all the statistical analyses. All tests were two-sided, and the significance level was set at  $p < 0.05$ .



## RESULTS

### Baseline and Treatment Features of the Study Cohort

Baseline and treatment features of the study cohort, stratified by group, are summarized in Table-1. No significant differences were noted in pre-treatment PSA, prostate volume, and PSAd between groups. Patients in group 1 exhibited worse clinical staging compared to group 2, with a higher cT2 rate (33% vs. 17%,  $p=0.003$ ). No differences were found between groups 1 and 3 ( $p=0.7$ ). Group 1 was characterized by having only one visible lesion at MRI, whereas 6% ( $n=11$ ) of group 2 and 32% ( $n=23$ ) of group 3 had more than one lesion ( $p=0.001$ ). Group 1 patients had a higher occurrence of PI-RADS 4 and 5 lesions compared to group 2 (77% vs. 29%,  $p<0.001$ ). Lesion dimensions at pre-treatment MRI were similar between groups 1 and 2 (10 mm, IQR: 8-12,  $p=0.3$ ) but lower than group 3 (12 mm, IQR: 10-14,  $p<0.001$ ). Group 3 patients had a greater median number of positive cores [3 (IQR: 2-4) vs. 2 (IQR: 1-3),  $p=0.002$ ] and a longer length [14mm (7-21) vs. 7mm (IQR:3-10),  $p=0.03$ ]. No differences in Gleason 4 percentages were noted between groups 1 and 3 ( $p=0.6$ ). Cancer adjacent to the target zone was found in 27% ( $n=8$ ) of group 1 and 21% ( $n=38$ ) of group 2 (all ISUP 1), while systematic adjacent biopsy was positive in 75% ( $n=53$ ) of group 3, with a rate of ISUP 2 at 65% ( $n=46$ ,  $p<0.001$ ). Systematic positive biopsies away from the target zone were 0% in group 1, 3% ( $n=5$ ) in group 2, and 24% ( $n=17$ ) in group 3, with an ISUP 2 rate of 14% ( $n=10$ ) in group 3 ( $p=0.01$ ). Focal One® HIFU was performed in most patients in groups 1 (60%,  $n=18$ ) and 3 (56%,  $n=40$ ), while the majority in group 2 underwent Ablatherm® HIFU (45%,  $n=81$ ,  $p<0.001$ ). Cryotherapy rates were 20% ( $n=6$ ) in group 1, 39% ( $n=71$ ) in group 2, and 24% ( $n=17$ ) in group 3. Quadrant ablation rates were lower in group 1 (43%,  $n=13$ ) compared to groups 2 (72%,  $n=130$ ) and 3 (69%,  $n=49$ ). Group 1 predominantly underwent hemiablation (57%,  $n=17$ ) compared to group 2 (28%,  $n=51$ ) and group 3 (31%,  $n=22$ ,  $p=0.01$  and  $p=0.02$ , respectively).

### Follow-up and survival analysis

Follow-up features of the study cohort after FT for PCa, stratified by group, are summarized in Table-2.

Median follow-up for the whole cohort was 75 months (IQR 54–105), calculated from FT to recurrence, death or last follow-up.

No statistical differences were found in terms of PSA nadir and %PSA reduction between groups (Table-2, Supplementary Figure-4). Median PSA nadir was 2.2 ng/mL (IQR 1.4–3.8) in G1, 2.7 ng/mL (IQR 1.4–4.4) in G2, and 2.2 ng/mL (IQR 1.3–3.8) in G3, with a median %PSA reduction of 63% (IQR 37–77), 60% (IQR 39–78), and 64% (IQR 51–82), respectively (all  $p>0.05$ ). No statistical difference was detected for local recurrence rate in any prostate site (infield vs outfield) nor ISUP grade (ISUP 1 vs ISUP  $\geq 2$ ). Local recurrence rates ranged from 60% to 77% (G1: 77% [23/30]; G2: 60% [109/181]; G3: 77% [55/71]); infield recurrence rate ranged from 51% to 69%; clinically significant infield recurrence rate ranged from 26% to 55%; clinically significant outfield recurrence ranged from 23% to 31%. Pathological upgrading at recurrence was experienced by 17% ( $n=5$ ) in G1, 33% ( $n=60$ ) in G2, and 24% ( $n=17$ ) in G3 compared to baseline ISUP grade.

Recurrence-free survival was higher for patients in group 2 compared to those in group 1. KM estimates indicated a median time to any recurrence of 68 months (95% confidence interval [CI]: 52–90) for group 2 vs. 18 months (95%CI: 13–56) for group 1 ( $p<0.001$ ). Infield recurrence-free survival was also significantly higher for group 2 compared to group 1 ( $p=0.006$ ), as well as infield clinically significant free survival ( $p=0.02$ ). No differences were observed in terms of outfield recurrence-free survival between the two groups ( $p=0.2$ ). Additionally, no specific differences were noted in recurrence rates, infield recurrence-free survival, infield clinically significant free survival, and outfield free survival between groups 1 and 3, all  $p>0.05$ , Figure-1.

Of the 187 patients presenting with recurrence after FT, 86% ( $n=160$ ) required additional treatment, while 14% ( $n=27$ ) underwent active surveillance due to low-risk disease. Active treatments listed in Table-2 included repeat FT using the same or different energy sources; salvage RP (sRP); salvage radiotherapy (sRT); androgen deprivation therapy (ADT); or multimodal treatment. Second treatment-free survival was higher for patients in group 2 compared to group 1, with KM

**Table 1 - Baseline, treatment, and follow-up features of 282 patients treated with focal therapy for prostate cancer, stratified by group.**

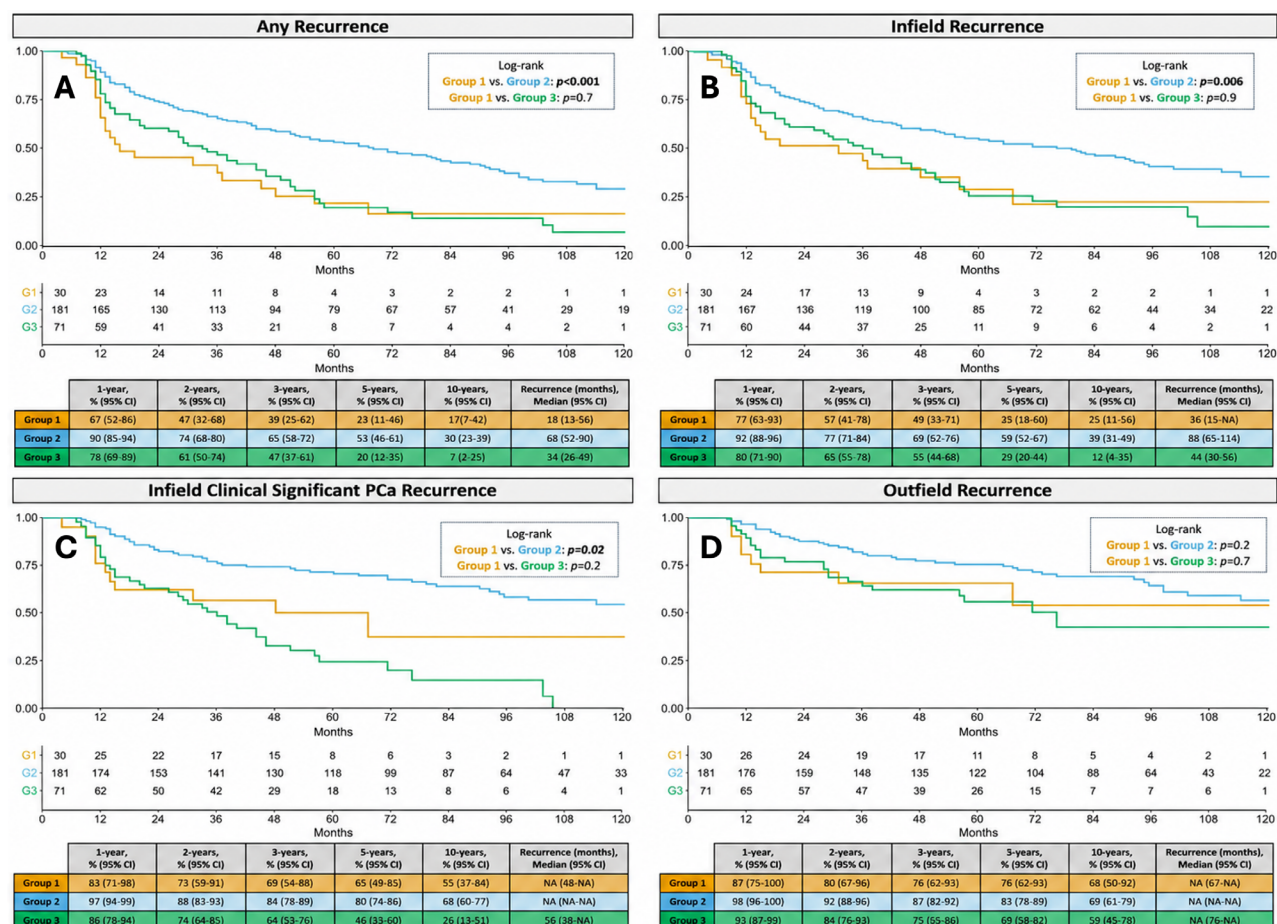
| Variables                                                       | Group 1 (30)  | Group 2 (181) | Group 3 (71)  | p G1/G2 (p G1/G3)      |
|-----------------------------------------------------------------|---------------|---------------|---------------|------------------------|
| <b>Baseline characteristics</b>                                 |               |               |               |                        |
| Age (years), Median (IQR)                                       | 68 (62-71)    | 67 (62-72)    | 69 (62-74)    | 0.6 (0.9)              |
| pre-treatment PSA (ng/mL), Median (IQR)                         | 6.1 (4.6-8.9) | 6.8 (5.7-9.5) | 5.7 (5.7-5.7) | 0.1 (0.05)             |
| Prostate volume (mL), Median (IQR)                              | 42 (35-48)    | 40 (34-50)    | 40 (34-49)    | 0.7 (0.7)              |
| PSAd (ng/mL <sup>2</sup> ), Median (IQR)                        | 0.2 (0.1-0.2) | 0.2 (0.1-0.2) | 0.2 (0.1-0.3) | 0.2 (0.07)             |
| <b>cT, n (%)</b>                                                |               |               |               | <b>0.003 (0.7)</b>     |
| 1                                                               | 20 (67)       | 151 (83)      | 53 (75)       |                        |
| 2                                                               | 10 (33)       | 30 (17)       | 18 (26)       |                        |
| <b>pre-treatment MRI single lesion, n (%)</b>                   |               |               |               | <b>0.3 (0.001)</b>     |
| No                                                              | 0 (0)         | 11 (6)        | 23 (32)       |                        |
| Yes                                                             | 30 (100)      | 170 (94)      | 48 (68)       |                        |
| <b>Pre-treatment MRI PIRADS, n (%)</b>                          |               |               |               | <b>&lt;0.001 (0.2)</b> |
| 2                                                               | 1 (3)         | 82 (45)       | 0 (0)         |                        |
| 3                                                               | 6 (20)        | 46 (25)       | 15 (21)       |                        |
| 4                                                               | 20 (67)       | 42 (23)       | 40 (56)       |                        |
| 5                                                               | 3 (10)        | 11 (6)        | 16 (23)       |                        |
| MRI lesion dimension (mm), Median (IQR)                         | 10 (8-12)     | 10 (8-12)     | 12 (10-14)    | 0.3 (<0.001)           |
| <b>Pre-treatment biopsy ISUP, n (%)</b>                         |               |               |               | <b>&lt;0.001 (0.2)</b> |
| 1                                                               | 0 (0)         | 181 (100)     | 0 (0)         |                        |
| 2                                                               | 30 (100)      | 0 (0)         | 71 (100)      |                        |
| <b>Pre-treatment biopsy ISUP systematic adjacent, n (%)</b>     |               |               |               | <b>0.6 (&lt;0.001)</b> |
| 0                                                               | 22 (73)       | 143 (79)      | 18 (25)       |                        |
| 1                                                               | 8 (27)        | 38 (21)       | 7 (10)        |                        |
| 2                                                               | 0 (0)         | 0 (0)         | 46 (65)       |                        |
| <b>Pre-treatment biopsy ISUP systematic non-adjacent, n (%)</b> |               |               |               | <b>0.8 (0.01)</b>      |
| 0                                                               | 30 (100)      | 176 (97)      | 54 (76)       |                        |
| 1                                                               | 0 (0)         | 5 (3)         | 7 (10)        |                        |
| 2                                                               | 0 (0)         | 0 (0)         | 10 (14)       |                        |

| Variables                                               | Group 1 (30)  | Group 2 (181) | Group 3 (71)  | p G1/G2 (p G1/G3)      |
|---------------------------------------------------------|---------------|---------------|---------------|------------------------|
| <b>Treatment</b>                                        |               |               |               |                        |
| <b>Treatment modality, n (%)</b>                        |               |               |               | <b>&lt;0.001 (0.9)</b> |
| Cryotherapy                                             | 6 (20)        | 71 (39)       | 17 (24)       |                        |
| Ablatherm® HIFU                                         | 6 (20)        | 81 (45)       | 14 (20)       |                        |
| Focal One® HIFU                                         | 18 (60)       | 29 (16)       | 40 (56)       |                        |
| <b>Year of treatment, n (%)</b>                         |               |               |               | <b>&lt;0.001 (0.8)</b> |
| 2009-2011                                               | 2 (6)         | 54 (30)       | 2 (2)         |                        |
| 2012-2014                                               | 8 (27)        | 79 (44)       | 22 (32)       |                        |
| ≥2015                                                   | 20 (66)       | 48 (27)       | 47 (67)       |                        |
| <b>Treatment extension, n (%)</b>                       |               |               |               | <b>0.01 (0.02)</b>     |
| Quadrant ablation                                       | 13 (43)       | 130 (72)      | 49 (69)       |                        |
| Hemiablation                                            | 17 (57)       | 51 (28)       | 22 (31)       |                        |
| <b>Follow-up and outcomes</b>                           |               |               |               |                        |
| PSA nadir (ng/mL), Median (IQR)                         | 2.2 (1.4-3.8) | 2.7 (1.4-4.4) | 2.2 (1.3-3.8) | 0.5 (0.9)              |
| %PSA reduction, Median (IQR)                            | 63 (37-77)    | 60 (39-78)    | 64 (51-82)    | 0.9 (0.4)              |
| <b>Recurrence, n (%)</b>                                |               |               |               | <b>0.1 (0.9)</b>       |
| No                                                      | 7 (23)        | 72 (40)       | 16 (23)       |                        |
| Yes                                                     | 23 (77)       | 109 (60)      | 55 (77)       |                        |
| <b>Infield recurrence, n (%)</b>                        |               |               |               | <b>0.3 (0.7)</b>       |
| No                                                      | 11 (37)       | 88 (49)       | 22 (31)       |                        |
| Yes                                                     | 19 (63)       | 93 (51)       | 49 (69)       |                        |
| <b>Clinically significant infield recurrence, n (%)</b> |               |               |               | <b>0.3 (0.1)</b>       |
| No                                                      | 19 (63)       | 134 (74)      | 32 (45)       |                        |
| Yes                                                     | 11 (37)       | 47 (26)       | 39 (55)       |                        |
| <b>Outfield recurrence, n (%)</b>                       |               |               |               | <b>0.9 (0.8)</b>       |
| No                                                      | 22 (73)       | 139 (77)      | 49 (69)       |                        |
| Yes                                                     | 8 (27)        | 42 (23)       | 22 (31)       |                        |
| <b>Recurrence ISUP, n (%)</b>                           |               |               |               | <b>0.5 (0.6)</b>       |
| Negative                                                | 7 (23)        | 73 (40)       | 16 (23)       |                        |
| 1                                                       | 8 (27)        | 48 (27)       | 10 (14)       |                        |
| 2                                                       | 10 (33)       | 41 (23)       | 28 (39)       |                        |
| 3                                                       | 4 (13)        | 15 (8)        | 11 (16)       |                        |
| 4                                                       | 1 (3)         | 3 (2)         | 6 (9)         |                        |
| 5                                                       | 0 (0)         | 1 (1)         | 0 (0)         |                        |
| <b>Pathological upgrading, n (%)</b>                    |               |               |               | <b>0.1 (0.6)</b>       |
| No                                                      | 25 (83)       | 121 (67)      | 54 (76)       |                        |
| Yes                                                     | 5 (17)        | 60 (33)       | 17 (24)       |                        |

| Variables                           | Group 1 (30) | Group 2 (181) | Group 3 (71) | p G1/G2 (p G1/G3) |
|-------------------------------------|--------------|---------------|--------------|-------------------|
| <b>Second treatment, n (%)</b>      |              |               |              | <b>0.6 (0.8)</b>  |
| No                                  | 12 (40)      | 85 (47)       | 25 (35)      |                   |
| Yes                                 | 18 (60)      | 96 (53)       | 46 (65)      |                   |
| <b>Second treatment type, n (%)</b> |              |               |              | <b>0.8 (0.3)</b>  |
| None                                | 12 (40)      | 80 (44)       | 24 (34)      |                   |
| HIFU                                | 3 (10)       | 15 (8)        | 6 (9)        |                   |
| Cryotherapy                         | 0 (0)        | 8 (4)         | 2 (3)        |                   |
| sRP                                 | 6 (20)       | 15 (8)        | 5 (7)        |                   |
| EBRT                                | 3 (10)       | 25 (14)       | 18 (25)      |                   |
| Brachytherapy                       | 2 (7)        | 12 (7)        | 7 (10)       |                   |
| ADT                                 | 3 (10)       | 13 (7)        | 3 (4)        |                   |
| sRP + ADT                           | 0 (0)        | 1 (1)         | 0 (0)        |                   |
| EBRT + sRP                          | 0 (0)        | 3 (2)         | 0 (0)        |                   |
| EBRT + ADT                          | 1 (3)        | 7 (4)         | 6 (9)        |                   |
| Brachytherapy + ADT                 | 0 (0)        | 1 (1)         | 0 (0)        |                   |
| sRP + ADT + EBRT                    | 0 (0)        | 1 (1)         | 0 (0)        |                   |
| <b>Progression, n (%)</b>           |              |               |              | <b>0.8 (1)</b>    |
| No                                  | 27 (90)      | 169 (93)      | 65 (92)      |                   |
| Yes                                 | 3 (10)       | 12 (7)        | 6 (9)        |                   |
| <b>Progression site, n (%)</b>      |              |               |              | <b>0.1 (0.1)</b>  |
| Bone                                | 1 (25)       | 3 (23)        | 5 (71)       |                   |
| Liver                               | 1 (25)       | 0 (0)         | 0 (0)        |                   |
| Pelvic                              | 1 (25)       | 6 (46)        | 1 (14)       |                   |
| Retroperitoneal                     | 1 (25)       | 4 (31)        | 1 (14)       |                   |
| <b>Death, n (%)</b>                 |              |               |              | <b>0.9 (0.9)</b>  |
| No                                  | 30 (100)     | 178 (98)      | 69 (97)      |                   |
| Yes                                 | 0 (0)        | 3 (2)         | 2 (3)        |                   |

PSA = prostate-specific antigen; PSAd = PSA density; cT = clinical stage; MRI = magnetic resonance imaging; PIRADS = Prostate Imaging-Reporting and Data System; ISUP = International Society of Urological Pathology grade; HIFU = high-intensity focused ultrasound; sRP = salvage radical prostatectomy; EBRT = external beam radiation therapy; ADT = androgen deprivation therapy. All deaths observed in the cohort were due to causes other than prostate cancer; no cancer-specific deaths were recorded. Additional pre-treatment biopsy variables (number and percentage of positive cores, positive length in mm and percentage of positive mm, and percentage of Gleason pattern 4) used in the baseline profile only are reported in Supplementary Table-2

**Figure 1 - Kaplan-Meier curves assessing any recurrence-free survival, infield recurrence-free survival, infield clinically significant PCa recurrence-free survival and outfield recurrence-free survival (Time 0 was time of first focal treatment for prostate cancer) of 282 patients treated with FT for PCa divided into 3 groups based on baseline PCa features.**



Panel A) any recurrence-free survival; Panel B) infield recurrence-free survival; Panel C) infield clinically significant PCa recurrence-free survival; Panel D) outfield recurrence-free survival.

Group 1 = perfect candidates (30 patients) following all the inclusion criteria recommended by the FT community (2,5,8-10) (ISUP 2, PSA<15ng/mL, single visible lesions  $\leq 12$  mm at pre-treatment MRI, max 1 positive core ISUP 1 outside target lesion at pre-treatment biopsy);

Group 2 = low-risk PCa (ISUP 1) (181 patients);

Group 3 = intermediate-risk PCa not included in Group 1 (71 patients).

estimates showing a median time to second treatment of 87 months (95% CI: 70-101) for group 2 compared to 50 months (95% CI: 35-not reached) for group 1 ( $p = 0.04$ ). No differences were found between groups 1 and 3 ( $p = 0.9$ ), Supplementary Figure-5. 21 patients (7%) experienced oncologic progression, and 5 patients (2%) died (no cancer-specific deaths were observed), although no

statistically significant differences were found regarding progression-free survival and overall survival between the three groups, Supplementary Figure-6.

### Secondary exploratory analysis

In the secondary exploratory analysis, no differences emerged between the perfect candidates



(Group 1) and the almost perfect candidates with more than one lesion at pre-treatment MRI (Sub-group 3), as well as those with more than one positive core outside the target lesion at pre-treatment biopsy (Sub-group 4), in terms of any recurrence-free survival, infield recurrence-free survival, infield clinically significant free survival, and outfield free survival (Figure-2). KM estimates revealed a median time to any recurrence of 18 months (95% CI: 13-56) for Group 1, 13 months (95%CI: 9-not reached) for Sub-group 2, 56 months (95%CI: 28-not reached) for Sub-group 3, and 28 months (95%CI: 14-71) for Sub-group 4 (Figure-2). A statistically significant difference was observed only between Group 1 and Sub-group 2 in terms of infield recurrence-free survival [36 months (95%CI: 15-not reached) vs. 13 months (95%CI: 9-not reached),  $p=0.04$ ] and infield clinically significant free survival [not reached (95%CI: 48-not reached) vs. 13 months (95%CI: 9-not reached),  $p=0.001$ ] (Figure-2).

Multivariate Cox regression analyses indicated that lesion dimension (based on the maximum lesion diameter) independently influenced infield clinically significant recurrence-free survival (hazard ratio [HR]: 1.21; 95% CI: 1.05-1.40;  $p=0.01$ ) (Table-3). The relationship between lesion size and the predicted probability of clinically significant recurrence appeared to be highly linear based on the estimates derived from the Cox model, with other covariates fixed at their mean values. Notably, the predicted probability exceeded 70% for lesions longer than 12 mm (Figure-3). Furthermore, the presence of more than one positive core outside the target lesion at pre-treatment biopsy independently influenced outfield recurrence-free survival (HR: 3.22; 95%CI: 1.18-8.76;  $p=0.02$ ) (Table-3).

## DISCUSSION

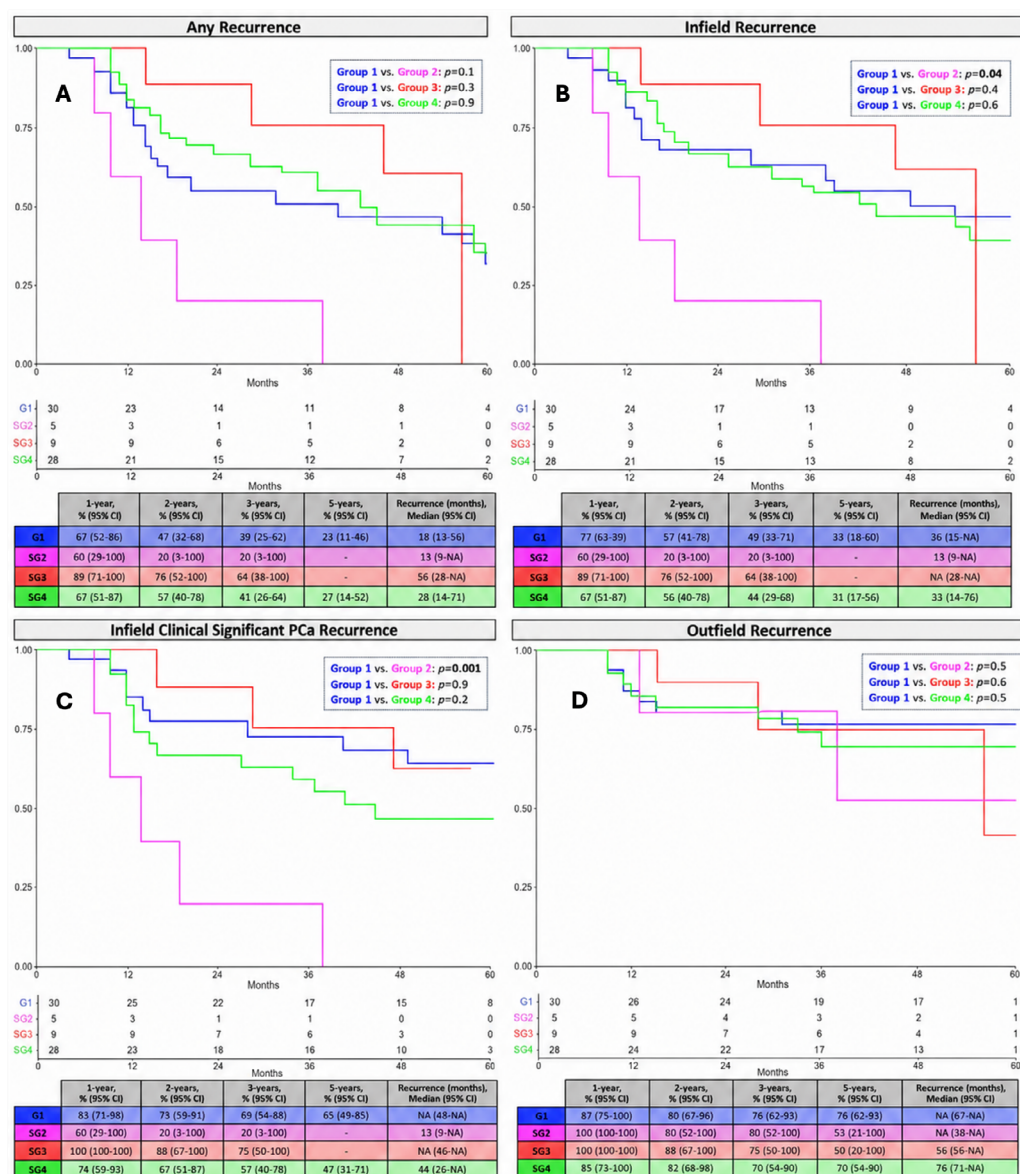
The selection criteria for successful focal therapy (FT) vary significantly across the literature (5, 8-10, 14, 15). Study protocols differ regarding PSA thresholds, local staging (based on digital rectal examination or MRI), ISUP grades, the number of visible lesions on MRI, and volume limits of the index lesion. This study investigates the feasibility and safety of expanding FT selection criteria for localized PCa. The results offer insights into

patient selection, highlighting key determinants that influence treatment outcomes.

Our findings indicate that FT can be safely administered to patients who do not fit the traditional "ideal" candidate profile, typically characterized by strict criteria regarding PSA levels, lesion size, and biopsy results. Notably, no significant differences were found in long-term outcomes such as progression-free survival and overall survival between ideal candidates (Group 1) and intermediate-risk patients who did not meet these criteria (Group 3). This suggests that broader selection criteria could enable more patients to benefit from FT without compromising their prognoses. Additionally, no differences were found between the perfect candidates (Group 1) and the almost perfect candidates with more than 1 lesion at pre-treatment MRI (Sub-group 3) and the almost perfect candidates with more than 1 positive core outside target lesion at pre-treatment biopsy (Sub-group 4) in terms of any recurrence free survival, infield recurrence free survival, infield clinically significant free survival and outfield free survival. However, patients with MRI-detected lesions larger than 12 mm (Sub-group 2) experienced significantly higher rates of infield recurrence compared to ideal candidates, suggesting that lesion size may be an important factor influencing FT success. Of note, Sub-group 2 included only 5 patients, so this result needs further validation in larger series.

The notion that FT could be effective for higher-risk patients aligns with earlier studies. For instance, Guillaumier et al. found that FT could control disease in intermediate- and high-risk patients with careful patient selection (16). Reddy et al. (17) analyzed data from 1,379 patients in the HIFU Evaluation and Assessment of Treatment (HEAT) registry, which included ISUP GG3 PCa. While differences in failure-free survival between ISUP GG2 and GG3 were significant, the study reported 7-year metastasis-free and PCa-specific survival rates exceeding 99%. Moreover, Scheltema et al. (18) noted a median 5-year outcome for primary FT in localized PCa, including a subset of ISUP GG3 patients, finding no significant differences in failure-free survival per ISUP grade, suggesting FT could extend to high-risk PCa with correct patient selection.

**Figure 2 - Kaplan-Meier curves assessing any recurrence-free survival, infield recurrence-free survival, infield clinically significant PCa recurrence-free survival and outfield recurrence-free survival (Time 0 was time of first focal treatment for prostate cancer) of the secondary exploratory analysis population (only considering intermediate-risk PCa).**



Panel A) any recurrence-free survival; Panel B) infield recurrence-free survival; Panel C) infield clinically significant PCa recurrence-free survival; Panel D) outfield recurrence-free survival. In all panels, "Sub-Group 2", "Sub-Group 3", and "Sub-Group 4" replace the previous "Group 2", "Group 3", and "Group 4" labels.

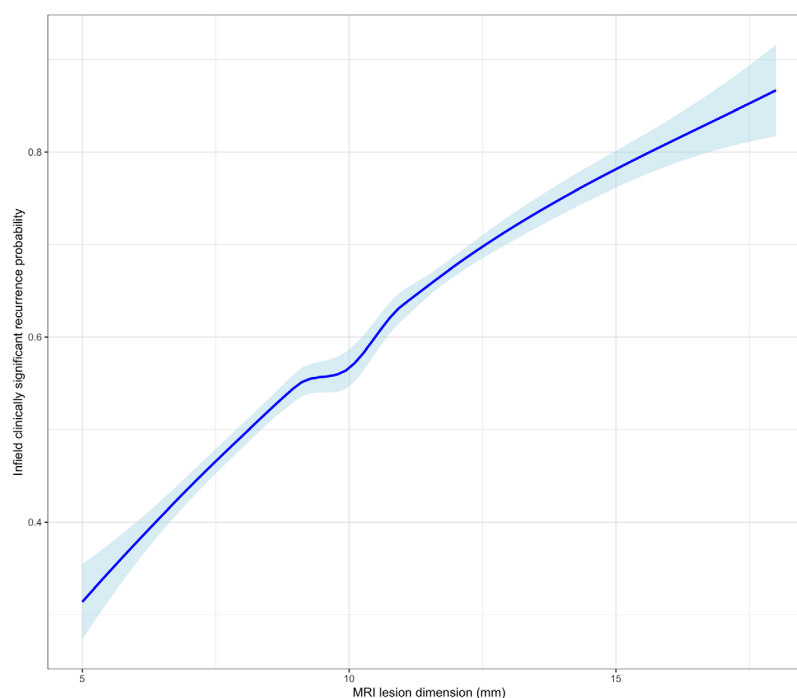
Group 1 = perfect candidates (30 patients) following all the inclusion criteria recommended by the FT community (2,5,8-10) (ISUP 2, PSA<15ng/mL, single visible lesions ≤12 mm at pre-treatment MRI, max 1 positive core ISUP 1 outside target lesion at pre-treatment biopsy);

Sub-group 2 = with a single pre-treatment MRI lesion > 12mm (5 patients);

Sub-group 3 = with more than 1 lesion at pre-treatment MRI (9 patients);

Sub-group 4 = with more than 1 positive core outside target lesion at pre-treatment biopsy (28 patients).

**Figure 3 - Probability of infield clinically significant PCa recurrence according to mpMRI lesion dimension in 72 patients treated with FT for intermediate-risk PCa.**



The curve represents the predicted probability of infield clinically significant prostate cancer recurrence (ISUP  $\geq 2$ ) as a function of maximum mpMRI lesion diameter, derived from the multivariate Cox regression model with all other covariates fixed at their mean values. The shaded area represents the 95% confidence interval. The relationship was highly linear, with predicted probability exceeding 70% for lesions >12 mm.

As noted, larger pre-treatment MRI lesion dimensions correlate with a higher risk of clinically significant infield recurrence, emphasizing the critical importance of accurate imaging and targeted biopsy for identifying suitable FT candidates. Previous studies indicate that lesion characteristics, particularly size and location, are vital in predicting FT success, with larger lesions resulting in higher recurrence rates post-FT (19–21). Additionally, positive biopsies outside the target area at pre-treatment biopsy predict an increased risk of outfield recurrence. It is acknowledged that multiparametric MRI (mpMRI) can underestimate tumor boundaries by up to 10 mm (22), advocating for at least a 10 mm treatment margin to ensure complete ablation (23). Studies, such as the one by Aslim et al. (24), emphasize how intralesional heterogeneity affects mpMRI performance, and advanced imaging techniques could enhance outcomes. Integrating MRI-histology co-registration for

defining three-dimensional treatment margins may also improve precision (23), and the concepts of “umbra” and “penumbra” underline the need for comprehensive perilesional sampling (25). Future advancements in prostate mpMRI aim to improve resolution and target lesion definition, potentially enhancing FT outcomes.

Of note, among emerging imaging techniques, PSMA-PET has attracted considerable interest for its potential both in guiding initial treatment planning and in evaluating response after FT. Although the current body of evidence is preliminary and not yet definitive, the potential applications of PSMA-PET in this setting are encouraging (26). Additional studies are essential to verify these possibilities and to broaden the integration of this promising modality into routine clinical practice.

Meticulous patient selection and precise targeting remain crucial objectives for FT's effectiveness (27, 28). Our research supports that expanding FT criteria to

include more GG2 and selected GG3 diseases can be both safe and beneficial, provided lesion-specific factors are carefully considered.

The recurrence rates seen in our series were somewhat higher than in some published cohorts. This is likely due to a longer follow-up, a more intensive post-treatment biopsy protocol used in the early FT era, and the inclusion of historical cases treated before improvements in mpMRI, targeting and focal therapy technology. The gap between the median time to recurrence and the median time to second treatment in Group 1 (18 vs. 50 months) can also be explained by the fact that some patients with low-risk recurrence were kept on active surveillance before salvage treatment. Our results are in line with other recent IBJU contributions on this topic, including the meta-analysis by Andrade et al. on ablative versus radical treatments (29), the nomogram by Kaneko et al. for predicting csPCa in patients with negative MRI (30), the work of Porcaro et al. on disease progression in intermediate-risk patients (31), the review by Ezequiel et al. on barriers to focal therapy in South America (32), and the series by Mate et al. on focal cryotherapy stratified by Gleason score (33), which also supports the idea that ISUP grade alone is not enough to select FT candidates.

Strengths of this study include a comprehensive analysis of a large, prospectively maintained institutional database. The use of multivariable regression analysis combined with propensity score matching adds statistical rigor to the findings. However, the study also has limitations. The observational nature of the study could introduce biases that are not entirely mitigable by statistical adjustments. Moreover, the study is based on a single high-volume center, which may limit the generalizability of the results to other healthcare settings with different patient populations and resources. An important limitation of the study is the lack of a standardized protocol for follow-up may contribute to variability in treatment outcomes and complicate comparisons across patient populations. This underscores the necessity for future multicenter studies to standardize protocols, thereby enhancing the consistency and reliability of outcomes achieved with FT for PCa. Another limitation of this study is the inclusion of a substantial

proportion of ISUP 1 patients, which poses challenges in interpreting treatment outcomes; while we advocate active surveillance as the primary management strategy for these patients, this study reflects also a period when focal therapy was more commonly applied to low-risk disease. To address this issue, we treated ISUP 1 patients as a separate group in the analysis. Furthermore, the small sample sizes of certain subgroups definitively limit the statistical power and precision of these findings. As these are secondary exploratory analysis, they cannot be used to inform clinical practice but should serve as a basis for further research. Additionally, changes in the PI-RADS version (PIRADS v1 vs. PIRADS v2) during the study period could have influenced the observed differences between groups, potentially affecting the consistency and comparability of the results. Furthermore, historical series dating back to 2009, along with evolving practices in MRI utilization, cancer detection methods (such as the types of biopsies), and advancements in focal treatment technologies, have likely influenced some outcomes, including recurrence rates and the need for additional treatment.

## CONCLUSIONS

Expanding FT selection criteria in localized PCa, including GG2 and selected GG3 disease, appears safe and acceptable, allowing more patients to benefit from FT. However, the importance of lesion size as a critical factor influencing treatment success highlights the need for careful patient selection and tailored follow-up strategies. Future studies are needed to validate these findings in larger, multicenter cohorts to enhance generalizability and prospective clinical trials are warranted to further investigate the long-term outcomes of expanded FT criteria and to establish standardized protocols for monitoring and managing post-FT recurrences.

## COMPLIANCE WITH ETHICAL STANDARDS

This retrospective study was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. According

to local institutional policies for retrospective anonymized database analyses, formal ethics committee approval and informed consent were not required.

## CONFLICT OF INTEREST

None declared.

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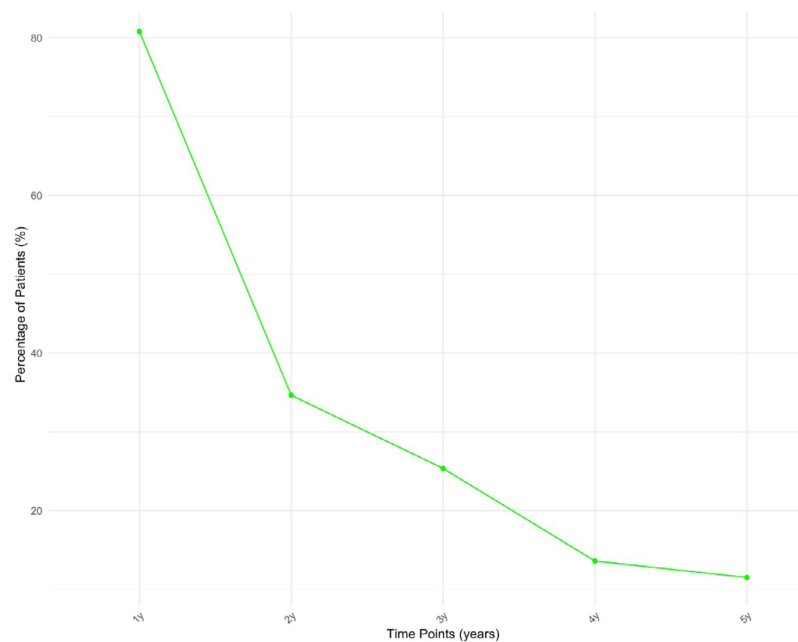
## APPENDIX 1

### Supplementary material

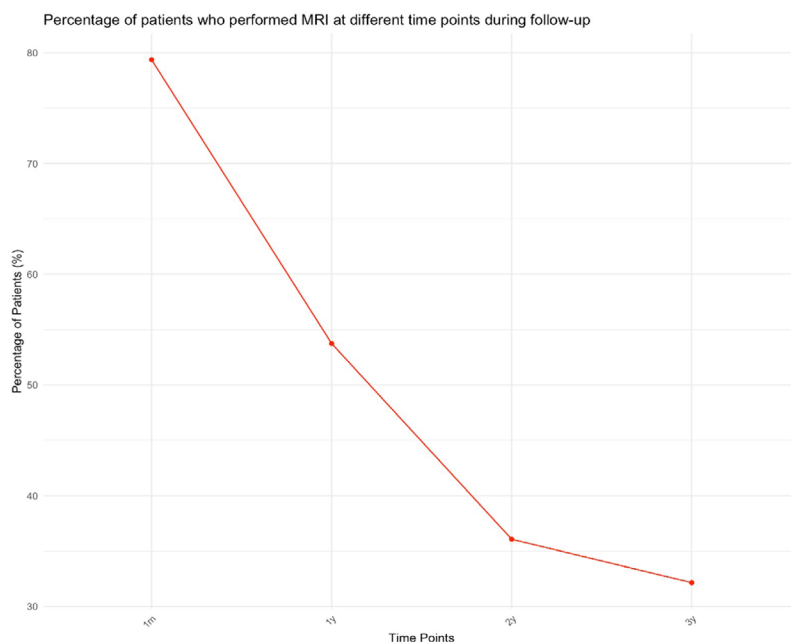
#### Supplementary Table-1

|                      | ISUP = 2 | PSA < 15 ng/mL | Single visible lesion at mpMRI | Lesion ≤ 12 mm | Max 1 positive core ISUP 1 outside target lesion |
|----------------------|----------|----------------|--------------------------------|----------------|--------------------------------------------------|
| Group 1 (30 pts)     | Yes      | Yes            | Yes                            | Yes            | Yes                                              |
| Sub-group 2 (5 pts)  | Yes      | Yes            | Yes                            | No             | Yes                                              |
| Sub-group 3 (9 pts)  | Yes      | Yes            | No                             | Yes            | Yes                                              |
| Sub-group 4 (28 pts) | Yes      | Yes            | Yes                            | Yes            | No                                               |

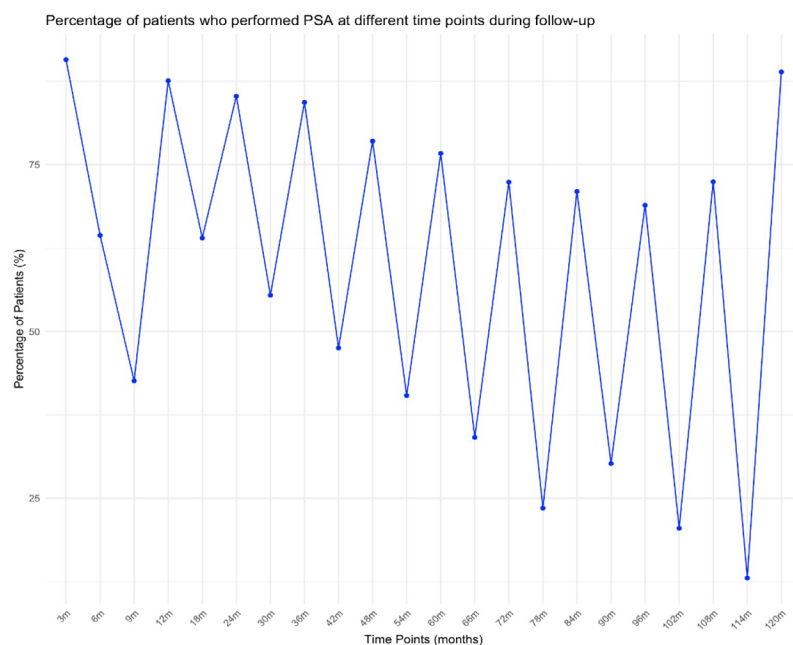
**Supplementary Figure 1 - Percentage of patients who performed biopsy at different time points during follow-up after focal treatments for prostate cancer.**



Percentages calculated based on patients at risk (without recurrence) at each time point

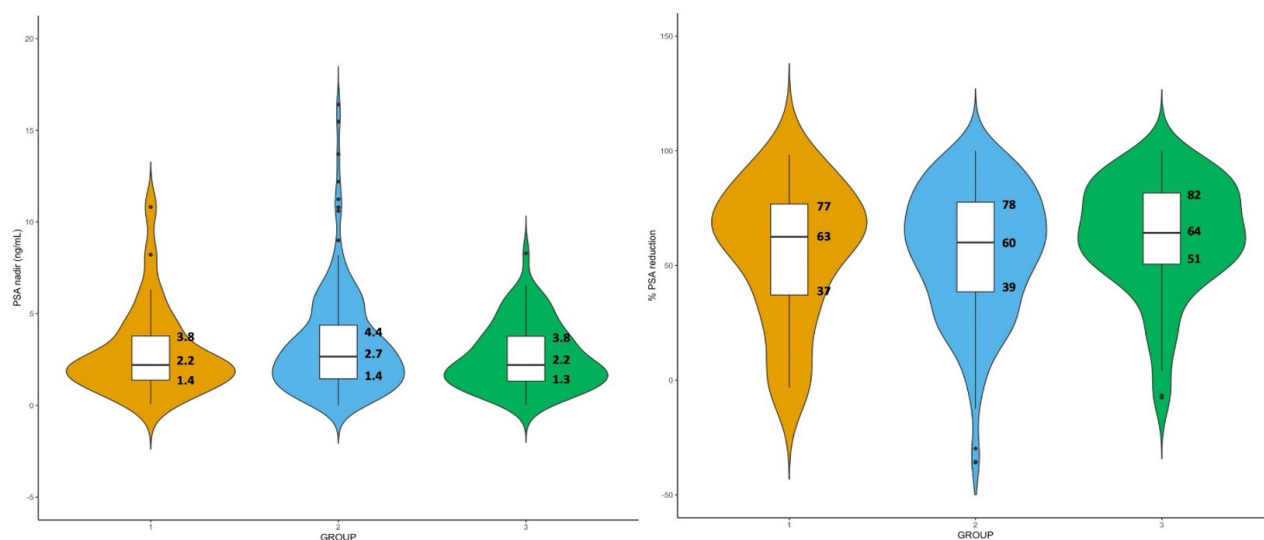
**Supplementary Figure 2 - Percentage of patients who performed multiparametric MRI at different time points during follow-up after focal treatments for prostate cancer.**

Percentages calculated based on patients at risk (without recurrence) at each time point.

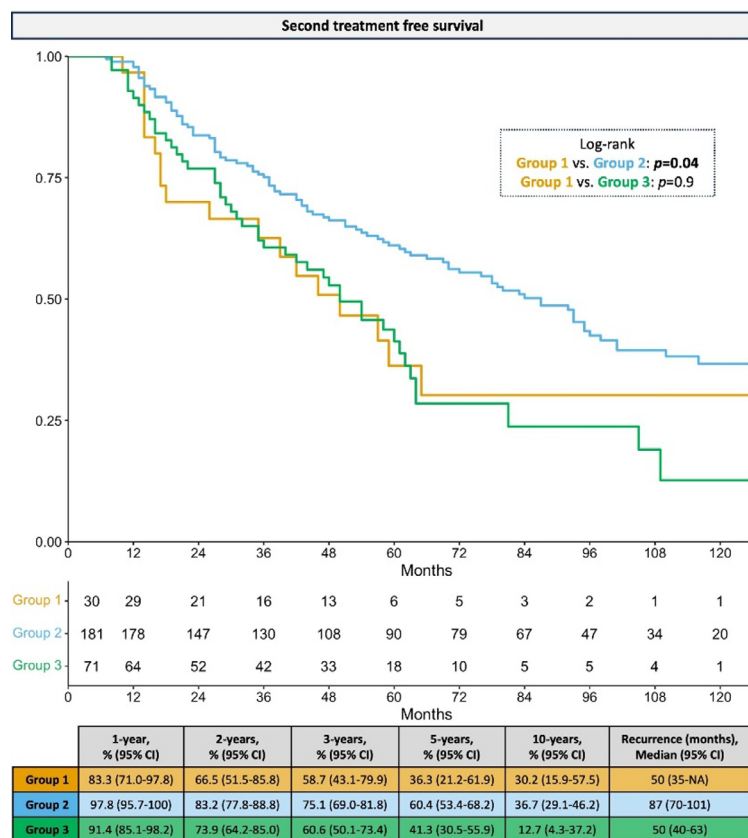
**Supplementary Figure 3 - Percentage of patients who performed PSA at different time points during follow-up after focal treatments for prostate cancer.**

Percentages calculated based on patients at risk (without recurrence) at each time point.

**Supplementary Figure 4 - Violin plot of PSA nadir and % PSA reduction after focal treatment for prostate cancer in 282 patients, stratified by group.**



**Supplementary Figure 5 - Kaplan-Meier curves assessing second treatment-free survival (Time 0 was time of first focal treatment for prostate cancer).**



**Supplementary Figure 6 - Kaplan-Meier curves assessing progression-free survival and all-cause mortality (Time 0 was time of first focal treatment for prostate cancer).**







# SwimCount Harvester™ versus Density Gradient Centrifugation: A Pilot Study exploring Sperm DNA Fragmentation and Motile Sperm Recovery

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## ABSTRACT

**Purpose:** To compare SwimCount Harvester™, a non-centrifugal sperm selection system, with Density Gradient Centrifugation (DGC) in terms of sperm DNA fragmentation (SDF), agreement between analytical methods, and total motile sperm recovery.

**Materials and Methods:** This pilot study evaluated semen samples processed using DGC and SwimCount Harvester™. SDF was assessed in raw and processed samples using the Sperm Chromatin Dispersion (SCD; Halosperm®) assay, analyzed both manually and via computer-assisted sperm analysis (SCA® CASA). Agreement between manual and CASA classification (>20% threshold) was evaluated using Cohen's kappa with bootstrap confidence intervals (10,000 resamples). Total motile sperm count (TMSC) was compared between DGC and Harvester (n=36), and effect size was calculated using Cohen's d.

**Results:** Both DGC and Harvester significantly reduced SDF compared with raw semen ( $p < 0.001$  for all comparisons), with no significant difference between techniques (CASA  $p = 0.219$ ; manual  $p = 0.341$ ). Agreement between manual and CASA assessment improved following processing, reaching perfect concordance after Harvester ( $\kappa = 1.00$ ; bootstrap 95% CI 0.54–1.00). Harvester yielded significantly higher TMSC compared with DGC ( $p = 0.001$ ), with a large effect size (Cohen's  $d = 0.81$ ).

**Conclusion:** SwimCount Harvester™ achieves SDF reduction comparable to DGC while significantly increasing motile sperm recovery. These findings support the potential of non-centrifugal sperm selection as an alternative to conventional methods. Larger studies are required to confirm these results and determine their clinical implications.

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Trial data will be made available on reasonable request to the corresponding author.

## INTRODUCTION

Sperm preparation is a critical step in assisted reproductive technology (ART), as the selection of functionally competent spermatozoa directly influences downstream reproductive processes, including fertilization and early embryonic development (1). While conventional semen analysis remains the cornerstone of male fertility evaluation, it provides limited insight into sperm functional competence, particularly at the level of chromatin integrity (2-4). Increasing evidence indicates that sperm DNA fragmentation (SDF) is associated with impaired reproductive outcomes, including reduced fertilization potential, compromised embryo development, and increased risk of miscarriage (5-9). These considerations reinforce the need to refine sperm selection strategies beyond conventional semen parameters, with increasing emphasis on functional biomarkers such as DNA integrity in both research and clinical practice.

Density Gradient Centrifugation (DGC) has long been the standard method for sperm preparation in ART laboratories, allowing enrichment of motile spermatozoa with improved morphology and reduced contamination from seminal plasma and debris (1). However, centrifugation exposes spermatozoa to mechanical stress and may promote the generation of reactive oxygen species (ROS), which have been implicated in DNA damage and functional impairment (10-12). These limitations have prompted the development of alternative sperm selection strategies aimed at minimizing iatrogenic damage during processing (12, 13).

In this context, non-centrifugal sperm selection systems have emerged as a promising approach (12, 14, 15). These technologies rely on the intrinsic ability of spermatozoa to migrate or navigate microenvironments, thereby enabling selection based on functional competence rather than physical separation alone. SwimCount Harvester™ is a migration-based sperm selection device designed to isolate motile spermatozoa without centrifugation, potentially reducing mechanical stress and oxidative injury while enriching for sperm with improved biological quality (16).

Despite these theoretical advantages, comparative evidence between non-centrifugal systems and

DGC remains limited, particularly with respect to sperm DNA fragmentation and laboratory performance metrics (13). In addition, variability between manual and computer-assisted methods for SDF assessment may influence the interpretation and reproducibility of results (17).

This pilot study was therefore designed to compare DGC and SwimCount Harvester™ with respect to SDF levels, agreement between manual and CASA-based SDF assessment, and total motile sperm recovery.

## MATERIALS AND METHODS

### Study Design and Ethical Approval

This pilot comparative study evaluated laboratory parameters following sperm preparation using Density Gradient Centrifugation and SwimCount Harvester™.

The Central Denmark Region Committees on Health Research Ethics approved the conduct of this study (File number 1-10-72-9-25).

### Participants

A total of 36 men (mean age  $35.8 \pm 5.1$  years; BMI  $26.1 \pm 2.7$  kg/m<sup>2</sup>) undergoing semen analysis as part of routine fertility evaluation were included. Thirteen of the included men had an SDF analysis made. The inclusion criterion was males attending the fertility clinic who were able to provide freshly ejaculated sperm for analysis. No clinical outcomes were evaluated in this pilot study.

### Semen Analysis

Participants were instructed to maintain a period of 2 days ejaculatory abstinence before semen collection on-site. Semen analysis was performed according to the 2021 WHO laboratory manual criteria (6th edition) using SCA® CASA System (Microptic, Spain) for sperm concentration and motility (18, 19).

### Sperm DNA Fragmentation Assessment

SDF was assessed using the Sperm Chromatin Dispersion (SCD) assay (Halosperm®, Halotech DNA, Madrid, Spain), following previously validated methodology (20). Briefly, semen aliquots were embedded in low-melting agarose on precoated slides. Controlled acid

denaturation generated single-stranded DNA at strand break sites, followed by protein removal through lysis. Spermatozoa with intact DNA developed large or medium chromatin dispersion halos, whereas those with fragmented DNA exhibited small or absent halos. Slides were dehydrated and stained using Diff-Quik.

For manual analysis, a minimum of 400 spermatozoa were scored per sample under bright-field microscopy by experienced technicians, following standardized halo classification criteria (8, 9, 20, 21). The SDF rate was calculated as the percentage of fragmented spermatozoa relative to total counted.

Slides were additionally analyzed using the SCA® DNA Fragmentation module (Sperm Class Analyzer, Microptic, Spain) (18). Prepared slides were examined using bright-field microscopy and a minimum number of 400 spermatozoa were automatically analyzed. Individual spermatozoa were identified and classified based on halo size surrounding the core, in accordance with the Sperm Chromatin Dispersion principle. Large and medium halos were indicative of intact DNA, whereas small or absent halos as well as degraded spermatozoa, were classified as exhibiting DNA fragmentation. Fragmentation status was determined by automated assessment of morphometric parameters, primarily halo size. Image acquisition parameters, including threshold settings, were established based on prior manual evaluation and applied consistently across samples. Up to 30 fields per sample were analyzed, with priority given to achieving the required number of evaluated spermatozoa. Like the manual assessment, the SDF rate was calculated as the percentage of fragmented spermatozoa relative to total counted.

### Quality control

Quality control included visual verification of halo morphology, ensuring absence of overlapping spermatozoa, homogeneous background, and structural integrity of the gel matrix. Only slides fulfilling predefined quality criteria were included in the final analysis.

### Sperm Processing

Density gradient centrifugation was performed using SpermGrad (Vitrolife, Göteborg, Sweden) gradient

(90–45%) (Figure-1). SpermGrad 100% was diluted using IVF medium (Vitrolife, Göteborg, Sweden) to obtain 90% and 45% dilutions. Two gradient columns were subsequently prepared in Falcon tubes (BD, USA) by gently layering 1.5 mL of each solution, with the 90% fraction at the bottom. The semen sample was carefully added on the top of the density gradient columns, and the samples were centrifuged at 300g for 15 min at room temperature. After centrifugation, the pellet was washed twice with 1.5 mL IVF medium followed by centrifugation at 200g for 10 min. The supernatant was removed and the pellet resuspended in IVF medium for semen analysis in the SCA® CASA System (Microptic, Spain) for concentration and motility.

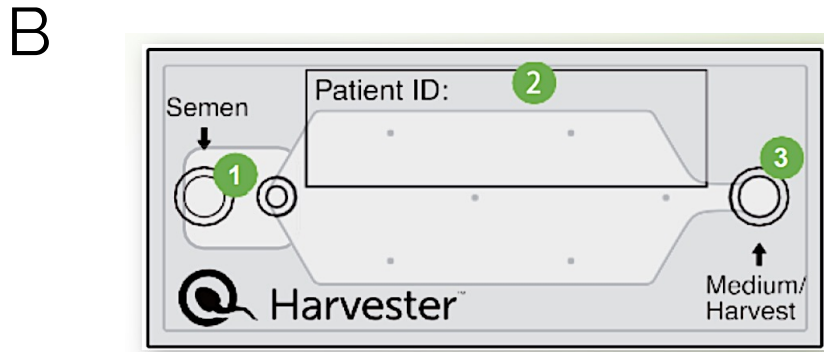
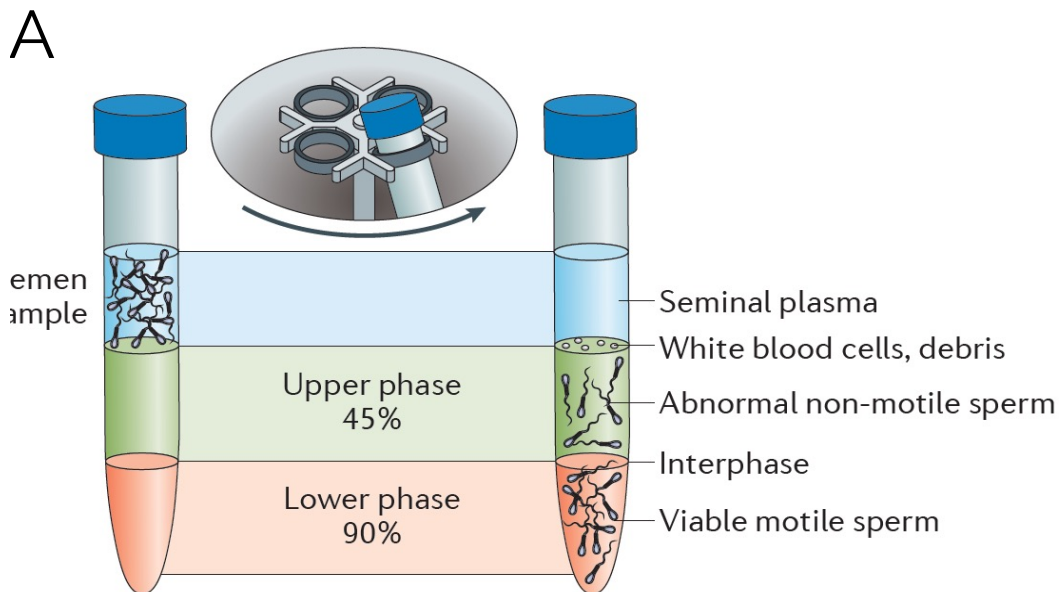
SwimCount Harvester™ preparation was performed using the SwimCount Harvester™ (MotilityCount ApS, Copenhagen, Denmark) 1 mL sperm purification device (Figure-1). The SwimCount Harvester™ has two chambers separated by a 10-μm-pore size membrane. One mL of semen was loaded into the lower chamber, and 0.8 mL of IVF medium (Vitrolife, Göteborg, Sweden) was loaded into the upper chamber. The device was incubated in a horizontal position at 37°C for 30 minutes, after which the medium from the upper chamber, enriched in highly motile spermatozoa, was carefully collected for further analysis in the SCA® CASA System (Microptic, Spain) for concentration and motility.

A schematic representation of the study design and analytical workflow is shown in Figure-2.

### Statistical Analysis

Descriptive statistics are presented as mean, standard deviation (SD), median, minimum, maximum, and interquartile range (IQR). Normality of continuous variables was assessed using the Shapiro–Wilk test. Homogeneity of variances between independent groups was evaluated using Levene's test. Given the exploratory nature of this pilot study, no formal sample size calculation was performed.

Because SDF measurements were obtained from the same samples under different processing conditions, paired comparisons were performed when ap-

**Figure 1 - Sperm preparation techniques: Density gradient centrifugation and SwimCount Harvester™.****1. Semen Inlet Port**

- For adding semen sample

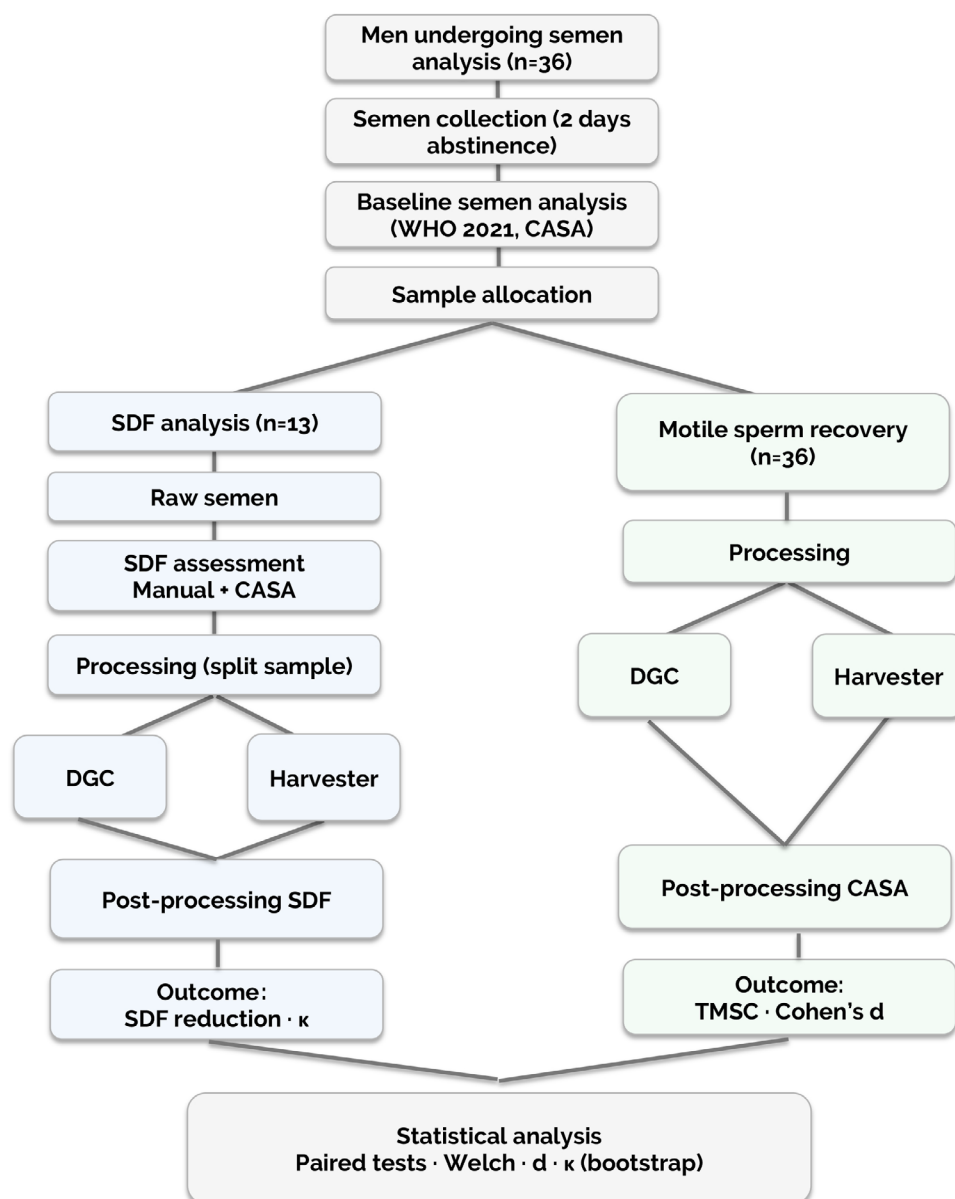
**2. Patient ID Label Space****3. Medium Inlet/Harvest Outlet Port**

- For loading sperm preparation medium
- For harvesting purified spermatozoa

(A) Schematic representation of density gradient centrifugation (DGC). Semen is layered over a discontinuous gradient (45% and 90%) and centrifuged, allowing separation of spermatozoa based on density. Debris, leukocytes, and non-motile or abnormal spermatozoa remain in the upper layers, while motile, morphologically normal spermatozoa are recovered in the pellet.

(B) Schematic representation of the SwimCount Harvester™ device. Semen is introduced into the inlet chamber, and spermatozoa migrate through a membrane into the upper chamber containing culture medium. Motile spermatozoa are subsequently collected from the harvest outlet, enabling selection without centrifugation. The device includes a semen inlet port, a medium inlet/harvest outlet port, and a designated space for patient identification.

Figure 2 - Study design and analytical workflow.



Semen samples from 36 men were collected and analyzed according to WHO 2021 criteria. A subset of samples ( $n = 13$ ) underwent sperm DNA fragmentation (SDF) assessment using the sperm chromatin dispersion (SCD) assay, analyzed manually and by computer-assisted semen analysis (CASA), in raw semen and following processing by density gradient centrifugation (DGC) or SwimCount Harvester™ in a within-subject design. Total motile sperm count (TMSC) was evaluated in all samples ( $n = 36$ ) following DGC and Harvester processing. Statistical analyses included paired comparisons, Cohen's  $d$ , and Cohen's  $\kappa$  with bootstrap confidence intervals.



appropriate. Paired t-tests were applied when normality assumptions were satisfied. In independent comparisons with unequal variances, Welch's correction was used. Non-parametric tests were employed when distributional assumptions were not met.

Agreement between manual and CASA SDF classification (using a 20% SDF threshold to classify non-pathological versus pathological SDF results) was evaluated using Cohen's kappa coefficient. Confidence intervals were estimated using both asymptotic standard error and bias-corrected accelerated (BCa) bootstrap resampling with 10,000 iterations to improve robustness given the limited sample size.

Effect sizes for SDF reductions were calculated as standardized mean differences (Cohen's *d*), using pooled standard deviations. For TMSC comparisons, effect size was calculated using Cohen's *d* based on pooled variance. Effect sizes were interpreted according to conventional thresholds (0.2 small, 0.5 medium, 0.8 large).

Statistical significance was defined as  $p < 0.05$ . Analyses were performed using JMP software (SAS Institute, Cary, NC, USA).

## RESULTS

### Sperm DNA Fragmentation in Raw and Processed Samples

In raw semen, SDF values demonstrated considerable variability, particularly when assessed using CASA. Mean SDF measured by CASA was 24.0% (SD 15.2%), ranging from 6.0% to 58.0%, with a median of 21.8%, indicating that a considerable proportion of samples exhibited elevated DNA fragmentation. Manual SCD assessment yielded a comparable mean SDF of 25.9% (SD 9.2%) and a median of 25.0%. The narrower dispersion observed with manual assessment suggests lower variability, although this may reflect methodological differences rather than true biological variation (Table-1).

Following DGC, SDF was significantly reduced. In CASA analysis, mean SDF decreased from 24.0% to 3.8% ( $p < 0.001$ ), corresponding to an approximate 84% relative reduction. The median value declined to 3.5%,

and the interquartile range narrowed considerably, indicating enrichment of a more homogeneous sperm population (Table-1). The standardized effect size for this reduction was large (Cohen's  $d = 1.81$ ). Manual SCD analysis showed a similar decrease from 25.9% to 7.5% ( $p < 0.001$ ), with a large effect size ( $d = 2.09$ ).

SwimCount Harvester™ processing also resulted in a significant SDF reduction relative to raw semen. In CASA analysis, the mean SDF decreased to 6.0% ( $p < 0.001$ ), with a large effect size ( $d = 1.59$ ). Manual SCD analysis showed a reduction to 6.8% ( $p < 0.001$ ), with an effect size of  $d = 2.64$  (Table-1).

Direct comparison between DGC and Harvester revealed no statistically significant difference in SDF reduction (CASA  $p = 0.219$ ; Manual  $p = 0.341$ ). Although DGC showed numerically lower mean SDF values in the CASA analysis, no statistically significant difference was observed between techniques, suggesting comparable efficacy under the conditions tested (Table-1).

The reduction in SDF across processing methods is illustrated in Figure-3A.

### Agreement Between Manual and CASA SDF Classification

Agreement between manual SCD scoring and CASA classification improved following sperm processing. In raw semen, the observed agreement was 76.9%, corresponding to a Cohen's kappa of 0.53 (bootstrap 95% CI 0.05–0.88), indicating moderate agreement. After DGC processing, agreement increased to 84.6%, with  $\kappa = 0.66$  (bootstrap 95% CI 0.18–0.93), consistent with substantial agreement. Following Harvester processing, complete concordance was observed ( $\kappa = 1.00$ ; bootstrap 95% CI 0.54–1.00), indicating perfect agreement (Table-2).

### Total Motile Sperm Count

TMSC differed significantly between processing methods. DGC preparations yielded a mean TMSC of  $1.8 \times 10^6$  (SD 2.6), whereas Harvester preparations yielded a mean of  $5.8 \times 10^6$  (SD 6.5) (Table-3). Levene's test confirmed unequal variances, and Welch's correction was applied. The difference was statistically significant ( $p = 0.001$ ). The calculated standardized effect size was

**Table 1 - Descriptive Statistics and Paired Effect Sizes of Sperm DNA Fragmentation According to Processing Method and Assessment Technique (n = 13).**

| Processing Method | Assessment | Mean $\pm$ SD   | Median (IQR)        | Min-Max   | p-value vs Raw | p-value DGC vs Harvester |
|-------------------|------------|-----------------|---------------------|-----------|----------------|--------------------------|
| Raw semen         | CASA       | 24.0 $\pm$ 15.2 | 21.8<br>(12.0–32.0) | 6.0–58.0  | —              | —                        |
| Post-DGC          | CASA       | 3.8 $\pm$ 4.2   | 3.5<br>(1.0–6.0)    | 0.0–15.1  | <0.001         | 0.219                    |
| Post-Harvester    | CASA       | 6.0 $\pm$ 5.0   | 4.3<br>(2.0–8.0)    | 0.3–14.0  | <0.001         | —                        |
| Raw semen         | Manual SCD | 25.9 $\pm$ 9.2  | 25.0<br>(20.0–32.0) | 10.0–40.0 | —              | —                        |
| Post-DGC          | Manual SCD | 7.5 $\pm$ 8.4   | 5.0<br>(2.0–9.0)    | 0.0–25.0  | <0.001         | 0.341                    |
| Post-Harvester    | Manual SCD | 6.8 $\pm$ 4.5   | 8.0<br>(3.0–10.0)   | 1.0–15.0  | <0.001         | —                        |

CASA = computer-assisted semen analysis; SCD = sperm chromatin dispersion test; DGC = Density-gradient centrifugation; IQR = interquartile range; SD = standard deviation

large (Cohen's  $d = 0.81$ ), indicating a substantial magnitude of difference favoring Harvester in motile sperm recovery. The comparison of total motile sperm recovery between DGC and Harvester is shown in Figure-3B.

## DISCUSSION

### Main findings

This pilot study provides a within-subject comparison of DGC and a non-centrifugal migration-based sperm selection system (SwimCount Harvester™) with respect to sperm DNA fragmentation (SDF), analytical agreement between manual and CASA-based assessment, and total motile sperm recovery.

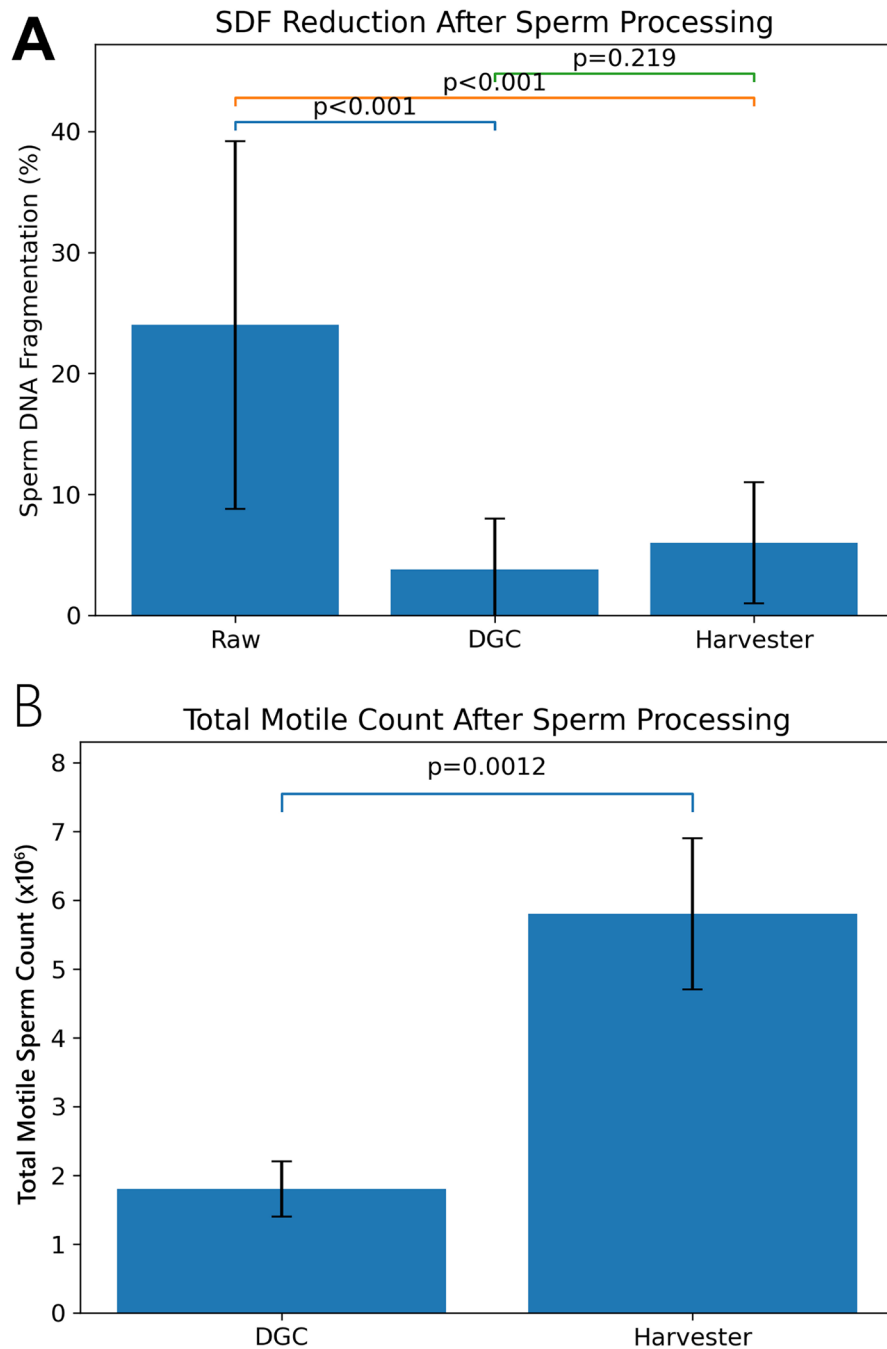
Three main findings emerge. First, both DGC and Harvester significantly reduced SDF compared with raw semen, with large, standardized effect sizes. Second, no statistically significant difference in SDF reduction was observed between techniques, suggesting comparable efficacy in selecting spermatozoa with improved chromatin integrity under the conditions tested. Third, Harvester yielded significantly higher total motile sperm counts compared with DGC, with a large effect size. In addition, agreement between manual and CASA

SDF assessment improved following sperm processing, reaching perfect concordance after Harvester selection. Collectively, these findings suggest that migration-based sperm selection can achieve chromatin integrity enrichment comparable to conventional centrifugation while substantially increasing motile sperm recovery.

### Interpretation

The reduction in SDF observed following both DGC and Harvester processing supports the concept that motility-based selection enriches for spermatozoa with improved chromatin integrity. This is biologically plausible, as SDF has been associated with reduced motility, oxidative stress, and impaired membrane integrity (5, 9, 15, 22, 23). By selecting motile spermatozoa, both techniques inherently reduce the proportion of fragmented cells (16, 24, 25).

The absence of a significant difference between DGC and Harvester in SDF reduction suggests that centrifugation is not essential for effective SDF reduction. Although DGC showed numerically lower SDF values in CASA-based analysis, the overlap in data dispersion and lack of statistical significance indicate comparable performance in DNA fragmentation reduction.

**Figure 3 - Effects of sperm processing on DNA fragmentation and motile sperm recovery.**

(A) Sperm DNA fragmentation (SDF) in raw semen and following Density Gradient Centrifugation (DGC) and SwimCount Harvester™ processing. Both DGC and Harvester significantly reduced SDF compared with raw semen ( $p < 0.001$  for both comparisons). No significant difference was observed between DGC and Harvester ( $p = 0.219$ ).

(B) Total motile sperm count (TMC) following DGC and Harvester processing. Harvester yielded significantly higher motile sperm recovery ( $p = 0.0012$ ).

Data are presented as mean  $\pm$  standard deviation.

**Table 2 - Agreement Between CASA and Manual SCD (>20% Threshold).**

| Processing Method | CASA+/Manual+ | CASA+/Manual- | CASA-/Manual+ | CASA-/Manual- | Agreement (%) | $\kappa$ (Bootstrap 95% CI) |
|-------------------|---------------|---------------|---------------|---------------|---------------|-----------------------------|
| Raw semen         | 6             | 1             | 2             | 4             | 76.9          | 0.53<br>(0.05–0.88)         |
| Post-DGC          | 3             | 1             | 1             | 8             | 84.6          | 0.66<br>(0.18–0.93)         |
| Post-Harvester    | 4             | 0             | 0             | 9             | 100           | 1.00<br>(0.54–1.00)         |

CASA = computer-assisted semen analysis; SCD = sperm chromatin dispersion test; DGC = Density-gradient centrifugation; CI = confidence interval

**Table 3 - Comparison of Semen Parameters following Density Gradient Centrifugation and SwimCount Harvester™ sperm selection (n=36).**

|                                            | Raw semen       | DGC             | Harvester       | p-value | Cohen's d (DGC vs Harvester) |
|--------------------------------------------|-----------------|-----------------|-----------------|---------|------------------------------|
| Concentration ( $\times 10^6$ /mL)         | 23.9 $\pm$ 18.6 | 3.4 $\pm$ 3.7   | 7.9 $\pm$ 8.4   | 0.004   | 0.69                         |
| Motility (%)                               | 57.1 $\pm$ 18.5 | 89.3 $\pm$ 14.1 | 88.2 $\pm$ 14.0 | 0.74    | 0.08                         |
| Total sperm count ( $\times 10^6$ )        | 67.6 $\pm$ 60.5 | 3.4 $\pm$ 3.7   | 6.3 $\pm$ 6.7   | 0.03    | 0.54                         |
| Total motile sperm count ( $\times 10^6$ ) | 43.8 $\pm$ 44.1 | 1.8 $\pm$ 2.6   | 5.8 $\pm$ 6.5   | 0.001   | 0.81                         |

Values are mean  $\pm$  SD

The improved agreement between manual and CASA-based SDF assessment following sperm processing likely reflects reduced heterogeneity in chromatin dispersion patterns (i.e., halo morphology). Raw semen samples contain a broad spectrum of halo morphologies, increasing classification variability. Following processing, the sperm population becomes more homogeneous, facilitating more consistent classification across analytical methods. The use of bootstrap confidence intervals strengthens the robustness of this observation despite the limited sample size.

The most notable laboratory difference between techniques was observed in total motile sperm recovery. Harvester yielded significantly higher TMSC compared with DGC, suggesting that avoidance of centrifugation may preserve a greater proportion of viable spermatozoa. Mechanical stress during centrifugation has been associated with sperm loss and increased reactive oxy-

gen species generation, providing a plausible biological explanation for this finding (12, 26).

Although both techniques effectively reduced SDF, the higher motile yield achieved with Harvester may provide a practical laboratory advantage. Similar reductions in DNA fragmentation after microfluidic sperm selection have been demonstrated in controlled laboratory settings (10, 13, 27). Moreover, previous comparative studies indicate that microfluidic selection may reduce oxidative stress markers compared with centrifugation-based methods, and enhanced recovery without centrifugation has also been reported in migration-based platforms, supporting the biological plausibility of our findings (13, 27-29).

### Clinical Relevance

Both DGC and Harvester appear effective in reducing baseline DNA fragmentation at the laboratory level. The higher motile sperm recovery observed with Harvester

may represent a practical advantage, particularly in cases with low sperm counts or compromised semen parameters. However, no clinical outcomes were evaluated in this pilot study. Therefore, the extent to which these laboratory differences translate into improved fertilization, embryo development, or live birth rates remains unknown and requires investigation in adequately powered clinical studies.

### Strengths and limitations

The strengths of this study include its within-subject design, minimizing inter-individual variability, and the use of a validated SCD methodology with both manual and CASA-based assessment. The incorporation of agreement analysis and bootstrap confidence intervals adds methodological robustness, particularly in the context of a limited sample size.

This study also has limitations. The small sample size restricts the precision of estimates and limits generalizability. Only a subset of samples underwent SDF assessment, and oxidative stress markers were not directly measured, precluding mechanistic conclusions. In addition, as a pilot study, no formal sample size calculation was performed, and findings should be interpreted as hypothesis-generating.

### Future Directions

Larger, prospective studies are needed to confirm these findings and determine whether non-centrifugal sperm selection translates into improved reproductive outcomes. Future research should incorporate clinical endpoints, oxidative stress biomarkers, and functional sperm assays to better elucidate the mechanisms underlying observed differences. Evaluation of reproducibility across laboratories and cost-effectiveness will also be important for broader clinical implementation.

## CONCLUSIONS

Both DGC and SwimCount Harvester™ significantly reduce sperm DNA fragmentation compared with raw semen, with no significant difference between methods. The Harvester system yields higher

total motile sperm recovery and demonstrates excellent agreement between manual and CASA-based SDF assessment. These findings support the potential of migration-based, non-centrifugal sperm selection as an alternative to conventional centrifugation, particularly in cases where maximizing motile sperm recovery is desirable. Further studies are required to establish clinical relevance.

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## CONFLICT OF INTEREST

None declared.

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# Staged Buried Oral Mucosal Strip Urethroplasty for Long-Segment Post-Hypospadias Urethral Strictures: Achieving Functional Recovery and Distal Meatal Preservation

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## ABSTRACT

**Purpose:** Long-segment urethral strictures following hypospadias repair (LUSPH) represent a formidable reconstructive challenge. Few techniques simultaneously achieve durable stricture resolution while preserving the distal urethral meatus. This study evaluates the efficacy, safety, and patient-reported outcomes of staged buried oral mucosal strip urethroplasty for LUSPH.

**Patients and Methods:** A retrospective analysis was conducted on patients undergoing this procedure between June 2016 and June 2024. Stage one involved inlay of an oral mucosal graft. In the second stage, the healed composite mucosal strip was tubularized using penile fascial flap. Outcomes assessed included maximum flow rate (Qmax), patient-reported outcome measures (USS-PROM, QoL-PROM, IIEF-5), surgical success (defined as unobstructed voiding without intervention, Qmax >15 mL/s, and absence of major complications), and complications.

**Results:** Sixty-one patients were enrolled, with a mean age of  $29.8 \pm 9.1$  years and mean stricture length of  $4.7 \pm 0.7$  cm. Ultimately, 51 patients (83.6%) achieved unobstructed voiding meeting the definition of surgical success. The mean Qmax at 1-year postoperatively was  $18.5 \pm 4.3$  mL/s. From preoperatively to 1-year postoperatively, USS-PROM scores significantly decreased from  $21.0 \pm 2.0$  to  $6.6 \pm 2.2$  ( $P < 0.001$ ), while QoL-PROM scores significantly improved from  $46.6 \pm 6.7$  to  $87.2 \pm 8.2$  ( $P < 0.001$ ). IIEF-5 scores showed no significant change. Finally, 54 patients (88.5%) maintained a meatus positioned above the coronal sulcus.

**Conclusions:** In this single-center retrospective cohort, staged buried oral mucosal strip urethroplasty demonstrated favorable mid-term efficacy and safety for LUSPH.

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## INTRODUCTION

Urethral strictures following hypospadias repair, particularly long-segment anterior urethral strictures (LUSPH) in post-pubertal patients, remain a significant clinical challenge in reconstructive urology (1, 2). Such cases are often characterized by poor local tissue quality, substantial loss of healthy urethral plate, and extensive scar fibrosis from multiple prior surgeries (3). These factors collectively limit the efficacy of conventional urethroplasty techniques, making it difficult to achieve both urethral patency and satisfactory cosmesis.

The evolution of anterior urethral stricture management reflects iterative advances in reconstructive techniques. To address complex strictures, classic staged repairs were developed. For instance, the staged Johanson repair utilized a buried skin strip to create a tension-free neourethra (4). However, inherent drawbacks of skin grafts, poor resistance to urine erosion and a propensity for contraction, often led to stricture recurrence, particularly in long-segment repairs. The Bracka two-stage buccal mucosal graft (BMG) urethroplasty improved graft material with better urinary resistance (4). Yet, this technique involves tubularization of the thin, mechanically weaker buccal mucosa during stage two, potentially increasing risks of graft necrosis and urethrocutaneous fistula due to tissue tension.

Standardized techniques specifically addressing LUSPH, combining the advantages of oral mucosa with principles of low-tension reconstruction, have not been systematically reported. We adopted the staged buried oral mucosal strip urethroplasty tailored for LUSPH. This technique abandons early graft tubularization, focusing first on graft inlay and vascular integration with the urethral bed. Stage two employs a fascial wrapping technique to tubularize the incorporated oral mucosal strip. Furthermore, it incorporates goals of orthotopic meatal reconstruction through flexible application of oral mucosa.

We hypothesized that staged buried oral mucosal strip urethroplasty could be a viable option for achieving durable urethral patency and distal meatal

reconstruction in post-pubertal LUSPH patients. As an uncontrolled, single-center retrospective study, this report presents our initial results.

## PATIENTS AND METHODS

### Study Design and Population

The study protocol was approved by the Ethics Committee of Shanghai Sixth People's Hospital (Approval No. 2025-KY-494K). Due to its retrospective nature and anonymized data, informed consent was waived. This is a retrospective observational study. All intraoperative clinical images used were obtained with separate written informed consent from the participants, and all clinical data have been anonymized.

This retrospective study evaluated the efficacy and safety of staged buried oral mucosal strip urethroplasty in LUSPH patients. We systematically reviewed electronic medical records, operative notes, and follow-up data of all eligible LUSPH patients undergoing this procedure in the Department of Urology, Shanghai Sixth People's Hospital, from June 2016 to June 2024.

Inclusion criteria were as follows: Male patients aged  $\geq 14$  years; A documented history of hypospadias repair; Intraoperatively confirmed long-segment (length  $> 3$  cm) stricture of the anterior urethra; First-time receipt of the oral mucosa urethroplasty described in this study; Complete surgical records and postoperative follow-up data. Exclusion criteria included: Urethral strictures caused by other etiologies (e.g., trauma, infection, post-prostatectomy); Presence of active urethral cancer or penile cancer; Incomplete follow-up data or lost to follow-up.

## SURGICAL TECHNIQUE

The buried oral mucosal strip urethroplasty is characterized by a two-stage strategy prioritizing the creation of a well-vascularized oral mucosal strip and fascia-mediated lumen formation, rather than traditional graft tubularization. Core steps:

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### Stage One: Establishing a Well-Vascularized Oral Mucosal Strip

**Exposure and Stricture Management:** An incision is made along the ventral midline of the penis, extended as needed. The stenotic urethra is opened longitudinally, proximally extending into healthy mucosa by ~0.5 cm. Fibrotic scar tissue is meticulously excised while carefully preserving healthy urethral mucosal edges (Figure-1A).

**Urethral Plate Preparation:** The preserved urethral plate is deepened via a midline dorsal incision to maintain graft bed vascularity (Figure-1B).

**Oral Mucosal Graft Harvesting and Fixation:** For strictures > 4 cm or requiring graft width  $\geq 1.5$  cm, tongue mucosa is preferred due to its larger harvestable area. For shorter strictures (< 4 cm) or limited tongue tissue (e.g., lesions, prior harvest), buccal mucosa is chosen. Graft length is designed to be 0.5 cm longer than the measured stricture length to cover proximal and distal healthy urethral edges. Graft width is typically 1.0–1.5 cm to ensure adequate epithelial coverage post-

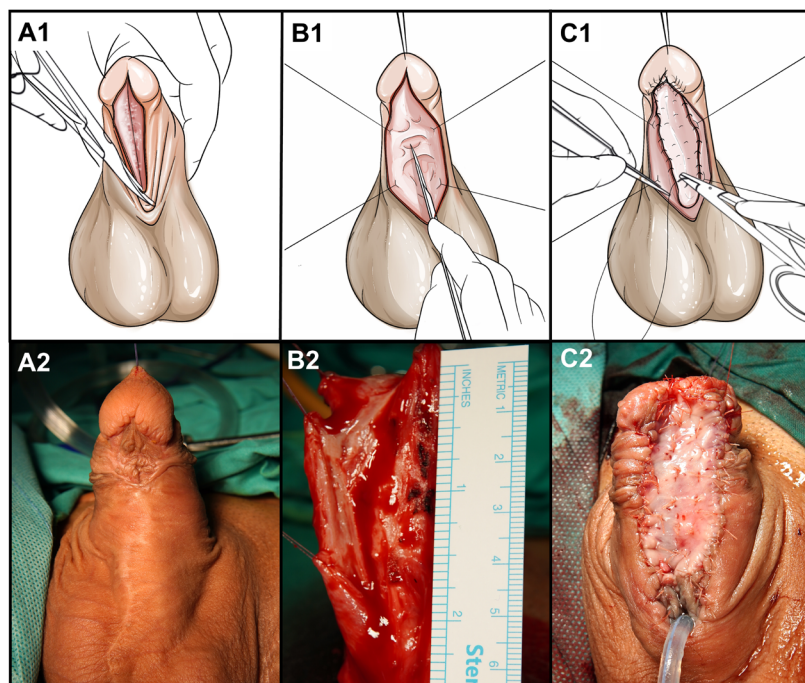
inlay. Tongue or buccal mucosal grafts are harvested per these criteria, defatted, trimmed, and sutured onto the prepared dorsal urethral bed using 6-0 PDS sutures. Graft edges are anastomosed to the preserved native urethral mucosa edges. Central mattress sutures fix the graft to the tunica albuginea to prevent dead space formation and graft mobility (Figure-1C).

### Stage Two: Fascial-Mediated Tubularization of the Oral Mucosal Strip

**Mucosal Strip Mobilization:** Stage two is typically performed around 3 months after graft fixation. The inlaid mucosal strip, together with the residual native urethral plate, is mobilized as a composite unit. It is dissected laterally down to the tunica albuginea, creating a strip approximately 1.4–2.0 cm wide (Figure-2A).

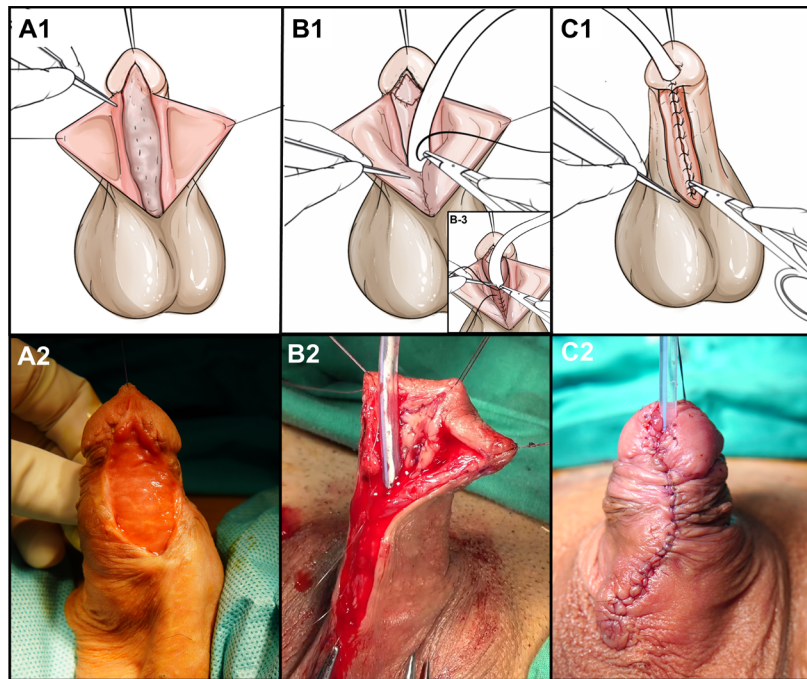
**Fascial Flap Harvesting and Urethral Tubularization:** A superficial fascial flap (Buck's fascia layer) is raised from the ventral penile subcutaneous tissue, supplied by branches of the superficial penile artery and fascial vascular plexus. Starting proximally,

**Figure 1 - Establishment of a well-vascularized oral mucosal strip.**



A1/2: Ventral penile incision exposing the strictured segment; B1/2: Thorough excision of scar tissue from the urethral plate; C1/2: Inlay of oral mucosa onto the urethral plate.



**Figure 2 - Fascial-mediated tubularization of the oral mucosal strip.**

A1/2: Appearance after oral mucosal inlay; B1/2: Neourethral reconstruction using a pedicled penile fascial flap wrap (compare with B3, direct tubularization of the urethral plate); C1/2: Closure of penile skin.

this vascularized fascial flap is wrapped over the oral mucosal strip, generally requiring it to cover a 12-14 Fr catheter without tension (Figure-2B).

**Closure:** Subcutaneous tissue and skin are closed in layers to approximate the penile skin (Figure-2C).

**Technical Distinction:** Unlike conventional staged graft urethroplasty, in which the grafted plate is directly rolled into a tube under epithelial tension, our technique mobilizes the healed composite mucosal strip and uses a penile fascial flap as the external supporting and wrapping layer. Thus, the epithelialized graft is incorporated into the neourethral lumen while the closure tension is mainly borne by the vascularized fascial tissue rather than by the graft edges alone.

#### Possible Adjunctive Procedures

**Meatal Reconstruction:** To achieve optimal meatal configuration and prevent stenosis, adjunctive techniques may include glans wing mobilization or small ventral inlay grafts (Figure-3A), or dorsal inlay of oral mucosa (Figure-3B).

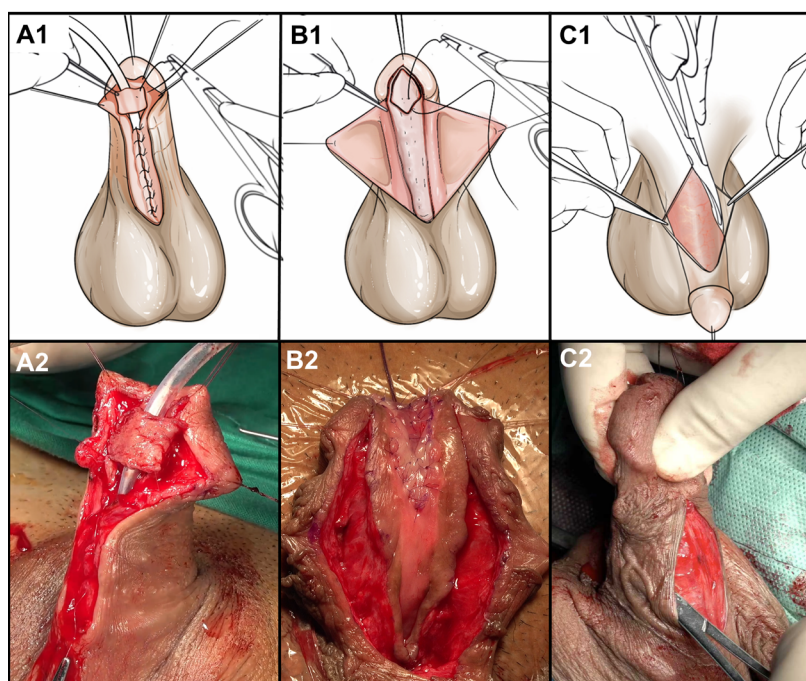
**Penile Dorsal Dissection:** If the initially harvested ventral subcutaneous fascial flap lacks sufficient

length or mobility to achieve tension-free coverage of the entire neourethra during stage two tubularization, a dorsal release maneuver is performed (Figure-3C).

#### Postoperative Management and Efficacy Evaluation

Prophylactic antibiotics were routinely administered postoperatively to reduce infection risk. Patients were instructed on gentle daily compression of the neourethra to express secretions, preventing mucus accumulation and blockage. Elastic compression dressings were removed on postoperative day 3. The urethral catheter was retained for 3 weeks. Oral care, including rinsing with saline or metronidazole solution, was emphasized to promote healing at the tongue donor site and prevent infection.

Regular follow-up was scheduled at 1, 3, 6, and 12 months postoperatively. Assessments utilized validated patient-reported outcome measures (PROMs) and objective parameters. PROMs included the Urethral Stricture Surgery PROM (USS-PROM), Quality of Life PROM (QoL-PROM)(5), and the 5-item International Index of Erectile Function (IIEF-5), alongside patient satisfaction with meatal

**Figure 3 - Possible adjunctive procedures.**

A1/2. Ventral onlay meatoplasty; B1/2. Dorsal inlay meatoplasty; C1/2. Penile dorsal dissection for fascial flap release.

appearance. The USS-PROM has been validated for cultural adaptation in Chinese populations (6, 7). The QoL-PROM assesses five domains: physical health, mental health, social function, living environment, and health habits (8). The IIEF-5 questionnaire was used for patients aged 18 and above; therefore, comparisons of preoperative and postoperative IIEF-5 were limited to adult patients (9). Objective assessments included uroflowmetry, urethroscopy, and urethrography, though the latter two were performed less frequently, making uroflowmetry the primary objective measure. Short- and medium-term complications were recorded, including graft necrosis, wound infection, stricture recurrence, urethrocutaneous fistula, and urethral diverticulum. Annual long-term follow-up was recommended thereafter to monitor durability and potential late complications.

Primary surgical success was defined as: >1 year postoperatively, subjectively unobstructed voiding without need for intervention (e.g., dilation, meatotomy), maximum flow rate (Qmax) >15 mL/s, and absence of complications like urethral fistula

or diverticulum. The Qmax >15 mL/s threshold follows internationally recognized success criteria for adult urethroplasty, applied and validated in lower urinary tract reconstruction studies (10-12).

Secondary outcomes included changes in PROMs (USS-PROM, QoL-PROM, IIEF-5) and the proportion of patients with the meatus located in an orthotopic position.

### Statistical analysis

All statistical analyses were performed using SPSS 26.0 software. Normally distributed continuous variables are presented as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ), with paired t-tests used to compare preoperative and postoperative values. Categorical variables are expressed as frequency and percentage (n, %), summarized using descriptive statistics. Multivariate logistic regression was used to explore potential factors for stricture recurrence. Two-tailed P-values < 0.05 were considered statistically significant.

**Table 1 - Descriptive characteristics of patients with LUSPH treated with staged buried oral mucosal strip urethroplasty.**

| Indicator Category        | Specific Indicator                              | Value                    |
|---------------------------|-------------------------------------------------|--------------------------|
| Baseline Characteristics  | Number of patients                              | 61                       |
|                           | Mean age (years)                                | 29.8 ± 9.1 (14-50)       |
|                           | Mean preoperative stricture duration (months)   | 23.0 ± 11.5 (3-48)       |
|                           | Mean number of previous surgeries               | 2.4 ± 1.1 (1-6)          |
|                           | Mean intraoperative stricture length (cm)       | 4.7 ± 0.7 (3.4-6.5)      |
| Surgery-related Data      | Mean duration of first-stage surgery (minutes)  | 72.6 ± 12.5 (53.4-105.1) |
|                           | Source of pre-placed oral mucosa:               |                          |
|                           | Tongue mucosa                                   | 54 (88.5%)               |
|                           | Buccal mucosa                                   | 7 (11.5%)                |
|                           | Mean duration of second-stage surgery (minutes) | 78.0 ± 21.9 (43.3-125.2) |
|                           | Dorsal penile incision                          | 6 (9.8%)                 |
|                           | Additional mucosa for urethral meatal plasty:   |                          |
|                           | Dorsal inlay                                    | 21(34.4%)                |
| Follow-up Outcomes        | Ventral onlay                                   | 4 (6.6%)                 |
|                           | Mean follow-up duration (months)                | 29.4 ± 20.1 (12-92)      |
|                           | Surgical success rate at final follow-up        | 51 (83.6%)               |
|                           | Mean Qmax at 1 year postoperatively (mL/s)      | 18.5 ± 4.3 (2.8-27.3)    |
|                           | Urethral meatus above the coronal sulcus        | 54 (88.5%)               |
|                           | Postoperative restenosis                        | 7 (11.5%)                |
|                           | Urethral fistula                                | 3 (4.9%)                 |
|                           | Graft necrosis                                  | 0 (0%)                   |
| Patient-Reported Outcomes | Preoperative USS-PROM score                     | 21.0±2.0 (18-24)         |
|                           | Postoperative 1-year USS-PROM score             | 6.6±2.2 (4-13)           |
|                           | Preoperative QoL-PROM score                     | 46.6±6.7 (34-61)         |
|                           | Postoperative 1-year QoL-PROM score             | 87.2±8.2 (51-100)        |
|                           | Preoperative IIEF-5 score (n=56)                | 21.1±1.8 (16-24)         |
|                           | Postoperative 1-year IIEF-5 score (n=56)        | 21.4±1.9 (17-25)         |
|                           | Satisfaction with postoperative appearance      | 57 (93.4%)               |

USS-PROM = Urethral Stricture Symptom Score-Patient Reported Outcome Measure; QoL-PROM = Quality of Life-Patient Reported Outcome Measure; IIEF-5 = International Index of Erectile Function-5. Continuous variables are expressed as mean ± standard deviation (minimum-maximum); categorical variables are presented as number (percentage).

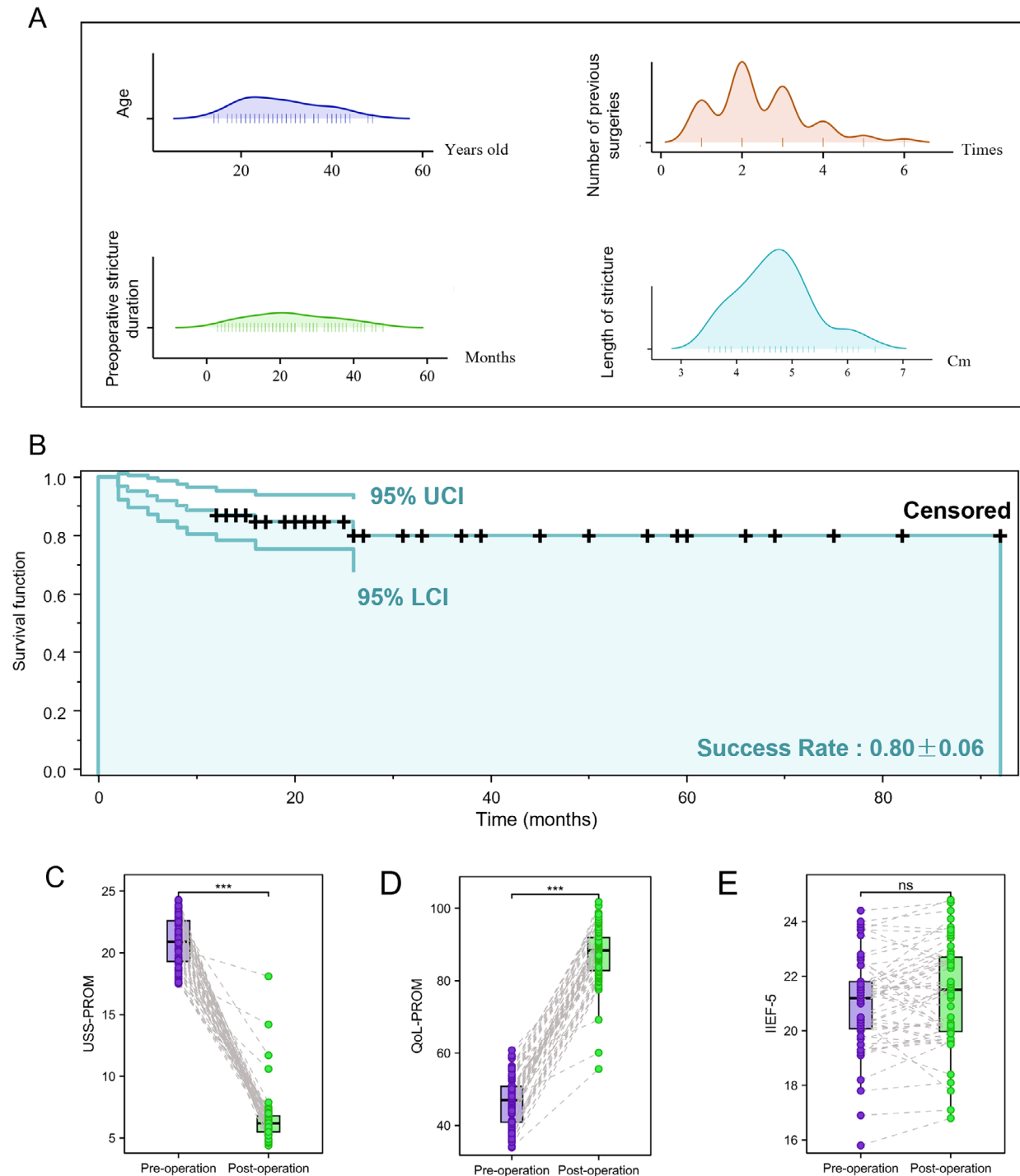
## RESULTS

During the study period, 61 LUSPH patients successfully underwent staged buried oral mucosal strip urethroplasty with complete follow-up records (Table-1, Figure-4). The mean patient age was 29.8 ± 9.1 years.

All patients presented with voiding difficulty. The mean intraoperative stricture length was 4.7 ± 0.7 cm, with 4 patients having strictures extending into the distal bulbous urethra.

Regarding the pre-placed oral mucosal grafts, 54 (88.5%) were tongue mucosa and 7 (11.5%) were buccal mucosa.

**Figure 4 - Distribution of patients' baseline characteristics and patient-reported outcome**



A: Ridge plot showing the distribution of age, symptom duration, number of previous surgeries, and intraoperative stricture length in patients with LUSPH. B: Kaplan-Meier survival analysis of surgical success. UCI, upper confidence interval, LCI, lower confidence interval. C-E: Paired plots of USS-PROM, QoL-PROM and IIEF-5 scores in patients with LUSPH before surgery and at 1 year postoperatively.

Six patients (9.8%) required a dorsal penile incision intraoperatively to release layers and reduce tension. For meatoplasty, 21 patients (34.4%) received additional dorsal oral mucosal inlay, and 4 patients (6.6%) received additional ventral oral mucosal inlay.

All patients had good postoperative wound healing. After catheter removal at 3 weeks, all patients initially voided spontaneously. Mean follow-up was  $29.4 \pm 20.1$  months. The mean Qmax at 1-year postoperatively for all patients was  $18.5 \pm 4.3$  mL/s. At final follow-up, 51 of 61 patients (83.6%, 95% CI: 71.9%–91.8%) achieved unobstructed voiding meeting the surgical success definition. Seven patients (11.5%, 95% CI: 4.7%–22.2%) had stricture recurrence, and 3 patients (4.9%, 95% CI: 1.0%–13.7%) developed urethrocuteaneous fistulas. Kaplan-Meier analysis showed a 1-year surgical success rate of  $88.89 \pm 4.32\%$  and a 2-year surgical success rate of  $79.95 \pm 6.41\%$ . No patients experienced graft necrosis, wound infection, or oral complications. Next, we conducted a preliminary exploration of the risk factors for restenosis. After adjusting for potential confounding factors, stenosis length was identified as a risk factor for the primary outcome (odds ratio = 9.88, 95% confidence interval: 1.49–65.42;  $P=0.021$ ). Other covariates, including patient age, number of prior surgeries, graft type, and operative time, showed no significant association with failure risk (all  $P > 0.05$ ).

Assessment using USS-PROM and QoL-PROM questionnaires showed that the mean USS score significantly decreased from  $21.0 \pm 2.0$  preoperatively to  $6.6 \pm 2.2$  at 1-year postoperatively ( $P < 0.001$ ), while the QoL score improved significantly from  $46.6 \pm 6.7$  to  $87.2 \pm 8.2$  ( $P < 0.001$ ). There was no significant change in IIEF-5 scores pre- vs. postoperatively (preoperative:  $21.1 \pm 1.8$ ; postoperative:  $21.4 \pm 1.9$ ,  $n=56$ ).

Preservation and reconstruction of the distal meatus appeared to be an advantage of the buried oral mucosal strip technique. At final follow-up, 54 patients (88.5%) maintained a meatus positioned above the coronal sulcus, while 7 had meatal retraction to or below the coronal sulcus. According to follow-up questionnaires, 57 patients (93.4%) were satisfied with the postoperative appearance.

Exploratory subgroup analyses were performed. Patients with  $\geq 3$  prior surgeries ( $n=26$ ) had a significantly longer mean stricture length ( $5.1 \pm 0.7$  cm) compared to those with  $\leq 2$  prior surgeries ( $n=35$ ,  $4.4 \pm 0.5$  cm,  $P < 0.001$ ). Nevertheless, the two subgroups showed no significant differences in final surgical success rate (76.9% vs. 88.6%,  $P = 0.308$ ), 1-year Qmax, or meatus position (Supplementary Table-1).

Comparing patients who received adjunctive mucosal grafts for meatoplasty ( $n=25$ ) versus those who did not ( $n=36$ ) reveal that the graft group had a longer preoperative stricture duration ( $26.9 \pm 12.5$  vs.  $20.2 \pm 10.1$  months,  $P = 0.030$ ). The groups were similar in other baseline characteristics, and no significant differences were found in surgical success rate (84.0% vs. 83.3%) or other key outcomes (Supplementary Table-2).

## DISCUSSION

Since the 1950s, urethroplasty has evolved into a systematic discipline. Johanson's "buried strip" technique, proposed in 1953, first established the principle of staged repair, becoming a milestone in modern urethral surgery (13). Numerous innovations followed, such as Duckett's tubularized prepuce island flap technique (1980) and the Snodgrass urethroplasty (tubularized incised plate urethroplasty, 1994) (14). However, urethral strictures emerging in adulthood after childhood hypospadias repair remain relatively common, accounting for approximately 12% of all adult urethral strictures (15). Among these, post-adolescent long-segment urethral strictures post-hypospadias repair (LUSPH) pose significant therapeutic challenges.

These strictures typically originate from the urethra reconstructed during childhood. Due to the lack of support from normal corpus spongiosum, this segment cannot grow synchronously with penile development during puberty, leading to relative shortening, increased tension, and subsequently, progressive fibrotic stricture (16, 17). Increased sexual activity and chronic urine irritation in adulthood further exacerbate mucosal damage and induce scar contracture, frequently complicating meatal retraction, penile curvature, or urethral diverticula. Thus, this study represents the first clinical series



reporting the staged buried oral mucosal strip urethroplasty specifically for LUSPH.

Existing literature on managing post-hypospadias repair strictures is limited, with reported success rates ranging from 14% to 95.1% (1, 18-21). The largest series, by Guido Barbagli et al. (20), reported an overall failure-free survival rate of 48% (95% CI 41-54%) at 5-year follow-up in 408 patients, but interventions were diverse,

including internal urethrotomy, end-to-end anastomosis, urethroplasty, and fistula closure. Akio Horiguchi et al.(22) reported on reconstructions including 22 (75.9%) staged urethroplasties, 3 (10.2%) one-stage onlay grafts, and 4 (13.8%) perineal urethrostomies; overall, 23 patients were "very satisfied" or "satisfied" with the reconstruction. In our single-center study, all 61 patients underwent staged buried oral mucosal strip urethroplasty,

**Supplementary Table 1 - Subgroup analysis by number of previous surgeries.**

| Indicators                                      | Number of previous surgeries ≤ 2 (n=35) | Number of previous surgeries ≥ 3 (n=26) | P value |
|-------------------------------------------------|-----------------------------------------|-----------------------------------------|---------|
| <b>Baseline characteristics</b>                 |                                         |                                         |         |
| Mean age (years)                                | 29.9 ± 9.2                              | 28.1 ± 9.0                              | 0.452   |
| Mean preoperative stricture duration (months)   | 22.3 ± 11.1                             | 23.8 ± 12.2                             | 0.602   |
| Mean intraoperative stricture length (cm)       | 4.4 ± 0.5                               | 5.1 ± 0.7                               | <0.001  |
| <b>Surgery-related data</b>                     |                                         |                                         |         |
| Mean duration of first-stage surgery (minutes)  | 70.1 ± 10.8                             | 76.2 ± 14.1                             | 0.058   |
| Mean duration of second-stage surgery (minutes) | 79.8 ± 24.0                             | 75.3 ± 18.5                             | 0.439   |
| Using auxiliary mucosal, n (%)                  | 13 (37.1%)                              | 12 (46.2%)                              | 0.479   |
| <b>Follow-up results</b>                        |                                         |                                         |         |
| Surgical success rate at final follow-up, n (%) | 31 (88.6%)                              | 20 (76.9%)                              | 0.308   |
| Mean Qmax at 1 year postoperatively (mL/s)      | 18.1 ± 4.1                              | 18.9 ± 4.5                              | 0.460   |
| Urethral meatus above the coronal sulcus, n (%) | 31 (86.1%)                              | 23 (92.0%)                              | 0.704   |
| <b>Patient-reported outcome</b>                 |                                         |                                         |         |
| Preoperative USS-PROM score                     | 21.1 ± 1.9                              | 20.7 ± 2.2                              | 0.402   |
| Postoperative 1-year USS-PROM score             | 6.4 ± 2.3                               | 6.7 ± 2.1                               | 0.615   |
| Preoperative QoL-PROM score                     | 46.8 ± 6.4                              | 46.2 ± 7.3                              | 0.691   |
| Postoperative 1-year QoL-PROM score             | 88.6 ± 8.2                              | 85.3 ± 10.5                             | 0.184   |
| Preoperative IIEF-5 score                       | 21.2 ± 2.2                              | 20.8 ± 1.9                              | 0.427   |
| Postoperative 1-year IIEF-5 score               | 21.7 ± 2.0                              | 21.0 ± 2.2                              | 0.236   |
| Satisfaction with postoperative appearance      | 35 (97.2%)                              | 22 (88.0%)                              | 0.330   |

USS-PROM = Urethral Stricture Symptom Score-Patient Reported Outcome Measure; QoL-PROM = Quality of Life-Patient Reported Outcome Measure; IIEF-5 = International Index of Erectile Function-5. Continuous variables are expressed as mean ± standard deviation; categorical variables are presented as number (percentage).

with initial patent voiding after catheter removal. At final follow-up, 51 patients (83.6%) maintained unobstructed voiding without need for re-intervention. These results are encouraging for this complex patient cohort.

The staged buried oral mucosal strip urethroplasty utilizes oral mucosa as graft material and employs a buried inlay strategy rather than direct tubularization, potentially facilitating low-tension reconstruction in this patient population. In our case series, we selected

patients with long-segment strictures (>3 cm intraoperatively) post-hypospadias repair. While thoroughly excising scars, we preserved the normal urethral plate as much as possible. Depending on the situation, the graft was inlaid medially or laterally onto the residual urethral plate. During stage two, the integrated plate was buried together to form the neourethra, adhering to the principle of maximizing the use of residual normal tissue. Patients proceeded to stage two after 3–4 months, timed

**Supplementary Table 2 - Subgroup Analysis by Use of Auxiliary Mucosal Graft.**

| Indicators                                      | Number of auxiliary mucosal (n=25) | Number of no-auxiliary mucosal (n=36) | P value |
|-------------------------------------------------|------------------------------------|---------------------------------------|---------|
| <b>Baseline characteristics</b>                 |                                    |                                       |         |
| Mean age (years)                                | 27.1 ± 7.1                         | 30.6 ± 10.1                           | 0.141   |
| Mean preoperative stricture duration (months)   | 26.9 ± 12.5                        | 20.2 ± 10.1                           | 0.030   |
| Mean number of previous surgeries               | 2.5 ± 1.4                          | 2.1 ± 0.8                             | 0.198   |
| Mean intraoperative stricture length (cm)       | 4.7 ± 0.8                          | 4.5 ± 0.6                             | 0.392   |
| <b>Surgery-related data</b>                     |                                    |                                       |         |
| Mean duration of first-stage surgery (minutes)  | 71.5 ± 10.8                        | 73.4 ± 14.2                           | 0.547   |
| Mean duration of second-stage surgery (minutes) | 81.0 ± 23.2                        | 75.2 ± 21.5                           | 0.320   |
| <b>Follow-up results</b>                        |                                    |                                       |         |
| Surgical success rate at final follow-up, n (%) | 21 (84.0%)                         | 30 (83.3%)                            | 0.935   |
| Mean Qmax at 1 year postoperatively (mL/s)      | 17.7 ± 4.9                         | 19.2 ± 2.5                            | 0.158   |
| Urethral meatus above the coronal sulcus, n (%) | 22 (88.0%)                         | 33 (91.8%)                            | 0.686   |
| <b>Patient-reported outcome</b>                 |                                    |                                       |         |
| Preoperative USS-PROM score                     | 21.1 ± 1.8                         | 20.7 ± 2.1                            | 0.403   |
| Postoperative 1-year USS-PROM score             | 6.8 ± 2.7                          | 6.4 ± 2.1                             | 0.501   |
| Preoperative QoL-PROM score                     | 45.3 ± 6.1                         | 47.1 ± 7.0                            | 0.282   |
| Postoperative 1-year QoL-PROM score             | 85.3 ± 9.7                         | 88.9 ± 8.2                            | 0.132   |
| <b>Preoperative IIEF-5 score</b>                |                                    |                                       |         |
| Postoperative 1-year IIEF-5 score               | 21.0 ± 1.7                         | 20.9 ± 2.2                            | 0.845   |
| Satisfaction with postoperative appearance      | 21.5 ± 1.8                         | 21.6 ± 2.1                            | 0.807   |
|                                                 | 24 (96.0%)                         | 33 (91.6%)                            | 0.640   |

USS-PROM = Urethral Stricture Symptom Score-Patient Reported Outcome Measure; QoL-PROM = Quality of Life-Patient Reported Outcome Measure; IIEF-5 = International Index of Erectile Function-5. Continuous variables are expressed as mean ± standard deviation; categorical variables are presented as number (percentage).

based on the condition of the urethral plate. If healing was slightly delayed, e.g., with mild inflammatory edema, the interval to stage two could be appropriately extended.

The staged approach allows the oral mucosal graft to integrate under stable vascular conditions before incorporation into the neourethra (23). During stage two, the well-fixed and healed neourethral plate can be further manipulated, with additional mucosal harvest for augmentation if necessary. For example, in this study, appropriate methods for external meatal reconstruction were selected based on individual circumstances, including 21 (34.4%) receiving additional dorsal oral mucosal inlay and 4 (6.6%) receiving additional ventral oral mucosal inlay, aiming to achieve a spacious, distal meatus intraoperatively. At final follow-up, 54 patients (88.5%) maintained a meatus above the coronal sulcus, and 57 patients (93.4%) were satisfied with the postoperative appearance.

Certainly, for LUSPH patients with complex local tissue conditions, the key to the buried technique lies in dissecting the correct planes of the subcutaneous fascia. Over-dissection damaging the tunica albuginea must be avoided, while dissection that is too superficial risks insufficient tissue, increasing the chance of urethrocutaneous fistula.

Future directions, with accumulating cases and advances in regenerative medicine, may see further refinements of the buried technique (24). For instance, selecting between staged or single-stage buried urethroplasty based on individual LUSPH patient characteristics, or utilizing decellularized scaffolds combined with stem cell technology to minimize donor site morbidity. At present, we advocate its core value: unleashing biological potential through the buried structural design to better achieve repair of strictures following hypospadias repair.

This study has several limitations that should be acknowledged. First, its single-center, retrospective design and the absence of a control group prevent a direct comparative assessment against other established staged repair techniques. Second, the inherent heterogeneity of the cohort, in terms of prior surgical history and stricture characteristics, along with the fact that all procedures were performed by specialized surgeons at a tertiary referral center, may introduce selection and

surgeon bias, limiting the generalizability of the findings to broader clinical settings. Third, while the mean follow-up of 29.4 months is sufficient for evaluating intermediate-term outcomes, it remains inadequate for assessing long-term durability, which is a critical concern in a population prone to late fibrosis. Finally, the evaluation of cosmetic outcomes was based on subjective patient reports rather than standardized, objective measures, which may introduce assessment bias.

## CONCLUSIONS

In this single-center cohort study, staged buried oral mucosal strip urethroplasty demonstrates promising mid-term functional and meatal outcomes as a reconstructive option for LUSPH patients. Future controlled, multi-center studies are needed to validate its long-term durability and comparative effectiveness.

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## ETHICAL APPROVAL

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Shanghai Sixth People's Hospital. (Approval No.: 2025-KY-494K).

## CONFLICT OF INTEREST

None declared.

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# cN2–cN3 Penile Squamous Cell Carcinoma: Patient Selection, Treatment Delivery, and Real-World Challenges

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## COMMENT

Regional lymph node metastasis remains the most important determinant of survival in penile squamous cell carcinoma (PSCC) (1). While outcomes for localized disease are generally favorable when appropriately managed, the development of clinically advanced nodal disease dramatically alters the natural history of PSCC. Patients presenting with cN2–cN3 involvement face high rates of recurrence, distant progression, and cancer-specific mortality, making this subgroup the greatest therapeutic challenge in contemporary penile cancer management and the leading cause of penile cancer-related death.

Historically, surgery represented the cornerstone of treatment for node-positive disease, based on the principle that complete surgical eradication of regional metastases could provide durable oncological control. However, clinical experience progressively demonstrated the limitations of surgery alone in patients with bulky, bilateral, fixed, or extranodal nodal metastases (2, 3). Even when technically feasible, surgical treatment was frequently followed by early recurrence and poor long-term survival in patients with advanced nodal disease, suggesting that locoregional control alone was insufficient for a subgroup of patients with biologically aggressive disease and a high likelihood of occult systemic dissemination.

These observations provided the rationale for introducing systemic therapy earlier in the treatment pathway. By addressing potential micro-metastatic disease, reducing tumor burden, and improving the likelihood of complete surgical resection, neoadjuvant chemotherapy (NAC) emerged as an attractive strategy for patients with locally advanced node-positive PSCC. The landmark phase II study by Pagliaro et al. demonstrated an objective response rate of approximately 50% with neoadjuvant TIP, establishing the foundation for contemporary treatment recommendations (4). The concept was further supported by experience with other squamous cell carcinomas, in which multimodal approaches had demonstrated advantages over local treatment alone in selected high-risk populations.

Over the last decade, NAC has progressively become the preferred treatment approach for patients with cN2–cN3 disease (1, 4). Contemporary evidence suggests that approximately half of patients achieve an objective response to neoadjuvant treatment, enabling potentially curative surgical consolidation (4, 5). In a recent international, multi-institutional study involving 209 patients with locally advanced, node-positive PSCC, the objective response rate was 57.2%, with a

pathologic complete response rate of 24.8% in the lymph nodes, and 97% of patients completed the planned consolidative lymphadenectomy (5). As a result, contemporary international guidelines recommend platinum-based NAC followed by lymph node dissection in appropriately selected patients (1). Yet an important paradox remains despite its widespread acceptance, the evidence supporting NAC in PSCC is largely derived from small, non-randomized studies, leaving many clinically relevant questions unanswered (6).

The contemporary debate is no longer whether NAC should be considered for patients with cN2–cN3 PSCC. Current evidence and guideline recommendations have largely established its role in appropriately selected individuals (1, 4). Instead, the more relevant question is which patients are most likely to benefit from this strategy. Although treatment algorithms frequently group cN2 and cN3 disease into a single therapeutic category, current guidelines distinguish between patients with pelvic lymph node involvement or extensive inguinal disease, for whom NAC is preferred, and selected patients with bulky mobile bilateral inguinal disease, in whom NAC may be considered as an alternative to upfront surgery (1). Differences in nodal burden, laterality, fixation, extranodal extension, performance status, and comorbidities may substantially influence treatment tolerance, response, and ultimately long-term oncological outcomes.

Disease burden is likely one of the most important yet insufficiently explored determinants of NAC benefit (1). Patients with limited bilateral nodal involvement may differ substantially from those presenting with bulky, fixed, or clinically extranodal disease, despite being broadly classified within the same treatment category. This distinction may be particularly relevant in cN2 disease, where neoadjuvant chemotherapy remains an alternative rather than a preferred strategy, in contrast to patients with pelvic nodal involvement or extensive inguinal disease for whom NAC is generally favored (1). Although current evidence does not permit robust stratification of outcomes by specific patterns of nodal presentation, it is reasonable to assume that the biological behavior,

probability of response, and feasibility of subsequent surgical consolidation are not uniform across this spectrum. Recognizing this heterogeneity may be essential to refining treatment decisions and designing future studies in locally advanced PSCC.

Patient-related factors deserve equal consideration when evaluating candidates for NAC. Beyond disease burden, the ability to tolerate and complete cisplatin-based treatment may substantially influence outcomes in patients with cN2–cN3 PSCC. Renal dysfunction, impaired performance status, neuropathy, and hearing loss may preclude the use of TIP, the preferred neoadjuvant regimen recommended by contemporary guidelines (1). For these patients, the decision to pursue alternative chemotherapy regimens or proceed directly to surgery remains poorly supported by high-quality evidence (7). Consequently, treatment selection should extend beyond anatomical staging to include a broader assessment of the patient's physiological reserve and capacity to successfully complete multimodal therapy.

An equally important and often underappreciated issue is treatment delivery. Discussions surrounding NAC in PSCC frequently focus on regimen selection and response rates, whereas considerably less attention has been paid to whether treatment is delivered as intended. Dose reductions, treatment delays, cycle omissions, and premature discontinuation may compromise the opportunity for timely surgical consolidation, particularly in patients with advanced nodal disease and limited physiological reserve. Consequently, the effectiveness of NAC may depend not only on the regimen prescribed but also on the ability to successfully deliver multimodal treatment according to plan.

Although rarely reported in penile cancer studies, treatment delivery metrics may represent important determinants of oncological outcomes. Delays in treatment initiation, reduced dose intensity, unplanned hospitalizations, and failure to complete the intended number of cycles have the potential to compromise both systemic disease control and the opportunity for timely surgical consolidation. In a recent international multi-institutional study, 97% of patients successfully

completed the planned consolidative lymphadenectomy following NAC, suggesting that the effectiveness of multimodal treatment depends not only on treatment response but also on the successful delivery of the entire therapeutic strategy (5). This issue may be particularly relevant in PSCC, where the therapeutic window between potentially curable locoregional disease and irreversible progression can be narrow. Future investigations should move beyond conventional response endpoints and incorporate measures of treatment delivery to better understand the real-world effectiveness of NAC.

Importantly, NAC should not be viewed as a substitute for surgery. Rather, its primary purpose is to facilitate definitive surgical management by reducing tumor burden, increasing resectability, and potentially improving long-term disease control. The best oncological outcomes reported in the literature have consistently been observed among patients who respond to systemic therapy and subsequently undergo consolidative lymph node dissection (4, 5). In the largest contemporary real-world cohort, patients who achieved an objective response to NAC had a markedly longer median overall survival than non-responders (73.0 vs. 17.0 months,  $P < 0.01$ ) (5). This observation reinforces the notion that surgery remains the cornerstone of curative-intent treatment, with NAC serving as an adjunct to optimize patient selection and enhance the effectiveness of locoregional therapy.

Response assessment after NAC represents another area of uncertainty in PSCC management. While patients achieving a marked clinical response are generally considered ideal candidates for consolidative surgery, the optimal approach for those with stable disease or incomplete responses remains less clear. In the absence of robust evidence, treatment decisions frequently rely on multidisciplinary discussion and individualized clinical judgment. Importantly, stable disease should not necessarily preclude surgical intervention, particularly when resection remains technically feasible and overt disease progression has been avoided. This pragmatic approach acknowledges both the biological heterogeneity of PSCC and the limitations of the current evidence base.

The future of NAC in PSCC will likely depend on moving beyond purely anatomical staging toward a more comprehensive understanding of both tumor biology and host factors. Emerging biomarkers, including HPV status, p16 expression, and tumor-infiltrating lymphocytes, may contribute to improved patient stratification and prediction of treatment response (8). At the same time, systemic factors such as sarcopenia and other body composition parameters have gained increasing attention as potential indicators of physiological reserve and treatment tolerance (9). Despite their potential clinical relevance, none of these factors have yet been incorporated into routine decision-making for patients undergoing NAC, highlighting an important opportunity for future investigation. Likewise, patient-reported outcomes and quality-of-life measures warrant greater consideration, particularly in a disease in which aggressive multimodal therapy may carry substantial physical and psychosocial consequences (10). Together, these dimensions may help define a more individualized approach to multimodal treatment in the years ahead.

Real-world implementation of NAC presents additional challenges that are often underrepresented in the available literature. In many regions where PSCC remains relatively prevalent, barriers such as delayed diagnosis, limited access to specialized multidisciplinary care, restricted availability of systemic therapy, and treatment interruptions may substantially influence outcomes. Under these circumstances, treatment delivery itself may become a major determinant of success, potentially influencing outcomes as much as the intrinsic efficacy of the selected regimen. This perspective highlights the importance of developing treatment strategies that are not only evidence-based but also adaptable to diverse healthcare environments.

Future research efforts should prioritize clinically meaningful questions that extend beyond conventional oncological endpoints. Despite an expanding literature, contemporary evidence remains largely derived from retrospective cohorts and small prospective studies, with no completed randomized trials available to guide practice (11). Collaborative prospective studies are needed to better define which patients derive the greatest benefit

from NAC, establish standardized treatment delivery metrics, and clarify the optimal integration of systemic therapy with surgery. Equally important, the incorporation of biological markers, body composition analyses, and patient-reported outcomes may foster a more comprehensive understanding of treatment effectiveness (8, 9). Ultimately, progress in this field will depend not only on the development of novel therapies but also on generating evidence that reflects the complexity of real-world clinical practice and the priorities of patients living with PSCC.

Immunotherapy is emerging as a promising therapeutic strategy in advanced PSCC and may further reshape the management of patients with cN2–cN3 disease. Early-phase studies have demonstrated encouraging activity with both single-agent immune checkpoint inhibitors and chemoimmunotherapy combinations, although the available evidence remains limited by small sample sizes and the absence of randomized trials (12, 13). The HERCULES study reported an objective response rate of 39.4% with pembrolizumab combined with platinum-based chemotherapy in patients with advanced PSCC, supporting the rationale for further investigation of immune-based approaches (12). However, important questions remain regarding optimal patient selection, treatment sequencing, biomarker integration, and access to these therapies in regions where penile cancer is most prevalent. As with NAC, the successful incorporation of immunotherapy into clinical practice will depend not only on efficacy but also on the ability to deliver these treatments within real-world healthcare environments.

In conclusion, the management of cN2–cN3 PSCC has evolved considerably over the past decade, with multimodal treatment strategies increasingly shaping contemporary practice. However, important uncertainties remain regarding patient selection, treatment delivery, response assessment, and the incorporation of emerging biological and patient-centered factors into clinical decision-making. The expanding therapeutic landscape, including the emergence of immunotherapy-based approaches, further underscores the need for evidence to guide increasingly complex treatment decisions. Addressing these challenges will require col-

laborative efforts to generate data that are both scientifically rigorous and applicable to real-world practice. Ultimately, the next frontier in the management of cN2–cN3 PSCC lies not simply in developing new therapies, but in ensuring that the right patient receives the right multimodal strategy at the right time.

## CONFLICT OF INTEREST

None declared.

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### Data Availability

All data generated or analysed during this study are included in the published article.





# Radiation Safety Practices and Occupational Exposure Among Brazilian Urologists: A National Survey

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on behalf of the Sociedade Brasileira de Urologia (SBU)

## COMMENTS

Ionizing radiation is an integral component of contemporary urological practice (1). In daily routine, fluoroscopy is frequently used to support diagnostic procedures such as retrograde pyelography, voiding cystourethrography, and videourodynamics, as well as a wide range of therapeutic interventions (2). In addition to endourology and stone disease management, including ureteral stent placement, ureteroscopy, and percutaneous nephrolithotomy, fluoroscopic guidance may also be required in other settings, including sacral neuromodulation lead implantation and selected reconstructive or functional procedures (3).

Although indispensable for procedural guidance and decision-making, recurrent occupational exposure raises concerns about radiological safety in urology (1, 4). Occupational risk is primarily determined by cumulative radiation dose, exposure geometry, and the consistency of protective measures applied during fluoroscopy-guided procedures (2, 3). Interventional specialties are consistently among the most exposed groups in healthcare, and in urology the frequency of fluoroscopy-guided procedures across various clinical settings may translate into substantial cumulative exposure over years of practice (2, 4).

Core protection principles are grounded in the ALARA concept ("As Low As Reasonably Achievable") and aim to minimize radiation exposure by reducing fluoroscopy time, maximizing distance from the source, and optimizing shielding while maintaining adequate image quality (1, 5). In clinical practice, these principles translate into consistent use of personal protective equipment (PPE), including lead aprons, thyroid shields, gloves, and leaded eyewear, along with individual dosimetry and institutional processes to ensure equipment integrity and exposure monitoring

(1, 2). However, real-world adherence to these measures remains heterogeneous and may be influenced by availability of protective equipment, workflow constraints, local safety culture, and the degree of institutional oversight (1, 6).

In Brazil, available data on occupational radiation exposure and radiation safety among urologists are still limited in scope, with previous nationwide efforts primarily focused on general behaviors and use of protective and monitoring equipment (6). Procedure-specific PPE use, availability of protective equipment in different practice settings, dosimeter adoption, and institutional monitoring processes have not been comprehensively evaluated, limiting the ability of institutions and professional societies to prioritize and implement targeted interventions.

Recent contributions from Brazilian urological research have also emphasized the importance of understanding real-world practice patterns and identifying gaps between recommendations and clinical practice across different domains of urology (7–9).

Therefore, we conducted a national, cross-sectional survey of Brazilian urologists to characterize self-reported sources and intensity of ionizing radiation exposure, PPE use across common fluoroscopy-guided procedures, availability of protective equipment, dosimeter use, institutional monitoring practices, perceived health consequences, and expectations regarding the role of the Brazilian Society of Urology (SBU) in promoting radiation safety. By defining current practices and gaps, this study aims to inform pragmatic, urology-centered strategies to strengthen radiation safety in Brazil and provide insights that may be applicable to similar practice settings worldwide.

## MATERIALS AND METHODS

### Study design and survey development

This study was conducted as a national, cross-sectional electronic survey designed to evaluate exposure to ionizing radiation, use of protective measures, and knowledge regarding radiation safety among Brazilian urologists. The survey was developed by urologists with

expertise in different subspecialties, aiming to identify the most relevant aspects of radiation exposure and radioprotection in routine urological practice, as well as institutional support and safety policies.

The initial draft of the questionnaire was reviewed by a panel of experienced urologists representing functional urology and voiding dysfunction, benign prostatic hyperplasia, general urology, uro-oncology, endourology, andrology and sexual medicine, and pediatric urology. This multidisciplinary review aimed to ensure content relevance, clarity of wording, and clinical applicability of the proposed items. Prior to nationwide dissemination, the survey instrument underwent pilot testing among 12 practicing urologists to assess comprehensibility, estimated completion time, and technical functionality of the electronic platform. Minor revisions were made based on feedback obtained during this phase.

The questionnaire consisted predominantly of closed-ended, multiple-choice questions, with selected items allowing open-ended responses. The survey included sections addressing sociodemographic characteristics and professional practice patterns; sources and frequency of radiation exposure; use of PPE during residency and in current practice; availability of protective equipment in healthcare institutions; use of dosimeters and institutional control of radiation exposure; knowledge of radiation-related health risks and self-reported complications potentially related to radiation exposure; and perceptions regarding the role of the Brazilian Society of Urology in radiation safety education. The full questionnaire is available in Figure-1.

### Participants and survey distribution

All urologists registered with the Brazilian Society of Urology were eligible to participate in the study. Participation was voluntary and anonymous. The survey was distributed electronically through official SBU communication channels, including e-mail and instant messaging platforms.

The invitation was sent to approximately 3,000 eligible urologists registered with the Brazilian Society of Urology. The survey was open from July 9, 2025, to

Figure 1 - Survey questionnaire.

| <b>1. CONSENT</b><br><input type="checkbox"/> I agree to participate in this research and accept the terms described above.<br><input type="checkbox"/> I do not agree to participate in this research.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <b>8. HOW MANY YEARS HAVE PASSED SINCE COMPLETION OF YOUR UROLOGY RESIDENCY?</b><br>_____ years (open-ended response)*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <b>15. DO YOU USE A PERSONAL DOSIMETER?</b><br><input type="checkbox"/> Never<br><input type="checkbox"/> Less than half of procedures<br><input type="checkbox"/> More than half of procedures<br><input type="checkbox"/> Always                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                        |                                      |                        |                                      |                               |             |                       |                       |                       |                          |                 |                       |                       |                       |                                          |                |                       |                       |                       |                            |  |  |  |  |                             |  |  |  |  |                                     |  |  |  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| <b>2. GENDER</b><br><input type="checkbox"/> Male <input type="checkbox"/> Female <input type="checkbox"/> Prefer not to answer                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | <b>9. WHAT PERCENTAGE OF YOUR UROLOGICAL PRACTICE IS PERFORMED IN: (enter numbers without the % symbol)</b><br>Private practice: _____<br>Public sector: _____<br>Academic/university hospital: _____<br>Non-academic hospital: _____                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <b>16. AVAILABILITY OF PPE IN YOUR MAIN WORKPLACE:</b><br><table border="1"> <thead> <tr> <th></th> <th>Available in 100% of procedures</th> <th>Available in 50-99%</th> <th>Available in &lt;50%</th> <th>Not Available</th> </tr> </thead> <tbody> <tr> <td>Lead aprons</td> <td><input type="radio"/></td> <td><input type="radio"/></td> <td><input type="radio"/></td> <td><input type="radio"/></td> </tr> <tr> <td>Thyroid shields</td> <td><input type="radio"/></td> <td><input type="radio"/></td> <td><input type="radio"/></td> <td><input type="radio"/></td> </tr> <tr> <td>Leaded eyewear</td> <td><input type="radio"/></td> <td><input type="radio"/></td> <td><input type="radio"/></td> <td><input type="radio"/></td> </tr> </tbody> </table> |                        | Available in 100% of procedures      | Available in 50-99%    | Available in <50%                    | Not Available                 | Lead aprons | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/>    | Thyroid shields | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/>                    | Leaded eyewear | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/>      |  |  |  |  |                             |  |  |  |  |                                     |  |  |  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| <b>3. DURING PREGNANCY (OR SUSPECTED PREGNANCY), HOW DID/DO YOU MANAGE YOUR PARTICIPATION IN PROCEDURES INVOLVING IONIZING RADIATION?</b><br><input type="checkbox"/> I have never been pregnant<br><input type="checkbox"/> I avoided all procedures involving radiation<br><input type="checkbox"/> I avoided only specific procedures<br><input type="checkbox"/> I avoided only during the first trimester<br><input type="checkbox"/> I did not avoid and participated normally<br><input type="checkbox"/> I participated normally with strict use of PPE and addominal protection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <b>10. WHAT IS YOUR PREDOMINANT SUBSPECIALTY (≥50% OF YOUR PRACTICE)?</b><br><input type="checkbox"/> General urology / no predominant subspecialty<br><input type="checkbox"/> Uro-oncology<br><input type="checkbox"/> Pediatric urology<br><input type="checkbox"/> Voiding dysfunction / female urology / reconstructive urology<br><input type="checkbox"/> Endourology / stone disease<br><input type="checkbox"/> Renal transplantation<br><input type="checkbox"/> Andrology / sexual medicine<br><input type="checkbox"/> Other (specify): _____                                                                                                                                                                                                                                                                                                                                    | <b>17. IS THERE INSPECTION /CONTROL OF PPE FUNCTIONALITY IN YOUR WORKPLACE?</b><br><input type="checkbox"/> No control <input type="checkbox"/> Semiannual <input type="checkbox"/> Do not know<br><input type="checkbox"/> Annual <input type="checkbox"/> Quarterly                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                        |                                      |                        |                                      |                               |             |                       |                       |                       |                          |                 |                       |                       |                       |                                          |                |                       |                       |                       |                            |  |  |  |  |                             |  |  |  |  |                                     |  |  |  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>4. HAVE YOU RECEIVED FORMAL GUIDANCE REGARDING THE RISKS OF IONIZING RADIATION FOR REPRODUCTIVE AND GESTATIONAL HEALTH?</b><br><input type="checkbox"/> Yes, during medical residency<br><input type="checkbox"/> Yes, in professional practice (institution/service)<br><input type="checkbox"/> Yes, informally (colleagues or supervisors)<br><input type="checkbox"/> No, I have not received any guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>11. REGARDING YOUR EXPOSURE TO IONIZING RADIATION (X-RAYS), WHAT PERCENTAGE DO YOU ESTIMATE COMES FROM: (enter numbers without the % symbol)</b><br>Diagnostic procedures: _____<br>Surgical procedures: _____<br>Other activities: _____                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <b>18. HOW OFTEN IS YOUR RADIATION EXPOSURE MONITORED?</b><br><input type="checkbox"/> No monitoring<br><input type="checkbox"/> Monitoring without defined periodicity<br><input type="checkbox"/> Annual<br><input type="checkbox"/> Semiannual<br><input type="checkbox"/> Quarterly<br><input type="checkbox"/> Other (specify): _____<br><input type="checkbox"/> Do not know                                                                                                                                                                                                                                                                                                                                                                                 |                        |                                      |                        |                                      |                               |             |                       |                       |                       |                          |                 |                       |                       |                       |                                          |                |                       |                       |                       |                            |  |  |  |  |                             |  |  |  |  |                                     |  |  |  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>5. ARE THERE INSTITUTIONAL POLICIES REGARDING RESTRICTION OR REMOVAL OF PREGNANT PROFESSIONALS FROM ROOMS WITH IONIZING RADIATION?</b><br><input type="checkbox"/> Yes, there are formal institutional guidelines<br><input type="checkbox"/> There is an informal consensus<br><input type="checkbox"/> It depends on the leadership or service<br><input type="checkbox"/> There are no policies or guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>12. ON AVERAGE, IN HOW MANY FLUOROSCOPY-ASSISTED SURGERIES DO YOU PERFORM PER MONTH?</b><br>_____ surgeries (open-ended response)*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <b>19. DO YOU THINK MONITORING UROLOGISTS RADIATION EXPOSURE IS IMPORTANT?</b><br><input type="checkbox"/> Strongly agree <input type="checkbox"/> Partially disagree <input type="checkbox"/> Do not know<br><input type="checkbox"/> Partially agree <input type="checkbox"/> Strongly disagree <input type="checkbox"/> Do not know                                                                                                                                                                                                                                                                                                                                                                                                                             |                        |                                      |                        |                                      |                               |             |                       |                       |                       |                          |                 |                       |                       |                       |                                          |                |                       |                       |                       |                            |  |  |  |  |                             |  |  |  |  |                                     |  |  |  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>6. WHAT IS YOUR AGE?</b><br>_____ years (open-ended response)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>13. IN PROCEDURES INVOLVING X-RAYS, YOU USUALLY:</b><br><input type="checkbox"/> Stay at a distance greater than 3 meters from the radiation source<br><input type="checkbox"/> Stay at a distance greater than 2 meters<br><input type="checkbox"/> Stay between 1 and 2 meters<br><input type="checkbox"/> Stay at a distance less than 1 meter<br><input type="checkbox"/> I am not exposed to ionizing radiation (X-rays)                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <b>20. HAVE YOU HAD ANY OF THE FOLLOWING CONDITIONS POTENTIALLY ASSOCIATED WITH RADIATION EXPOSURE? (Check all that apply)</b><br><input type="checkbox"/> Thyroid cancer <input type="checkbox"/> Lymphoma<br><input type="checkbox"/> Infertility <input type="checkbox"/> Cataract<br><input type="checkbox"/> Child with congenital malformation <input type="checkbox"/> None<br><input type="checkbox"/> Leukemia or myelodysplastic disorders <input type="checkbox"/> Prefer not to answer<br><input type="checkbox"/> Skin cancer <input type="checkbox"/> Other (specify): _____                                                                                                                                                                         |                        |                                      |                        |                                      |                               |             |                       |                       |                       |                          |                 |                       |                       |                       |                                          |                |                       |                       |                       |                            |  |  |  |  |                             |  |  |  |  |                                     |  |  |  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>7. IN WHICH STATE DO YOU PRIMARILY PRACTICE? (Check one)</b><br><input type="checkbox"/> Acre (AC) <input type="checkbox"/> Maranhão (MA) <input type="checkbox"/> Rio de Janeiro (RJ)<br><input type="checkbox"/> Alagoas (AL) <input type="checkbox"/> Mato Grosso (MT) <input type="checkbox"/> Rio Grande do Norte (RN)<br><input type="checkbox"/> Amapá (AP) <input type="checkbox"/> Mato Grosso do Sul <input type="checkbox"/> Mato Grosso do Sul<br><input type="checkbox"/> Amazonas (AM) <input type="checkbox"/> Minas Gerais (MG) <input type="checkbox"/> Rondônia (RO)<br><input type="checkbox"/> Bahia (BA) <input type="checkbox"/> Pará (PA) <input type="checkbox"/> Santa Catarina (SC)<br><input type="checkbox"/> Ceará (CE) <input type="checkbox"/> Paraíba (PB) <input type="checkbox"/> São Paulo (SP)<br><input type="checkbox"/> Distrito Federal (DF) <input type="checkbox"/> Paraná (PR) <input type="checkbox"/> Sergipe (SE)<br><input type="checkbox"/> Espírito Santo (ES) <input type="checkbox"/> Pernambuco (PE) <input type="checkbox"/> Tocantins (TO)<br><input type="checkbox"/> Goiás (GO) <input type="checkbox"/> Piauí (PI) <input type="checkbox"/> Other (specify): _____ | <b>14. PLEASE INDICATE THE PERCENTAGE (0-100%) OF PPE USE IN EACH PROCEDURE:</b><br><table border="1"> <thead> <tr> <th>PROCEDURE</th> <th>Lead apron (0-100)</th> <th>Thyroid shield (0-100)</th> <th>Leaded eyewear (0-100)</th> <th>Radiation-attenuating gloves (0-100)</th> </tr> </thead> <tbody> <tr> <td>Retrograde ureteropyelography</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Double J stent placement</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Distal ureterolithotripsy (small stones)</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Complex ureterolithotripsy</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Flexible ureterolithotripsy</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Percutaneous nephrolithotomy (PCNL)</td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table> | PROCEDURE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Lead apron (0-100)     | Thyroid shield (0-100)               | Leaded eyewear (0-100) | Radiation-attenuating gloves (0-100) | Retrograde ureteropyelography |             |                       |                       |                       | Double J stent placement |                 |                       |                       |                       | Distal ureterolithotripsy (small stones) |                |                       |                       |                       | Complex ureterolithotripsy |  |  |  |  | Flexible ureterolithotripsy |  |  |  |  | Percutaneous nephrolithotomy (PCNL) |  |  |  |  | <b>21. DO YOU BELIEVE RADIATION EXPOSURE CONTRIBUTED TO THIS CONDITION?</b><br><input type="checkbox"/> Highly likely <input type="checkbox"/> Moderately likely <input type="checkbox"/> Unlikely<br><input type="checkbox"/> No influence <input type="checkbox"/> Not applicable<br><b>22. WHAT ROLE SHOULD THE BRAZILIAN SOCIETY OF UROLOGY (SBU) PLAY REGARDING RADIATION EXPOSURE? (multiple answers allowed)</b><br><input type="checkbox"/> Educational campaigns on risks and good practices<br><input type="checkbox"/> Advocacy with medical entities to ensure PPE availability<br><input type="checkbox"/> Advocacy with hospitals and health institutions to ensure PPE availability<br><input type="checkbox"/> All of the above<br><input type="checkbox"/> The SBU has no role in this issue |
| PROCEDURE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Lead apron (0-100)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Thyroid shield (0-100)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Leaded eyewear (0-100) | Radiation-attenuating gloves (0-100) |                        |                                      |                               |             |                       |                       |                       |                          |                 |                       |                       |                       |                                          |                |                       |                       |                       |                            |  |  |  |  |                             |  |  |  |  |                                     |  |  |  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Retrograde ureteropyelography                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                        |                                      |                        |                                      |                               |             |                       |                       |                       |                          |                 |                       |                       |                       |                                          |                |                       |                       |                       |                            |  |  |  |  |                             |  |  |  |  |                                     |  |  |  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Double J stent placement                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                        |                                      |                        |                                      |                               |             |                       |                       |                       |                          |                 |                       |                       |                       |                                          |                |                       |                       |                       |                            |  |  |  |  |                             |  |  |  |  |                                     |  |  |  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Distal ureterolithotripsy (small stones)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                        |                                      |                        |                                      |                               |             |                       |                       |                       |                          |                 |                       |                       |                       |                                          |                |                       |                       |                       |                            |  |  |  |  |                             |  |  |  |  |                                     |  |  |  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Complex ureterolithotripsy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                        |                                      |                        |                                      |                               |             |                       |                       |                       |                          |                 |                       |                       |                       |                                          |                |                       |                       |                       |                            |  |  |  |  |                             |  |  |  |  |                                     |  |  |  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Flexible ureterolithotripsy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                        |                                      |                        |                                      |                               |             |                       |                       |                       |                          |                 |                       |                       |                       |                                          |                |                       |                       |                       |                            |  |  |  |  |                             |  |  |  |  |                                     |  |  |  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Percutaneous nephrolithotomy (PCNL)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                        |                                      |                        |                                      |                               |             |                       |                       |                       |                          |                 |                       |                       |                       |                                          |                |                       |                       |                       |                            |  |  |  |  |                             |  |  |  |  |                                     |  |  |  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

The questionnaire included items on demographics, professional practice, radiation exposure, use and availability of personal protective equipment, dosimetry, institutional monitoring, and perceptions regarding radiation safety.

Open-ended responses were collected for selected items.

was conducted in accordance with national regulations and international ethical standards for research involving human participants.

### Variables and outcomes

Collected variables included age, sex, geographic region of practice, years since completion of residency, type of practice setting (private, public, or mixed), and predominant urological subspecialty. Radiation-related variables included self-reported sources of radiation exposure, frequency of fluoroscopy use, distance from the radiation source during procedures, use of PPE, availability of protective equipment in institutions, use of dosimeters, and existence of institutional monitoring of radiation exposure and equipment safety.

Knowledge-related variables assessed awareness of potential adverse health effects of ionizing radiation, while perception-related variables explored attitudes toward radiation safety and the perceived role of professional societies in promoting radioprotection.

### Statistical Analysis

Quantitative variables were described using measures of central tendency (means or medians) and dispersion (standard deviations or interquartile ranges), as appropriate. Qualitative variables were expressed as absolute numbers and proportions. Comparisons between groups were performed using Student's t test or analysis of variance (ANOVA) for continuous variables, and the chi-square test or Fisher's exact test for categorical variables.

Logistic regression analyses were conducted to explore factors associated with key outcomes related to radiation safety practices and protective behaviors. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated. Analyses were based on complete cases, with participants excluded from specific analyses when data for the variables of interest were missing.

All statistical tests were two-sided, and a p value < 0.05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism, version 10.0.01 (GraphPad Software, San Diego, CA, USA).

## RESULTS

A total of 325 urologists (83.0% men) completed the survey, representing 10.8% of Brazilian urologists who received the survey link. The median age was 46 years [38–54]. Sociodemographic and practice characteristics are summarized in Table-1. Denominators vary across analyses due to missing responses.

Among respondents, 42.1% completed their urology residency more than 20 years ago, 24.5% completed it 10-20 years ago, and 33.4% completed it less than 10 years ago. Most respondents (95.1%) reported working at least part-time in private practice, while 197 (60.6%) reported some degree of involvement in the public sector. Additionally, 112 (34.5%) worked in university-affiliated hospitals, 221 (68.0%) in private hospitals, and 94 (28.9%) in multidisciplinary clinics.

The distribution according to predominant urological subspecialty is presented in Table-1, most participants reported general urology (35.1%), followed by endourology/stone disease (23.7%) and uro-oncology (19.4%), while 11.1% reported a predominant practice in voiding dysfunction/female urology.

### Exposure profile

In terms of self-reported exposure sources, most participants attributed the majority of their ionizing radiation exposure to surgical procedures (median 95% [80-100]), whereas a smaller proportion was attributed to diagnostic examinations (median 5% [0-10]) and other activities (median 0% [0-0]). Participants reported performing a median of 10 fluoroscopy-assisted surgeries per month [5-15]. Fluoroscopy workload differed significantly by predominant subspecialty ( $p < 0.001$ ), being highest among endourology/stone disease practitioners (median 15 [10-20.5]) compared with general urology (median 10 [6-15]), uro-oncology (median 6 [5-10]), and voiding dysfunction/female urology (median 6 [3-10]). During X-ray-guided examinations and procedures, most urologists reported standing at a distance <1 m (169/324, 52.2%) or 1-2 m (129/324, 39.8%) from the radiation source.

**Table 1 - Participants' demographic and practice patterns.**

|                                                    |             |
|----------------------------------------------------|-------------|
| Age (years)                                        | 46 [38–54]  |
| <b>Gender</b>                                      |             |
| Male                                               | 269 (83.0%) |
| Female                                             | 55 (17.0%)  |
| <b>Distribution by geographic Brazilian region</b> |             |
| Southeast                                          | 162 (50.0%) |
| South                                              | 58 (17.9%)  |
| Northeast                                          | 63 (19.4%)  |
| Central-West                                       | 26 (8.0%)   |
| North                                              | 15 (4.6%)   |
| <b>Time since residency completion</b>             |             |
| < 10 years                                         | 108 (33.4%) |
| 10–20 years                                        | 79 (24.5%)  |
| > 20 years                                         | 136 (42.1%) |
| <b>Workplace (admitted more than one option)</b>   |             |
| Some affiliation with private practice             | 309 (95.1%) |
| Some involvement in the public sector              | 197 (60.6%) |
| University-affiliated hospitals                    | 112 (34.5%) |
| Private hospitals                                  | 221 (68.0%) |
| Multidisciplinary clinics                          | 94 (28.9%)  |
| <b>Predominant urological subspecialty</b>         |             |
| General urology / no predominant subspecialty      | 114 (35.1%) |
| Endourology / stone disease                        | 77 (23.7%)  |
| Uro-oncology                                       | 63 (19.4%)  |
| Voiding dysfunction / female urology               | 36 (11.1%)  |
| Andrology / sexual medicine                        | 18 (5.5%)   |
| Pediatric urology                                  | 9 (2.8%)    |
| Renal transplantation                              | 5 (1.5%)    |
| Other                                              | 3 (0.9%)    |

Values are presented as n (%) unless otherwise indicated. Age is reported as median [interquartile range]. Workplace variables allowed multiple responses; therefore, percentages may exceed 100%. Denominators may vary across variables due to missing responses.



**Table 2 - Use of personal protective equipment (PPE) by procedure.**

| Procedure                                       | Lead apron, median [IQR] | Thyroid shield, median [IQR] | Leaded eyewear, median [IQR] | Radiation-attenuating gloves, median [IQR] |
|-------------------------------------------------|--------------------------|------------------------------|------------------------------|--------------------------------------------|
| <b>Retrograde ureteropyelography</b>            | 100 [100-100]            | 100 [0-100]                  | 0 [0-0]                      | 0 [0-0]                                    |
| <b>Double-J stent placement</b>                 | 100 [90-100]             | 90 [0-100]                   | 0 [0-0]                      | 0 [0-0]                                    |
| <b>Distal ureterolithotripsy (small stones)</b> | 100 [90-100]             | 90 [0-100]                   | 0 [0-0]                      | 0 [0-0]                                    |
| <b>Complex ureterolithotripsy</b>               | 100 [100-100]            | 100 [50-100]                 | 0 [0-0]                      | 0 [0-0]                                    |
| <b>Flexible ureterorenolithotripsy</b>          | 100 [100-100]            | 100 [50-100]                 | 0 [0-0]                      | 0 [0-0]                                    |
| <b>Percutaneous nephrolithotripsy</b>           | 100 [100-100]            | 100 [75-100]                 | 0 [0-0]                      | 0 [0-0]                                    |

Values represent the self-reported percentage of PPE use (0-100%) during each procedure and are presented as median [interquartile range]. PPE: personal protective equipment.

### Patterns of personal protective equipment (PPE)

The estimated use of PPE varied substantially according to the type of equipment and procedure (Table-2). Lead apron use was consistently high across all assessed procedures, with median values of 100% in all scenarios (IQR 90-100 or 100-100). Thyroid shield use was lower and more variable, with median use ranging from 90% [0-100] during double-J stent placement and distal ureterolithotripsy to 100% [50-100] in more complex endourological procedures and 100% [75-100] during percutaneous nephrolithotripsy. In contrast, leaded eyewear and radiation-attenuating gloves were rarely used in any of the evaluated procedures, with median use of 0% [0-0] throughout.

Thyroid shield use varied according to time since residency completion, with lower adherence among respondents who completed residency >20 years ago (Kruskal-Wallis  $p=0.014$ ; Spearman  $\rho=-0.175$ ,  $p=0.0015$ ). No significant association was observed for lead apron, leaded eyewear, or radiation-attenuating glove use (all  $p>0.20$ ).

### Monitoring practices and institutional policies for radiation protection

Regarding individual dose monitoring, 57/324 (17.6%) reported using a dosimeter. Dosimeter use was more frequent among urologists reporting higher monthly volumes of fluoroscopy-assisted surgeries ( $\geq 10$ /month vs  $<10$ /month; OR 2.96, 95% CI 1.52-5.76;  $p=0.001$ ).

All respondents who answered the question regarding the importance of monitoring agreed (fully or partially) that urologists' radiation exposure should be controlled (302/302, 100%). However, the reported presence of institutional processes for PPE maintenance and verification was limited: 52/324 (16.0%) reported any periodic control (annual, semi-annual, or quarterly), while 120/324 (37.0%) reported no control and 152/324 (46.9%) did not know. Similarly, regarding monitoring of individual radiation exposure, 202/324 (62.3%) reported that no monitoring is performed in their services, 73/324 (22.5%) did not know, and 49/324 (15.1%) reported some form of monitoring (with or without a defined periodicity).

Concerning PPE availability in the main workplace, lead aprons for surgeons were reported to be available in 100% of procedures by 232/322 (72.0%), and in 50-99% of procedures by 76/322 (23.6%). Thyroid shields were reported to be available in 100% of procedures by 165/321 (51.4%) and in 50-99% by 105/321 (32.7%). Consistent thyroid shield use was more frequent when thyroid shields were reported as available in 100% of procedures (OR 1.92, 95% CI 1.15-3.20;  $p=0.012$ ). In contrast, leaded eyewear was reported as unavailable by 268/324 (82.7%).

### Pregnancy-related radiation safety practices

Among female respondents ( $n=55$ ), 54 answered additional questions addressing reproductive and pregnancy-related radiation safety. Regarding

participation in procedures involving ionizing radiation during pregnancy (or suspected pregnancy), most reported avoiding all radiation-exposing procedures (21/54, 38.9%), while 3/54 (5.6%) reported continuing to participate with strict PPE use and abdominal shielding, 3/54 (5.6%) reported avoiding exposure only during the first trimester, and 2/54 (3.7%) reported avoiding only specific procedures; 25/54 (46.3%) reported never having been pregnant. Only 6/54 (11.1%) reported having received formal counseling on the reproductive and gestational risks of ionizing radiation (during residency or in professional practice), whereas 27/54 (50.0%) reported only informal guidance and 21/54 (38.9%) reported no guidance. In current practice, formal institutional policies restricting or removing pregnant professionals from radiation rooms were reported by 9/53 (17.0%), while 11/53 (20.8%) described an informal consensus, 9/53 (17.0%) reported that this depended on leadership or service, and 24/53 (45.3%) reported no guidance or policy.

### **Role of the Brazilian Society of Urology (SBU)**

Most respondents supported an active role for the SBU in addressing ionizing radiation exposure. Suggested actions included educational campaigns on radiation risks and best practices (113/324, 34.9%), advocacy with medical entities (95/324, 29.3%), and advocacy with healthcare institutions to improve the availability of PPE (96/324, 29.6%). Notably, 276/324 respondents (85.2%) selected the option "all of the above," indicating support for a combined strategy encompassing education and institutional advocacy. Only 3/324 (0.9%) believed that the SBU should have no role in this matter. One participant did not respond to this question.

### **Radiation-related health concerns**

Regarding the development of clinical conditions potentially associated with ionizing radiation exposure, 32/324 (9.9%) reported at least one condition. The most frequently reported conditions were cataract (3.7%), thyroid malignancy (2.5%), infertility (2.2%), and skin cancer (2.2%), followed by having a child with congenital malformations (1.5%), leukemia

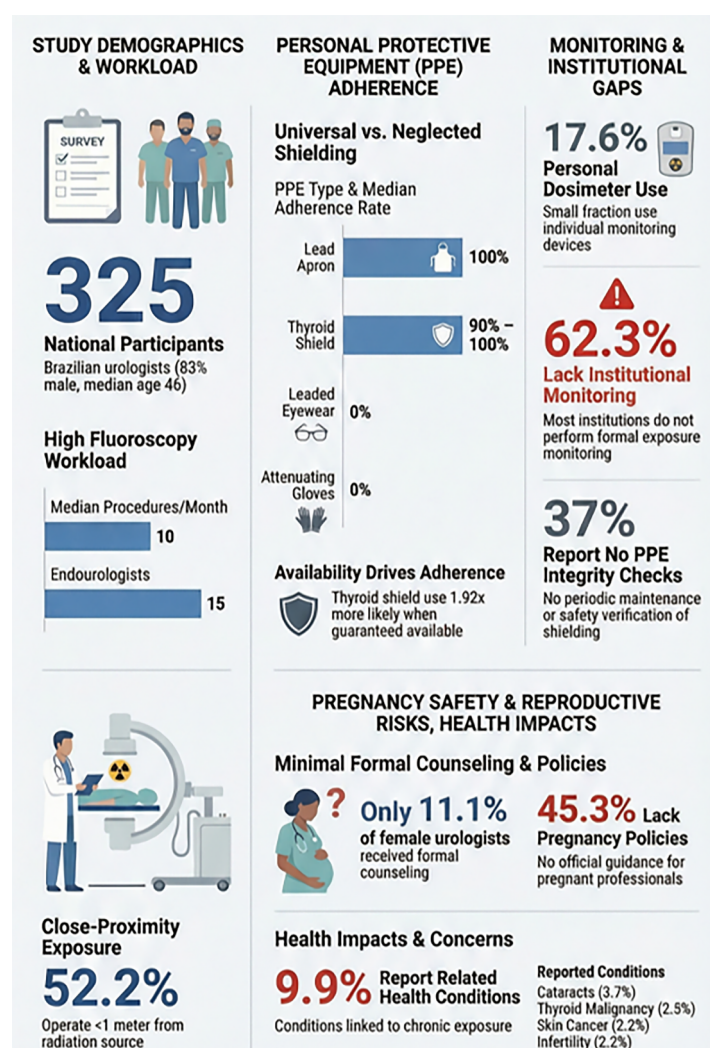
and other myelodysplastic disorders (0.9%), and lymphoma (0.6%). Among respondents reporting any condition, 50.0% considered it highly or moderately likely that lifetime ionizing radiation exposure contributed to the development of their condition (Figure-2).

## **DISCUSSION**

This national survey provides a contemporary overview of radiation exposure patterns, protective behaviors, institutional monitoring practices, and pregnancy-related safety considerations among Brazilian urologists. The findings demonstrate a persistent gap between awareness of radiation risks and the consistent implementation of structured radio-protection strategies in daily practice. PPE use varied according to procedural complexity: lead apron adherence was nearly universal, and thyroid shield utilization was higher in complex endourological procedures. However, leaded eyewear and radiation-attenuating gloves were virtually absent. When compared with previous national data, partial improvement is evident: in the nationwide survey by Borges et al. (2015) (6), 84.4% of respondents reported consistent lead apron use and 53.9% reported thyroid protection. In the present study, conducted roughly a decade later, apron adherence approached universal levels and thyroid shield use demonstrated higher median rates. Nonetheless, the continued absence of eye protection and the low prevalence of dosimeter use indicate that radiation safety remains incomplete and that key anatomical risk sites (lens, hands, thyroid) are still insufficiently protected.

Individual dose monitoring represents one of the most critical deficiencies identified. Only 17.6% of respondents reported personal dosimeter use, more than 60% indicated the absence of institutional exposure monitoring, and nearly half were unaware of periodic PPE integrity verification. Although higher fluoroscopy workload was associated with greater dosimeter use, radiation protection cannot rely on subjective perception of exposure alone. As highlighted in recent educational reviews on radiation safety in urology (10), sustainable safety culture requires structured

Figure 2 - Patterns of Radiation Exposure, Personal Protective QSafety Gaps Among Brazilian Urologists.



PPE = personal protective equipment.

training, systematic monitoring, and institutional accountability. Contemporary dosimetry data reinforce this concern. Measurable scatter radiation exposure has been demonstrated across multiple professional roles during endourological procedures, with significant correlations between dose-area product and staff exposure (3). Systematic analyses have also shown substantial variability in effective radiation doses to urologists and have emphasized the importance of shielding and structured education in reducing occupational exposure by up to 94–100% (2). Together, these findings further suggest that cumula-

tive exposure may be underestimated, particularly in high-volume settings.

The biological risks of chronic radiation exposure, including cataract formation, radiation-induced skin injury, and increased malignancy risk, are well documented (3, 4, 11, 12). Although causality cannot be established from self-reported data, the fact that 9.9% of respondents reported at least one medical condition potentially associated with radiation exposure underscores the perceived and potential occupational impact. Half of these respondents considered radiation exposure a likely contributing

factor, highlighting not only biological concerns but also psychological and professional implications.

A notable and innovative aspect of this study is the detailed assessment of pregnancy-related radiation practices, an area that has been infrequently addressed in urological surveys. Formal counseling regarding reproductive risks was uncommon, and institutional policies restricting radiation exposure during pregnancy were inconsistently reported. Although most pregnant or previously pregnant respondents avoided radiation-exposing procedures, strategies varied and were frequently based on informal arrangements. This variability gains further relevance in light of the increasing representation of women in urology globally (13, 14). As the proportion of female urologists grows, the need for structured and transparent reproductive radiation safety frameworks becomes progressively more critical. Recent literature supports the feasibility of pregnancy-compatible fluoroscopic practice when protective strategies are rigorously applied. Koolik et al. (2025) emphasized adherence to ALARA principles with lead shielding and low-dose protocols (5), while Song et al. (2025) quantified uterine exposure during PCNL and demonstrated that active dose-reduction strategies allow procedures to remain within recommended fetal exposure thresholds (15). Together, these findings suggest that safe practice during pregnancy is achievable, but only within clearly defined institutional protocols that explicitly address role allocation, shielding, and dose monitoring.

Our data further indicate that radiation safety behavior is strongly influenced by infrastructure. The association between equipment availability and its use suggests that adherence is not solely an individual decision. The reported absence of leaded eyewear in most workplaces illustrates how structural limitations directly constrain compliance. Radiation protection therefore requires both professional awareness and institutional commitment, including investment in appropriate PPE and routine maintenance and monitoring processes.

The present study has several limitations. As a voluntary survey with a response rate of 10.8%, it is

subject to selection and self-reporting bias, and respondents may not fully represent the broader Brazilian urologist population in terms of practice patterns, access to equipment, or attitudes toward radiation safety. However, this response rate is consistent with those commonly observed in large-scale web-based surveys among physicians, particularly when participation is voluntary and no incentives are provided. Importantly, the sample included urologists from all geographic regions of Brazil and across diverse practice settings, including public and private sectors as well as academic and non-academic institutions, supporting the heterogeneity of the sample and supporting the external validity of the findings. Objective radiation dose measurements were not performed and perceptions of exposure and risk may be distorted in either direction. We also did not perform stratified analyses according to geographic region, city size, or predominant practice setting (public vs private vs mixed), which may influence both access to protective equipment and institutional safety culture. No causal relationship between reported health conditions and radiation exposure can be established. Finally, although the survey provides a comprehensive national overview, these findings reflect the Brazilian context and cannot be directly extrapolated to other countries or healthcare systems without consideration of local infrastructure, regulations, and training environments.

Despite these limitations, this study has several strengths. It represents a comprehensive, contemporary national assessment of radiation exposure and radioprotection practices among Brazilian urologists, encompassing diverse practice settings and subspecialties through the institutional reach of the SBU. The survey instrument underwent multidisciplinary expert review and pilot testing, supporting content validity and clinical applicability. Importantly, the study evaluated not only personal protective equipment use but also institutional infrastructure, dosimetry practices, and pregnancy-related policies—domains that have seldom been examined simultaneously in prior surveys. By integrating behavioral and structural variables and identifying factors

associated with protective practices, the findings provide data that may inform targeted educational and institutional strategies to enhance radiation safety in Brazilian urology.

Although foundational protective measures such as lead apron use are widely incorporated, comprehensive radiation safety culture remains underdeveloped. Systematic monitoring, broader PPE adoption, structured pregnancy policies, and institutional oversight are necessary to ensure that increasing reliance on fluoroscopy is accompanied by proportional commitment to occupational health and long-term risk mitigation.

## CONCLUSIONS

This national survey reveals that, although radiation protection is widely recognized as important, its structured application in Brazilian urology remains inconsistent. Limited use of dosimetry, heterogeneous institutional monitoring, inconsistent availability of PPE, and insufficiently defined pregnancy policies indicate that radioprotection is not yet fully integrated into routine practice. These findings reinforce the need for targeted educational initiatives and institutional standardization, supported by active engagement of professional societies and renewed emphasis on the ALARA principle to ensure sustained protection of both medical personnel and patients in fluoroscopy-guided urological care. Although focused on Brazil, these findings may be informative for other settings with similar resource constraints and practice patterns.

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## DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

## ABBREVIATIONS

ALARA = As Low As Reasonably Achievable

CI = Confidence Interval

IQR = Interquartile Range

OR = Odds Ratio

PPE = Personal protective equipment

SBU = Brazilian Society of Urology (Sociedade Brasileira de Urologia)

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## CONFLICT OF INTEREST

None declared.

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# Quality of life: a neglected aspect in male infertility studies

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## INTRODUCTION

Male infertility is increasingly recognized not only as a reproductive disorder but also as a significant public health concern affecting the physical, emotional, social, and sexual well-being of affected individuals and their partners (1). While considerable attention has been devoted to understanding its causes, diagnostic pathways, and treatment options, relatively little emphasis has been placed on how infertility affects the daily lives of men and whether medical interventions meaningfully improve their quality of life (QoL) (2). This gap is particularly relevant given the growing recognition that patient-reported outcomes should complement traditional clinical endpoints such as semen quality, fertilization rates, pregnancy, and live birth.

The importance of this issue has been highlighted by the international Priority Setting Partnership for Infertility, which identified the psychological and emotional impact of infertility as one of the highest priorities for future research (3). Specifically, patients, healthcare professionals, and other stakeholders emphasized the need to understand how infertility affects emotional health and whether interventions addressing these concerns can improve patient outcomes. Despite these priorities, QoL remains one of the least investigated outcomes in male infertility research.

Although QoL has become an established outcome measure across multiple medical disciplines, there is no universally accepted definition. In the context of infertility, the concept of health-related quality of life (HRQoL) is particularly relevant because it encompasses the impact of disease and treatment on physical, psychological, emotional, social, and functional well-being (4). HRQoL recognizes that patients' experiences extend beyond biological abnormalities and laboratory findings and are influenced by how disease affects their ability to live satisfying and productive lives.

## MEASURING QoL IN MALE INFERTILITY

Several generic and fertility-specific instruments have been developed to measure QoL in infertile individuals. Commonly used generic tools include the Short Form Health Survey (SF-36) and the World Health Organization Quality of Life Questionnaire (WHOQOL-BREF). Fertility-specific instruments include the Fertility Quality of

Life questionnaire (FertiQoL), the Fertility Problem Inventory, and the Copenhagen Multi-Center Psychosocial Infertility (COMPI) Fertility Problem Stress Scales (1, 5-12) (Table-1). Among these, FertiQoL has become the most widely adopted instrument because it was specifically designed for infertile individuals and assesses emotional, social, relational, mind-body, treatment environment, and treatment tolerability domains.

## PSYCHOLOGICAL BURDEN OF MALE INFERTILITY

Despite the availability of validated instruments, studies specifically addressing QoL in men with infertility remain scarce, although recent systematic reviews have emphasized that male infertility is consistently associated with impaired emotional, social, relational, and sexual well-being (13-15). Historically, infertility research has focused primarily on women because they bear most of the physical burden associated with assisted reproductive technology (ART). Consequently, the male experience has often been overlooked, despite evidence indicating that infertility can profoundly affect men's psychological health, sexuality, interpersonal relationships, social functioning, and self-perception (15).

Still, a few studies indicate that the QoL of men experiencing infertility appears to be dynamic and may evolve throughout the patient journey. Men may experience emotional distress during attempts to conceive, at the time of diagnosis, throughout infertility treatment, and particularly following unsuccessful ART cycles (16-18). The inability to achieve biological fatherhood may trigger a grieving process similar to that observed in other forms of loss. Furthermore, repeated treatment failures may compound emotional distress and contribute to treatment discontinuation (19). Studies have identified predictors of poorer QoL among infertile men, including lower educational attainment, unemployment, poor marital relationships, longer infertility duration, and previous failed IVF attempts (20-22). When the QoL of men with infertility is compared with infertile females, it has been observed that women consistently exhibit poorer FertiQoL scores than their male counterparts (16).

A 2024 systematic review evaluating the psychological consequences of male infertility highlighted the breadth

of these effects (14). Men diagnosed with infertility frequently experience grief, loss, diminished self-esteem, feelings of inadequacy, anxiety, and depressive symptoms. The diagnosis may challenge deeply rooted perceptions of masculinity and fatherhood, leading some men to experience shame, social isolation, and stigmatization. Importantly, the review noted that men often internalize distress and are less likely than women to seek psychological support, potentially resulting in under-recognition of their emotional suffering. These observations reinforce the need for a patient-centered model of care that addresses the psychosocial consequences of infertility regardless of the underlying diagnosis.

## BEYOND SEMEN PARAMETERS: QoL, SEXUAL HEALTH AND HORMONAL FUNCTION

Interestingly, infertility-related QoL is not always closely linked to conventional reproductive biomarkers. One of the largest studies addressing this question evaluated more than 700 men participating in a multicenter randomized trial involving couples with unexplained infertility (23). The investigators examined relationships among fertility-related QoL, depression, gonadal function, semen quality, and erectile function. Contrary to expectations, neither QoL nor depressive symptoms were associated with testosterone concentrations or semen parameters. However, lower QoL scores were strongly associated with erectile dysfunction, and men with depressive symptoms were significantly more likely to experience erectile dysfunction than those without depression (Table-2). These findings suggest that psychological and sexual health dimensions may be more important determinants of perceived well-being than conventional biological markers of male reproductive function.

The observations discussed above carry important clinical implications. Physicians often focus on semen quality and endocrine parameters when evaluating infertile men, yet these measures may inadequately capture the patient's lived experience. Men with relatively preserved semen parameters may still suffer substantial psychological burden, whereas others with severe abnormalities

**Table 1 - Tools to assess quality of life and infertility-related distress in individuals and couples affected by infertility.**

| Name                                                                                     | Characteristics                                                                                                                                                                                                                                                                                              | Website                                                                                                                                                                       | Reference |
|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>Generic</b>                                                                           |                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                               |           |
| Short Form Health Survey (SF-36)                                                         | A 36-item questionnaire including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health.                                                                                                                                          | Available from: <a href="https://www.clintools.com/victims/resources/assessment/health/sf36.html">https://www.clintools.com/victims/resources/assessment/health/sf36.html</a> | 9         |
| World Health Organization Quality of Life (WHOQOL-BREF)                                  | An abbreviated version of WHOQOL-100, including 26 items distributed into four domains (physical, psychological, social relationship, and environmental)                                                                                                                                                     | <a href="https://www.who.int/tools/whoqol">https://www.who.int/tools/whoqol</a>                                                                                               | 10        |
| <b>Condition-specific</b>                                                                |                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                               |           |
| Copenhagen Multi-Center Psychosocial Infertility (COMPI) Fertility Problem Stress Scales | Fourteen items assessing the impact of infertility on personal, social, and marital domains. Items are scored using a four or five-point Likert scale, with higher scores indicating higher stress.                                                                                                          | NA                                                                                                                                                                            | 8         |
| Fertility Quality of Life (FertiQoL)                                                     | A 36-item questionnaire measuring fertility quality of life in four personal domains (emotional, social, relational, mind/body) and two treatment domains (tolerability, environment).                                                                                                                       | <a href="http://www.fertiqol.com/">http://www.fertiqol.com/</a>                                                                                                               | 11        |
| Fertility Problem Inventory                                                              | A 46-item self-rating scale including five domains: social concern, sexual concern, relationship concern, need for parenthood, and rejection of a childless lifestyle. Participants respond on a 6-point Likert scale ranging from 1 to 6. A high item score indicates significant fertility-related stress. | NA                                                                                                                                                                            | 12        |

NA = not applicable

may report acceptable QoL. Consequently, QoL assessment may provide clinically relevant information that is not apparent from traditional diagnostic testing (24, 25).

The relationship between infertility and sexual health deserves particular attention. Erectile dysfunction reduced sexual satisfaction, and diminished sexual confidence have been reported more frequently among infertile men than fertile controls (23). While these disturbances may partly reflect underlying hormonal or vascular conditions, psychological distress appears to play a major role. The association between lower QoL and erectile

dysfunction observed in infertile men suggests that sexual and emotional health should be routinely assessed during infertility evaluations. Recognition of these issues may create opportunities for interventions capable of improving overall well-being independently of reproductive outcomes.

## INFERTILITY AS A DYADIC DISEASE

Another emerging concept is that infertility should be regarded as a dyadic condition rather than an individual disease. Although infertility diagnoses are traditionally assigned to one partner, the consequences

**Table 2 - Key primary studies evaluating quality of life in men with infertility.**

| Study                     | Population                                        | Instrument            | Main findings                                                                                                         | Clinical implications                                                                            |
|---------------------------|---------------------------------------------------|-----------------------|-----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Coward et al., 2019 (23)  | 708 men from couples with unexplained infertility | FertiQoL, PHQ-9, IIEF | Lower QoL associated with erectile dysfunction but not testosterone levels or semen parameters                        | Psychological and sexual health may be more relevant determinants of QoL than biological markers |
| Asazawa et al., 2019 (33) | 38 infertile couples                              | FertiQoL              | Spousal-support program improved emotional and relational QoL domains                                                 | Psychosocial interventions may improve patient well-being                                        |
| Danis et al., 2023 (27)   | 201 men undergoing fertility evaluation           | FertiQoL              | Men evaluated by reproductive urologists reported lower QoL but overwhelmingly considered the consultation beneficial | Supports specialist male infertility evaluation and patient education                            |
| Pan et al., 2026 (26)     | 105 couples undergoing ART                        | FertiQoL              | Female infertility negatively affected male partner QoL; infertility operates as a dyadic stressor                    | Supports couple-centered infertility care                                                        |

are often experienced by both members of the couple. Recent studies using actor-partner interdependence models have provided important insights into these interactions (26). In a study involving couples undergoing ART, female infertility was associated with significantly lower QoL among male partners, particularly in emotional and mind-body domains (Table-2). Interestingly, the converse effect was not observed. These findings suggest that men may experience substantial distress when witnessing the physical and emotional burden of treatment imposed on their partners, even when the infertility diagnosis is not attributed to them. Such observations challenge traditional assumptions regarding gender differences in infertility experiences and emphasize the need for couple-centered care models.

## THE ROLE OF SPECIALIST MALE INFERTILITY CARE

Additional evidence supporting the importance of male-centered infertility care comes from studies examin-

ing fertility-related QoL according to provider type. Men evaluated by reproductive urologists have been reported to exhibit lower FertiQoL scores than those evaluated exclusively by reproductive endocrinologists (27) as it likely reflects referral pathways and case complexity rather than differences in quality of care. Men referred for reproductive urology assessment often have already undergone reproductive endocrinology evaluation and may present with greater diagnostic uncertainty, disease burden, or treatment-related distress.

Importantly, the same study suggested that men seen by reproductive urologists felt more informed and better understood regarding their condition, underscoring the potential value of male-focused evaluation despite the higher distress observed in this subgroup (27) (Table-2). These findings suggest that specialist male infertility evaluation may provide benefits extending beyond diagnosis and treatment, including education, reassurance, empowerment, and improved health awareness (2, 28).

The latter point is particularly relevant because male infertility is increasingly recognized as a marker of



overall health. A growing body of evidence indicates that infertile men face higher risks of metabolic disorders, hypogonadism, cardiovascular disease, malignancies, and reduced life expectancy (29). Consequently, infertility evaluation represents a unique opportunity to identify previously undiagnosed health conditions and promote preventive healthcare strategies. From a QoL perspective, improved understanding of one's health status and access to appropriate treatment may yield benefits extending far beyond reproductive outcomes.

This broader view of male infertility has been reinforced by the recently published World Health Organization (WHO) Infertility Guidelines, which emphasize that infertility care should be delivered as an integrated component of sexual and reproductive healthcare across the life course (30-32). Importantly, the WHO recognizes that infertility affects both members of the couple and recommends that men and women undergo concurrent evaluation rather than the traditional sequential approach in which the female partner is often investigated first and the male partner only later, particularly when assisted reproductive technologies are being considered. The guideline highlights that infertility assessment should begin with a comprehensive medical, reproductive, and sexual history, focused physical examination, and semen analysis performed according to WHO standards. Such an approach acknowledges the substantial contribution of male factors to infertility and seeks to avoid delays in diagnosis and treatment.

## CAN QoL BE IMPROVED?

Despite increasing recognition of the psychosocial burden of infertility, remarkably little research has evaluated interventions designed to improve QoL among infertile men. For example, the effects of varicocele repair, hormonal therapies, sperm retrieval procedures, sperm DNA fragmentation management strategies, lifestyle interventions, and ART itself on patient-reported QoL outcomes remain poorly characterized. Consequently, clinicians often lack evidence regarding whether treatments that improve reproductive outcomes also improve patients' lives.

One notable exception is a pilot study investigating a structured spousal-support program for men undergoing infertility treatment (Asazawa et al. 2020) (33) (Ta-

ble-2). The intervention significantly improved emotional and relational QoL domains and was well accepted by participants. Although preliminary, these findings suggest that psychosocial and educational interventions may represent promising strategies for alleviating infertility-related distress. In another study, treating male hypogonadotropic hypogonadism with gonadotropins improved scores of all SF-36 QoL domains (34).

The paucity of intervention studies represents one of the most important gaps in current knowledge. This gap is particularly concerning because patients frequently value outcomes extending beyond conception and live birth. Many seek explanations for their infertility, reassurance regarding their health, and opportunities to regain a sense of control over their reproductive future. In some cases, successful diagnosis and treatment may improve QoL even when pregnancy is not achieved. Conversely, interventions associated with significant physical, emotional, or financial burdens may adversely affect QoL despite improving reproductive outcomes. These considerations underscore the importance of incorporating patient-reported outcome measures into both clinical practice and research (24, 25).

Notwithstanding the limited data about the impact of male infertility treatment on QoL, it has been recognized that education provision and proper andrological evaluation provide a unique opportunity for identifying correctable conditions causing infertility and health-threatening issues or coexistent diseases that require medical attention (such as obesity, metabolic syndrome, erectile dysfunction, hypogonadism, kidney diseases, and cancer) (2, 35, 36). Still, in real-world settings, most men are poorly educated about infertility risk factors and do not follow basic recommendations for a healthy lifestyle (37). This is aggravated by the fact that the clinical evaluation of men having infertility is suboptimal, particularly in IVF clinics, where about 40% of specialists report taking only a brief medical history and 24% reported that they never perform a physical examination (38).

Future studies should therefore move beyond traditional reproductive endpoints and routinely incorporate validated QoL instruments. Such efforts would provide a more comprehensive understanding of the impact of infertility and its treatment on affected individuals and couples. Longitudinal studies are particularly needed to character-

ize changes in QoL over time and to identify factors predicting resilience or vulnerability. Randomized trials evaluating medical, surgical, lifestyle, educational, and psychosocial interventions should determine not only whether these interventions improve fertility outcomes but also whether they enhance patients' overall well-being.

## CONCLUSIONS

Quality of life remains a neglected outcome in male infertility research despite growing recognition of its clinical importance. Available evidence indicates that infertility can profoundly affect psychological health, sexual function, interpersonal relationships, and overall well-being. Emerging data further suggest that infertility should be viewed as a shared condition affecting both partners and that specialist male infertility evaluation may provide meaningful benefits beyond reproductive diagnosis alone. Nevertheless, substantial knowledge gaps remain regarding the mechanisms linking infertility and QoL and, more importantly, regarding interventions capable of improving patient well-being. Addressing these gaps will be essential for advancing truly patient-centered infertility care and ensuring that treatment success is measured not only by reproductive outcomes but also by improvements in the lives of the men and couples we serve.

## CONFLICT OF INTEREST

None declared.

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# Editorial Comment: Female Urethroplasty: A Critical Review of Indications, Techniques and Concerns

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## COMMENT

Urethral stricture is one of the most challenging conditions in reconstructive surgery (1-4). Many techniques have been described and there is extensive experience regarding the treatment of urethral strictures in men; however, urethral strictures in women are rarer and are the subject of far fewer publications. In this paper of Chakraborty and colleagues (5) we can observe a very nice narrative review about the indications, techniques and concerns of female urethroplasty. The authors show a practical guide for urologists managing female urethral strictures, including an overview of the female urethral sphincter mechanism and the most common urethroplasty techniques. Institutional ethics board approval is not required for this review article; however, proper consent for using operative images involving human participants has been obtained from the respective patients before surgery. We congratulate the authors for the interesting paper.

## CONFLICT OF INTEREST

None declared.



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# Extraperitoneal Single-Port Robot-Assisted Bilateral Retroperitoneal Lymph Node Dissection for Primary Non-Seminomatous Germ Cell Tumor: Technique and Surgical Considerations

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## ABSTRACT

**Introduction:** Retroperitoneal lymph node dissection (RPLND) is an established treatment option for clinical stage I-II non-seminomatous germ cell tumors (NSGCT), among which bilateral template dissection represents the most oncologically rigorous approach (1, 2). Robot-assisted RPLND has demonstrated reduced surgical morbidity while maintaining oncologic equivalence to open surgery (3). However, the prevailing multiport transperitoneal approach requires extensive bowel mobilization for bilateral exposure, adding operative complexity and bowel-related complication risk (4-6). A completely extraperitoneal single-port approach may circumvent these limitations by avoiding peritoneal entry and visceral manipulation (7).

**Materials and Methods:** We present a 21-year-old male with clinical stage IIA NSGCT who underwent right radical orchiectomy and was found to have multiple enlarged retroperitoneal lymph nodes on CT.

The procedure was performed using the da Vinci Xi system with the patient in the supine position. A 4.0-cm right pararectal incision was made to access the retroperitoneal space, and a single-port multichannel device was deployed. Robotic instruments were introduced in a chopstick configuration, including a 30° endoscope, monopolar scissors, and bipolar forceps. The bilateral ureters and great vessels were first exposed to delineate the standard boundaries of the bilateral template while establishing an adequate retroperitoneal working space. A split-and-roll technique was then applied from the right ureter medially, progressively skeletonizing and preserving the vascular structures through sharp dissection to achieve complete lymphadenectomy within the bilateral template, with meticulous clipping of lymphatic channels.

**Results:** Operative time was 175 minutes with an estimated blood loss of 35 mL. The patient resumed oral intake on postoperative day 1 and was discharged on day 2 (VAS: 2) without complications. Thirty-two lymph nodes were retrieved; three harbored teratoma (pN1). At 36-month follow-up, the patient remains disease-free with normal tumor markers and no retroperitoneal recurrence.

**Conclusions:** To our knowledge, this represents the first reported extraperitoneal single-port bilateral robot-assisted RPLND. This approach achieves oncologically thorough dissection while minimizing morbidity and facilitating rapid recovery.

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# Penile Urethral Stricture After Radical Prostatectomy – Use of Aldehyde-Free Bovine Pericardium Graft

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## ABSTRACT

**Objective:** Penile urethral stricture is a potential complication after any form of urethral instrumentation. Treatment options may be limited when considering direct urethrotomies or urethroplasties without grafting, due to the increased risk of penile shortening and functional compromise. In this context, among the various graft materials described in the literature (including buccal mucosa, lingual mucosa, bladder mucosa, colonic mucosa, augmentation urethroplasty with skin flaps, and injectable antifibrotic agents) (1, 2) the use of bovine pericardium appears promising (3).

In this video, we present a clinical case in which the L-Hydro<sup>®</sup> tissue treatment technology 100% aldehyde free, VIVENDI<sup>™</sup> graft was used as a graft for the surgical repair of penile urethral stricture following radical prostatectomy.

**Materials and Methods:** The present study was approved by the hospital's Institutional Ethics Committee in accordance with ethical standards for research involving human subjects. A 65-year-old male patient developed a penile urethral stricture following urethral instrumentation and prolonged urinary catheter use after radical prostatectomy. Preoperative evaluation included cystourethrography, which demonstrated a 1.2 cm stricture in the penile urethra.

Urethroplasty was indicated for definitive surgical management. Under regional anesthesia, a longitudinal penile incision was made, followed by a ventral sagittal urethrotomy directly over the stricture segment. A free aldehyde-free bovine pericardium graft (VIVENDI<sup>™</sup>) was tailored to the defect and placed as a dorsal onlay within the urethrotomy. The graft was secured with interrupted 4-0 poliglecaprone 25 sutures. The ventral urethrotomy was closed over a 16 Fr silicone Foley catheter, and the penile incision was closed in layers. Follow-up assessments included uroflowmetry and post-void residual urine measurement at 4 weeks, with urethroscopy performed at 7 weeks postoperatively to evaluate urethral patency and graft integration.

**Results:** No intraoperative or postoperative complications occurred. Seven weeks after surgery, the patient underwent urethroscopy, which demonstrated a well-appearing urethral lumen without evidence of stricture or signs of infection. The graft was observed to be well incorporated into the urethral wall with no adverse tissue reaction. At follow-up, the patient also demonstrated adequate bladder emptying, with satisfactory voiding parameters and low post-void residual urine.

**Conclusions:** In this reported case, the use of a bovine pericardium graft demonstrated satisfactory results in penile urethroplasty for the treatment of a urethral stricture. Based on current evidence, bovine pericardium appears to be a feasible graft option for complex urethral reconstruction. However, further studies involving larger patient cohorts and multicenter collaboration are necessary to confirm these findings and better define the long-term efficacy and safety of this approach.

## CONFLICT OF INTEREST

None declared.

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# Opportunities, Challenges, and Perspectives for Equity and Capacity Building in Robotic Urological Surgery in Africa

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To the editor,

We read with great interest the article by Moschovas et al. (1) entitled "Redefining Surgical Collaboration: The First Structured Transcontinental Robotic Telementoring Experience Between Africa and South America." This study emerges within the context of the rapid evolution of robotic surgery, now widely recognized as a major advancement in minimally invasive surgery, improving technical precision, three-dimensional visualization, and postoperative outcomes while reducing tissue trauma and surgical complications (2). Robotic surgery is currently implemented across several surgical specialties through a variety of technological platforms (3). Concurrently, telementoring and telesurgery have emerged as innovative tools capable of delivering surgical expertise remotely and reducing disparities in access to specialized care (4). These approaches are particularly relevant in low- and middle-income countries, where shortages of skilled personnel and infrastructural limitations continue to hinder the adoption of advanced surgical technologies (5).

Moschovas et al. (1) highlighted the feasibility and safety of a structured transcontinental robotic telementoring model. This achievement builds upon the earliest proof-of-concept experiences in remote robotic surgery and demonstrates that international surgical collaboration can be conducted safely when supported by a clear distribution of responsibilities, an autonomous local surgical team, and rigorous ethical oversight (6). Previous studies have already shown that telesurgery and telementoring may improve access to surgical care in resource-limited regions while simultaneously promoting knowledge transfer and standardization of surgical practices (5). Within the African context, transcontinental robotic telementoring represents a major strategic opportunity to strengthen local capacities in minimally invasive and robotic surgery by enabling real-time interaction between African centers and international expert teams, providing indirect access to highly specialized expertise without requiring the physical displacement of either patients or surgeons (7).

Recent evidence has further reinforced the technical feasibility and reproducibility of long-distance robotic telesurgery. In a pioneering study conducted between China and Kuwait over a distance of approximately 7,000 kilometers, Aldousari et al. (8) reported successful completion of robotic radical prostatectomies and partial nephrectomies without clinical or technical complications using a low-latency fiber-optic and 5G network infrastructure.

Likewise, a recent systematic review by Ferreira et al. (9) analyzing 54 urological telesurgical procedures demonstrated that robotic telesurgery can be safely performed with acceptable operative outcomes, minimal blood loss, and no conversion to open surgery, despite the considerable geographic distances involved. Beyond the surgical team itself, the safe deployment of telesurgery also requires a fundamental reframing of anesthetic practice. As Barani et al. (10) recently emphasized, telesurgery represents a natural evolution of robotic surgery in which established anesthetic protocols, the mandatory presence of an on-site surgical and anesthetic team, and structured communication strategies are essential to ensure patient safety and optimize outcomes. Beyond these technical and clinical considerations, as recently demonstrated in the Brazilian experience, the safe implementation of telesurgery requires clear ethical and legal frameworks, rigorous research governance, and strong multidisciplinary collaboration involving surgical societies, hospitals, governmental agencies, and technology providers (11).

Despite these promising advances, the adoption of robotic telesurgery across Africa remains constrained by major structural, economic, and technological barriers. These include the high cost of robotic platforms,

maintenance expenses, limited access to consumables, insufficient specialized training programs, and fragile hospital infrastructures characterized by recurrent power outages and unstable high-speed internet connectivity (7). The cybersecurity vulnerabilities inherent to remote surgical systems, the protection of medical data transmitted across international networks, the complexity of informed consent in transnational settings, and unresolved questions of medico-legal liability further compound these challenges (12). In this context, the progressive development of regional hubs, reinforcement of digital infrastructures, implementation of hybrid training models, and strengthening of South-South collaborations could facilitate sustainable knowledge transfer and contribute to reducing inequalities in access to specialized surgical care — ultimately making telesurgery a genuine instrument of equity across the African continent.

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## CONFLICT OF INTEREST

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In response to the concerns of the editors of scientific medical journals with ethics, quality and seriousness of published articles, a Committee on Publication Ethics (COPE) was established in 1997 and a guideline document was published. The International Braz J Urol signed, approved, and follows the COPE guidelines. The Editor strongly encourages the authors to carefully read these guidelines before submitting a manuscript (**[www.publicationethics.org.uk/guidelines](http://www.publicationethics.org.uk/guidelines)** or **[www.brazjurol.com.br](http://www.brazjurol.com.br)**, vol. 26 (1): 4-10, 2000).

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**Page and Video Section.** The articles should be written in Portuguese or English official orthography.

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Every manuscript submitted to publication should have a cover page containing the title, short title (up to 50 characters), authors and institution. Up to six key words should be provided. These words should be identical to the medical subject headings (MeSH) that appear in the Index Medicus of the National Library of Medicine (<http://www.nlm.nih.gov/mesh/meshhome.html>). One of the authors should be designated as correspondent and the complete correspondence address, telephone and fax numbers and E-mail should be provided.

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- **Main findings:** Report case(s) relevant aspects
- **Case(s) hypothesis:** Proposed premise substantiating case(s) description
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#### **Papers published in periodicals:**

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





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

**Books:**

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

**Chapters in Books:**

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

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

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

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**Conclusions** must be strictly based on the study findings.

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

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

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- An Abstract was provided for all type of articles. The length of the Abstract is about 250 words.
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